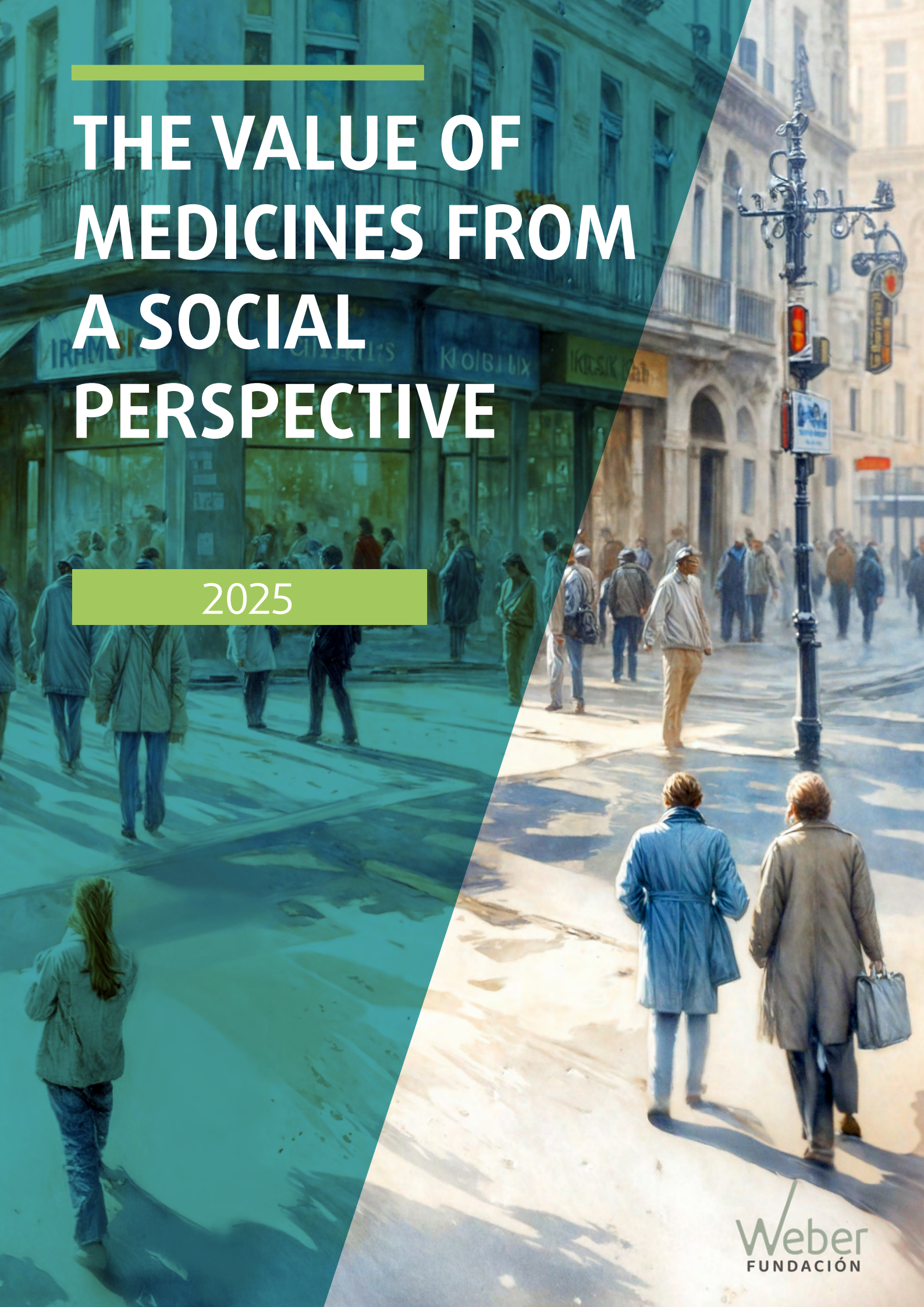
THE VALUE OF MEDICINES FROM A SOCIAL PERSPECTIVE

2025



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The value of medicines from a social perspective

2025

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PRESENTATION

Medicines represent a clear example of the tangible benefits that innovation brings to social welfare. In recent decades, the introduction of new medicines has played a crucial role in improving life expectancy, population health and quality of life.

These advances have been instrumental in curing or preventing diseases, reducing symptoms, improving survival, speeding up treatment and recovery processes, as well as minimising adverse effects and offering alternative forms of administration to improve adherence.

From a broader perspective, therapeutic innovations have a significant impact on health systems, shaping their structure, dynamics and sustainability. In this context, medicines emerge as extremely useful tools for potentially optimising healthcare resources, by allowing more effective prevention or treatment of a variety of specific pathologies. This efficacy translates into a potential reduction in the use of both healthcare (such as hospitalisations, doctor visits or diagnostic tests) and non-healthcare (including personal care) resources. This reduction may free up resources for other purposes and may generate potential savings in the system. Furthermore, clinical improvement from pharmaceutical innovation can have a positive impact on patient productivity at work, reducing both absenteeism and presenteeism.

Moreover, medicines are at the forefront of the advancement of knowledge and play a key role in the shaping and future evolution of technology in society. The pharmaceutical industry is among the most innovative and dynamic sectors of the economy, generating both added value and highly specialised employment. This sector, characterised by its high level of specialisation, offers a significant social return on investment in human capital and exerts a powerful tractor effect on other economic sectors, thus multiplying its positive impacts on the economy.

Therefore, assessing the societal value of pharmaceutical innovation involves considering its impact both on health outcomes and quality of life of patients, and on the reduction of individual and societal costs, including improvements in labour productivity, as well as its contribution to overall economic development.

In 2018, the Weber Foundation launched The Social Value of Medicines from a Social Perspective Report to provide an overview of the economic, clinical and social value of pharmaceutical innovations in Western societies, based on data and evidence up to September 2017. The rapid advance of pharmaceutical innovations made it timely to publish an update of the original report in 2021, revising the latest data, compiling new evidence and highlighting successful innovative experiences in the field of pharmaceutical innovations, focusing on health, quality of life and efficiency of the healthcare system. Now, three years later, we are carrying out a further update of the work, summarising developments between 2021 and 2024 and presenting recent examples of the contribution of medicines to societal value.

The report has been prepared through a narrative literature review, including scientific publications, grey literature sources and documents from relevant organisations, such as business associations, the Organisation for Economic Co-operation and Development (OECD) and the European Commission, with data collected up to February 2024. For the analysis of the contribution to the economy, official databases of the National Institute of Statistics, Eurostat and SABI, among others, were consulted. In the preparation of the report, priority has been given to information related to Spain and the European Union (EU), replacing references to studies in previous reports with more recent evidence relevant to the Spanish and European context, thus avoiding excessive length in the final report.

The studies included in previous reports have been replaced by more recent and relevant evidence for the Spanish and European context, thus avoiding the excessive length of the final report.

The first report on the social value of medicines was published in 2018 and updated in 2021. Now, three years later, it is time to update it again, to review the latest data and analyse the new evidence published.

The structure of the report remains similar to that of the preliminary report, with three central chapters. The first examines the value of the pharmaceutical industry in terms of its contribution to the national economy, covering aspects such as job creation, value added, research and development, foreign trade and tax revenues, with an emphasis on spill-over effects on other economic sectors.

The second chapter explores the impact of the introduction of new medicines on the efficiency of the health system and society in general, reviewing situations where drugs have led in certain cases to health or indirect cost savings. Two specific sections focus on the role of adherence to treatment and the effect of vaccines on resource consumption, respectively.

The third and most comprehensive chapter reviews the main advances in treatments to date, assessing their effects on health outcomes and patients' quality of life. It begins with a general analysis and then delves into the specific results obtained in various chronic diseases, such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), cancer, cardiovascular diseases, diabetes mellitus, rheumatoid arthritis, mental disorders or migraine, to name a few. In this issue, a new section on other immunomediated dermatological diseases is added.

Finally, the report concludes with a brief summary of the most relevant findings and reflections. In addition, the digital version includes an annex with a series of summary factsheets on the key publications in this review. These factsheets provide a synthesis of the original publication, together with a brief commentary highlighting its importance, with automatic links throughout the document to access them, indicated by the symbol ◎.

** Download available at: www.weber.org.es and www.farmaindustria.es*

The first report on the social value of medicines was published in 2018 and updated in 2021. Now, three years later, it is time to update it again, to review the latest data and analyse the new evidence published.

LIST OF ACRONYMS

95%CI	95% Confidence Interval
ART	Antiretroviral treatment
COPD	Chronic obstructive pulmonary disease
DAA	Direct-acting antiviral therapy
DALY	Disability-adjusted life year
LYG	Life Year Gained
DMARD	Disease-modifying antirheumatic drugs
EM	Episodic migraine
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GAD	Generalised anxiety disorder
GDP	Gross Domestic Product
HBV	Hepatitis B virus
Hib	Haemophilus influenzae type b
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HPV	Human papillomavirus
HR	Hazard Ratio
HRQOL	Health-related quality of life
IBD	Inflammatory bowel disease
INE	National Institute of Statistics
LABA	Long-acting β2-agonists
LAMA	Long-acting muscarinic antagonists
LDL	Low Density Lipoproteins
MDD	Major Depressive Disorder
MS	Multiple sclerosis
NHS	National Health Service
ODs	Orphan drugs
OECD	Organisation for Economic Co-operation and Development
PD	Parkinson's disease
PFS	Progression-free survival
pp	Percentage points
QALY	Quality-adjusted life year
RA	Rheumatoid arthritis
RD	Rare Diseases
R&D&I	Research, development and innovation
RR	Risk Ratio
UK	United Kingdom
YLL	Years of life lost

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THE CONTRIBUTION OF THE PHARMACEUTICAL INDUSTRY TO THE ECONOMY

The pharmaceutical industry plays a crucial role as one of the main scientific, technological and industrial drivers in developed economies. Its essential contribution is reflected in the generation of significant economic value, which can be estimated through its contribution to development, knowledge, added value and employment. This chapter seeks to provide a perspective on the economic contribution of the pharmaceutical industry in Spain, Europe and worldwide. This analysis is based on the main economic magnitudes, extracted from official sources, as well as from various reports and studies specialising in this field.

The pharmaceutical industry is one of the main scientific, technological and industrial drivers in developed economies, generating a significant contribution to the economy in terms of employment and value added. In addition to producing value directly, the sector also plays an important role in the development of the pharmaceutical industry. A key role in the indirect and induced generation of employment and value added. This is achieved through its tractor effects on other economic sectors, from which it feeds and to which it supplies.

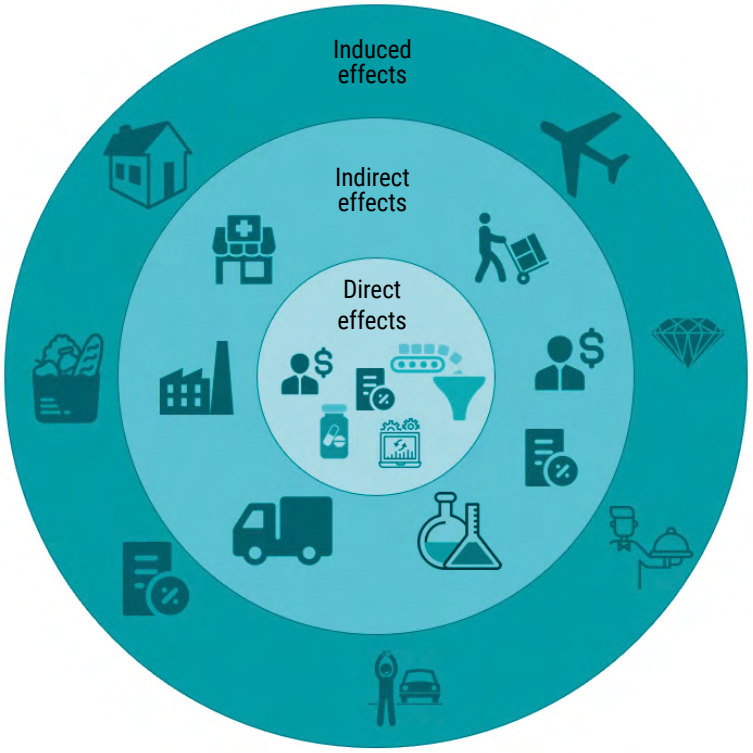
Indirect effects relate to output and employment generated in sectors that benefit indirectly from pharmaceutical industry investments and consumption, i.e. those sectors that provide goods and services essential to their activity (e.g. the chemical and food industry). On the other hand, induced impacts are those arising from the consumption of goods and services by employees in sectors that directly or indirectly benefit from pharmaceutical industry investment and spending (Figure 1).

FIGURE 1. DIRECT, INDIRECT AND INDUCED ECONOMIC EFFECTS

Direct effects
Immediate economic impact generated by the company's activity: production, wages, taxes, etc.

Indirect effects
Result of the company's activity on the intermediate consumption of goods and services by the company's suppliers throughout the supply and production process: production, wages, taxes, distribution, logistics, etc.

Induced effects
Result of the impact of spending on goods and services by the company's employees and its suppliers on the economy as a whole: personal expenses, taxes, rent, leisure, etc.



Source: Ostwald (2013)[1]

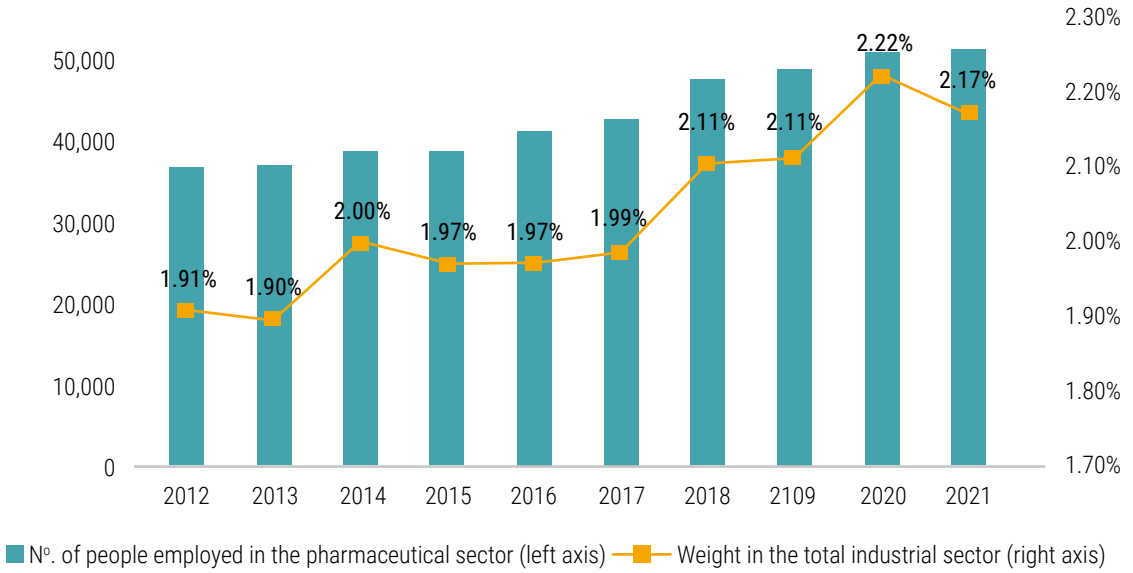
In this chapter, we examine the role of the pharmaceutical industry as a technology leader and a major investor in research, development and innovation (R&D&I) and explore its contribution to foreign trade and national tax revenues.

EMPLOYMENT IN THE PHARMACEUTICAL INDUSTRY

In 2021, the pharmaceutical industry in Spain achieved an all-time record in terms of job creation, reaching 51,310 people, an increase of 13% compared to 2018. In absolute terms, the sector created 6,094 new jobs between 2018 and 2021. Employment in the pharmaceutical industry has seen an average annual increase of 3.1% since 2012, compared to an average annual growth of 2% for the industrial sector. Employment in R&D has also grown significantly in the last four years (+7.6%), with the number of new employees joining pharma companies in the last four years (+7.6%).

The number of new researchers in the pharmaceutical industry is almost 300. In 2021, this sector accounted for 2.17% of total employment in the industry (Figure 2)[2].

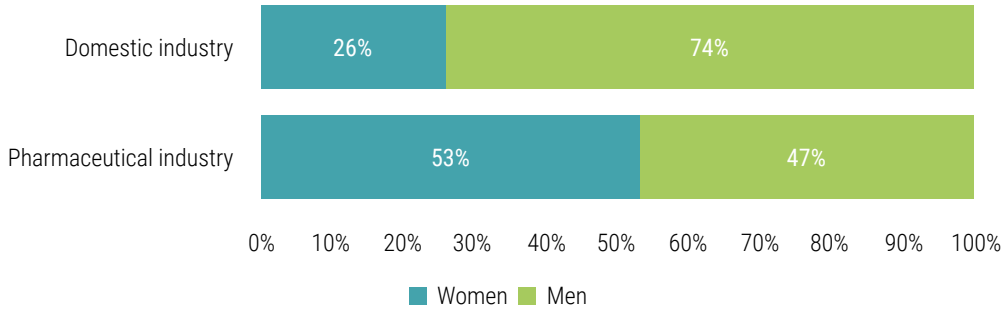
FIGURE 2. EVOLUTION OF THE NUMBER OF PEOPLE EMPLOYED IN THE PHARMACEUTICAL INDUSTRY AND ITS SHARE OF TOTAL EMPLOYMENT IN THE INDUSTRY IN SPAIN, 2012-2021



Source: Own compilation based on the Main magnitudes according to main activity, INE[2]

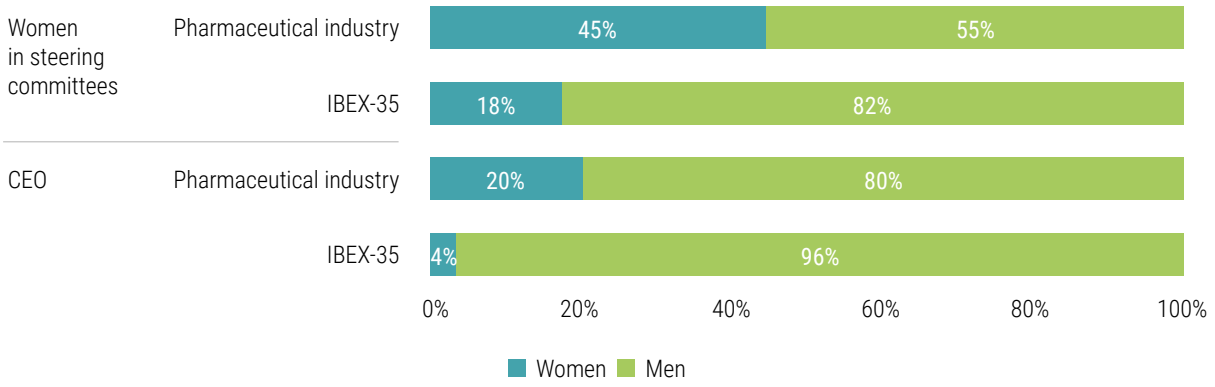
On the other hand, and according to the results of the Farmaindustria employment survey conducted in 2021, 93% of employees had full-time permanent contracts (compared to 62% in the Spanish economy as a whole) and 64% had university studies (46% in the national economy). Meanwhile, 53% of employees in the sector were women (26% in the national economy) (Figure 3)[3]. On the other hand, 45% of pharmaceutical companies' management committees are women, compared to an average of 18% in the IBEX-35, and 20% of CEOs in the pharmaceutical industry are women, compared to 4% in the IBEX-35 (Figure 4)[3].

FIGURE 3. DISTRIBUTION OF EMPLOYMENT BY GENDER IN THE PHARMACEUTICAL INDUSTRY AND IN THE INDUSTRIAL SECTOR, 2021



Source: Prepared by the authors based on the Pharmaceutical Industry Employment Survey, Farmaindustria (2022)[3]

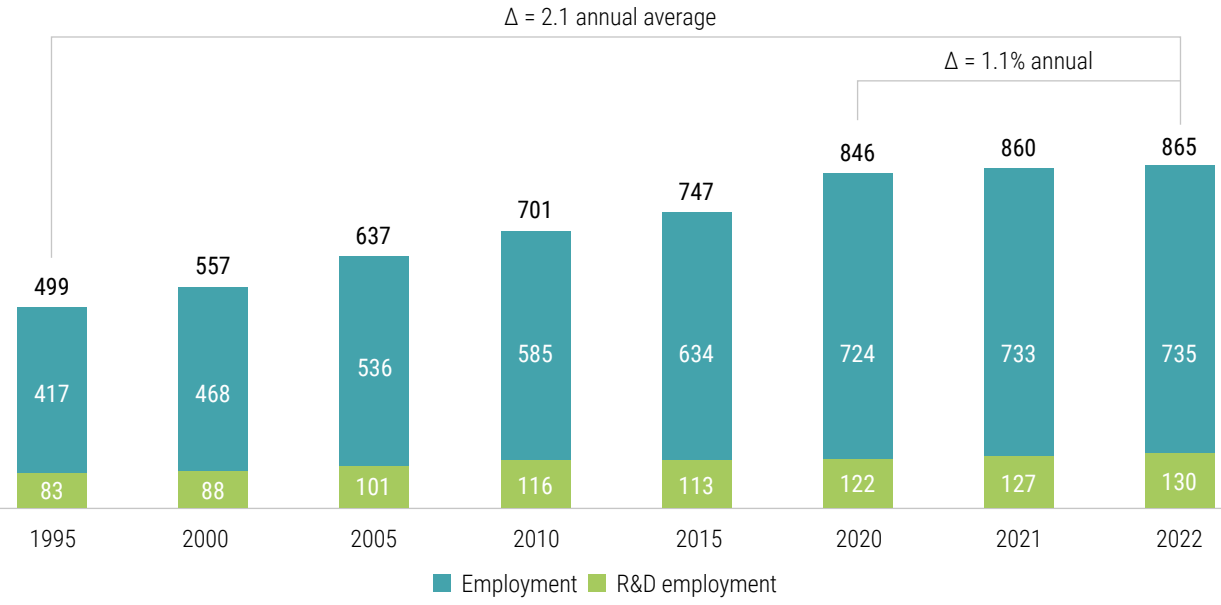
FIGURE 4. DISTRIBUTION OF EMPLOYMENT BY GENDER AT MANAGEMENT LEVEL IN THE PHARMACEUTICAL INDUSTRY AND IN THE TOTAL NUMBER OF COMPANIES COMPRISING THE IBEX-35, 2021



Source: Prepared by the authors based on the Pharmaceutical Industry Employment Survey, Farmaindustria (2022)[3]

At European level, the pharmaceutical industry employs an estimated total of 865,000 people directly, 15% of whom are engaged in research and development (Figure 5). The number of employees in the sector has experienced an average annual growth of 2.1%, reaching a total increase of 73% between 1995 and 2022. In other words, during this period, the pharmaceutical industry generated 37 new jobs in Europe every day. However, average annual growth has slowed down in recent years, averaging 1.1% between 2020 and 2022[4].

FIGURE 5. EVOLUTION OF EMPLOYMENT AND R&D EMPLOYMENT IN THE PHARMACEUTICAL INDUSTRY IN EUROPE (THOUSANDS OF PEOPLE), 1995-2022

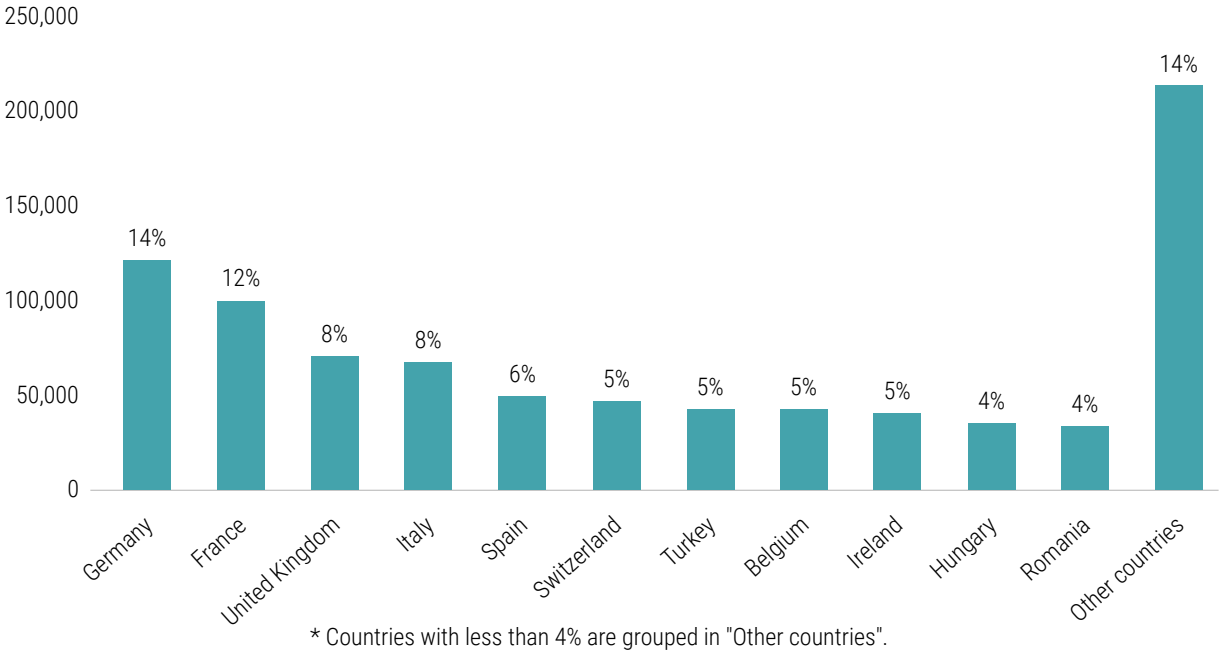


Note: 2022 values are estimates.

Source: EFPIA (2024)[4]

With 6% of the total, Spain ranks fifth in terms of direct employment generated by the pharmaceutical industry in Europe (Figure 6). Moreover, a significant proportion of these jobs are skilled, for example in the academic research sector, which can help to maintain a high-level knowledge base and avoid a European "brain drain"[4].

FIGURE 6. DISTRIBUTION OF DIRECT, INDIRECT AND INDUCED EMPLOYMENT GENERATED BY THE PHARMACEUTICAL INDUSTRY IN EUROPE, IN %, 2016



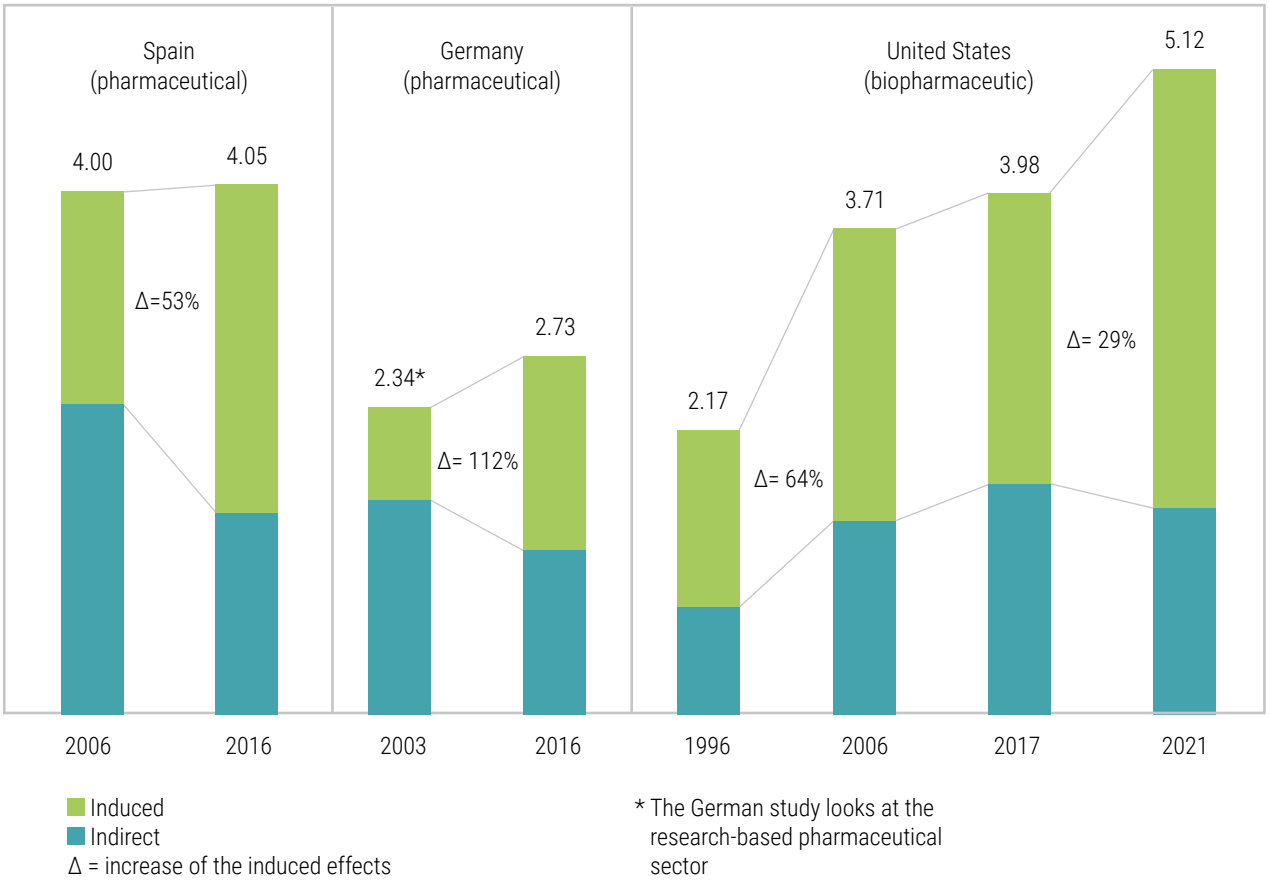
* Countries with less than 4% are grouped in "Other countries".

Source: EFPIA (2024)[4]

Worldwide, the pharmaceutical industry employs more than 5.5 million people directly and more than 74 million people including indirect and induced employment[5]. In terms of its impact on other economic sectors, it has been estimated that globally for every direct job created by the pharmaceutical industry, 12.5 additional jobs (8.2 indirect and 4.3 induced) were generated in 2017. India generates a very high indirect employment effect (indirect multiplier of 23), reflecting a more labour-intensive production structure[6]. In Europe, job creation in 2016 was lower, with 2.9 additional jobs (1.2 indirect and 1.7 indirect and 1.7 indirect) generated for every direct job[7]. For its part, in Spain in 2016, this effect was more pronounced than in Europe, but less than globally, as it is estimated that for each direct job, 4 additional jobs were generated (1.5 indirect and 2.5 induced)[7]. This variation highlights the different implications for employment depending on the geographical area.

Multipliers in the biopharmaceutical and pharmaceutical sectors have increased over time, reflecting greater interconnectedness between the economic sectors. In Spain, multipliers have remained around 4.0, but with a 53% growth in the induced effect in the comparison of the period between 2006 and 2016[8,9]. Another paper has obtained higher figures, estimating that in 2017, each job in the pharmaceutical sector in Spain generated around 8.8 new jobs in the economy as a whole, taking into account only the direct and indirect effect, and 13.4 jobs if the induced effect (variation partially due to the methodology used) is added[10]. In Germany, increases of 15% in the multiplier have been recorded (2003 vs. 2016), with a growth of the induced effect of 112%[9],[11]. On the other hand, in the United States, the multiplier effect has increased by 83% between 1996 and 2017, with the induced effect being the main culprit, with a growth of 64%[12,13]. The multiplier effect has continued to increase between 2017 and 2021 with an increase of 29%[14] (Figure 7).

FIGURE 7. MULTIPLIER EFFECT OF EACH DIRECT JOB GENERATED IN THE PHARMACEUTICAL/ BIOPHARMACEUTICAL SECTOR IN SPAIN, GERMANY, AND THE UNITED STATES



Source: Own elaboration based on Nueno (2006)[8] , Nusser (2007)[11] , Archstone Consulting (2009)[12] , EFPIA (2019)[9] , PhRMA (2019)[13] and PhRMA (2023)[14]

In 2021, the pharmaceutical industry in Spain reached an all-time employment record, generating 51,310 jobs, which is 13% more than in 2018. Ninety-three per cent of employees were full-time permanent, 64% were university educated and 53% were women. In addition, employment in the sector has experienced higher growth than in the industrial sector in general (3.1% vs. 2.0%).

In addition to the direct effects on employment, there are also economic spillover effects on other sectors, since for every direct job created in the pharmaceutical industry, between 3 and 5 additional jobs are generated.

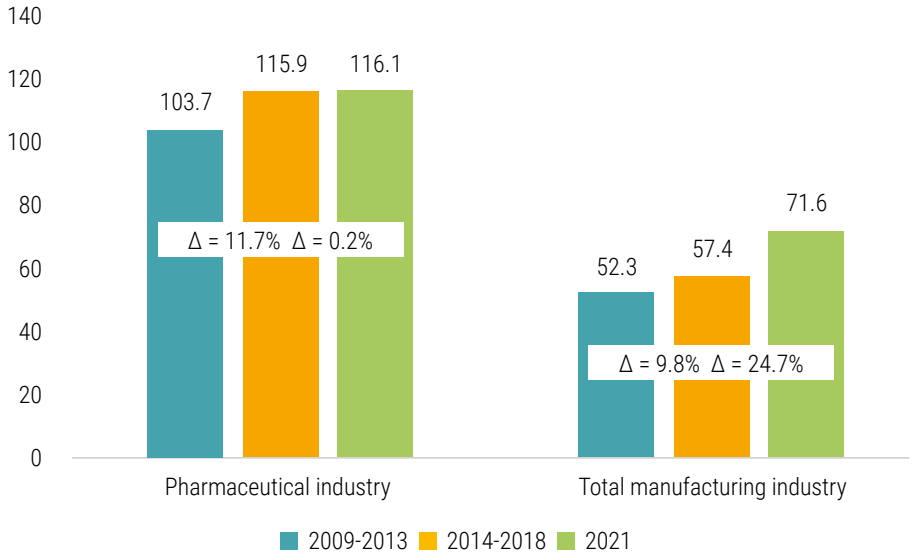
INE (2024)[2], Farmaindustria (2022)[3], PhRMA (2019)[13] and PhRMA (2023)[14]

PRODUCTION AND ADDED VALUE OF THE PHARMACEUTICAL INDUSTRY

Due to the characteristics of its products and its workers, the pharmaceutical industry stands out as an industrial sector that generates high value added (or "value added at factor cost", which represents the net value of the goods produced) and output (or "value of production", which is the gross value of the goods produced valued at selling prices), significantly higher than the average value of the industrial sector.

The productivity of the pharmaceutical industry, measured as value added per employee (full-time equivalent), is double the average of the manufacturing industry. In the period from 2009-2013 to 2014-2018, productivity in the pharmaceutical industry experienced an average growth of 11.7% (increasing from 103.7 to 116 thousand euros per employee), outperforming the average growth of 9.8% observed in the total industry in the second period analysed (increasing from 52.3 to 57.4 thousand euros per employee). In 2021, productivity in the pharmaceutical industry increased by 0.2% compared to 2014-2018, almost doubling the industry average productivity (of 71.6 thousand euros per employee) (Figure 8)[15].

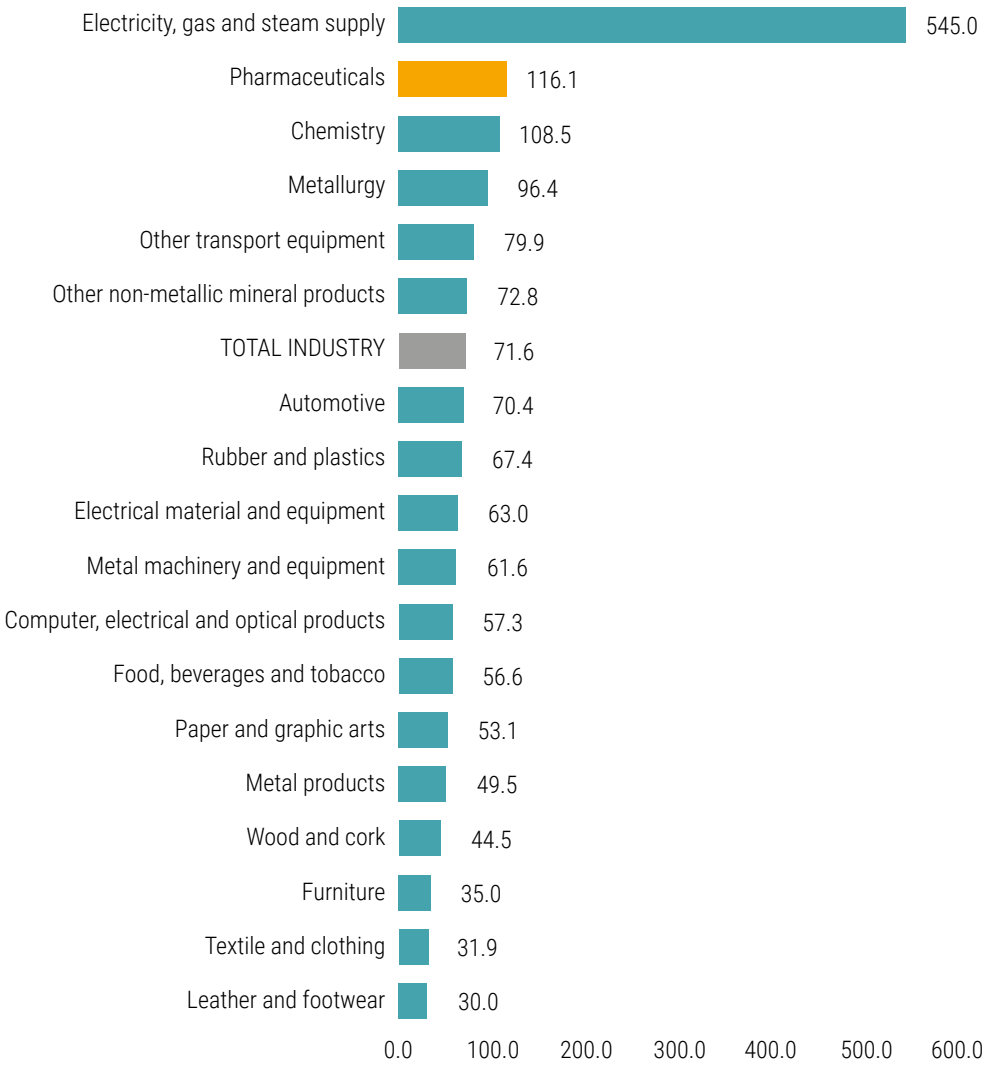
FIGURE 8. PRODUCTIVITY (VALUE ADDED PER EMPLOYEE) OF THE PHARMACEUTICAL INDUSTRY INCOMPARISON WITH THE AVERAGE FOR THE MANUFACTURING INDUSTRY. AVERAGE PER PERIOD, IN THOUSANDS OF EUROS. SPAIN, 2009-2021



Source: Compiled by the authors on the basis of Eurostat[15]

Moreover, in 2021, the pharmaceutical sector stood out as the second most productive of all manufacturing sectors, behind only the electricity, gas and steam supply sector (Figure 9). It is also worth noting the improvement in its relative position compared to 2018, as it then held third place in terms of productivity per employee (up from 109 to 116 thousand euros)[15].

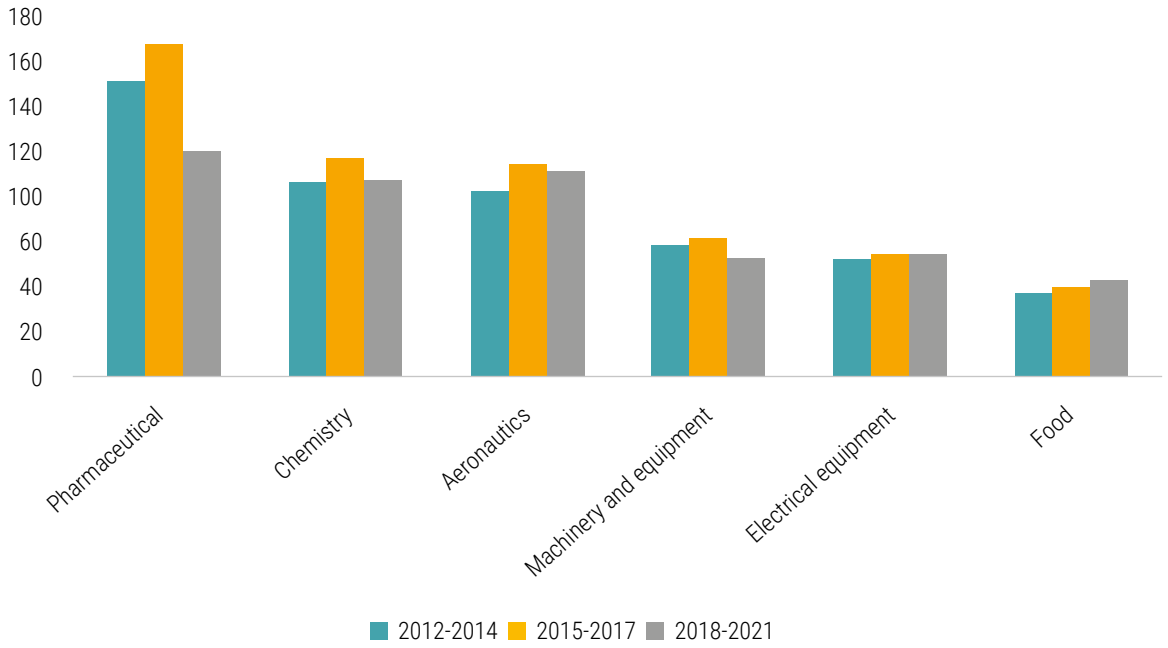
FIGURE 9. PRODUCTIVITY OF INDUSTRY SECTORS. VALUE ADDED PER EMPLOYEE, IN THOUSANDS OF EUROS, SPAIN, 2021



Sourface: Compiled by the authors on the basis of Eurostat[15]

At the European level, the productivity of the pharmaceutical industry is also significantly higher than that of other high-tech sectors. In the period 2018-2021, the average value added per employee was €114k, significantly higher than other sectors such as chemicals (15% higher), aeronautics (10% higher) and machinery (90% higher), among others, although the gap has narrowed recently, due to the productivity decline in 2020 (Figure 10)[15]. This lower productivity may be related to the halting of projects and trials during the pandemic.

FIGURA 10. EVOLUTION OF AVERAGE PRODUCTIVITY (VALUE ADDED PER EMPLOYEE) IN THE MAIN INDUSTRIAL SECTORS, IN THOUSANDS OF EUROS. EU, 2012-2021



Source: Compiled by the authors on the basis of Eurostat[15]

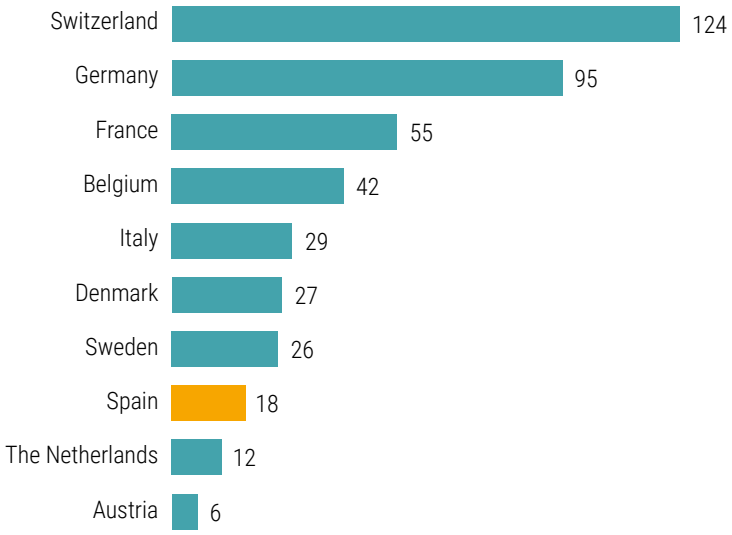
In 2017, the pharmaceutical industry generated an added value of USD 532 billion globally, which is equivalent to one percent of global Gross Domestic Product (GDP) or roughly the national GDP of a region like the Netherlands (Figure 11)[6].

FIGURE 11. COMPARATIVE MAGNITUDE OF THE VALUE ADDED OF THE PHARMACEUTICAL INDUSTRY WORLDWIDE

Source: Own elaboration

In terms of production, the Spanish pharmaceutical industry stands out at European level, occupying eighth position, with a volume of 17,756 million euros in 2022, which represents 3.9% of the sector's production in Europe (Figure 12)[16] and 5.3% of the sector's production in the EU-27.

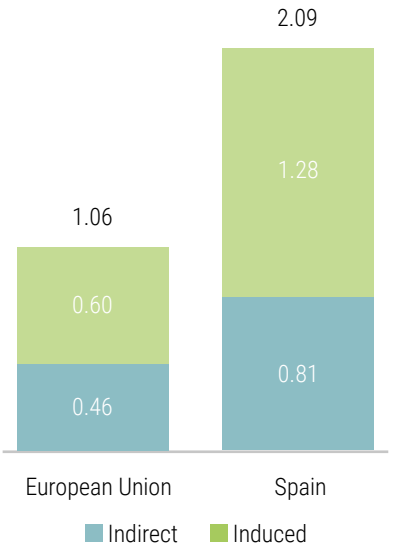
FIGURE 12. PHARMACEUTICAL INDUSTRY PRODUCTION IN THE TOP 10 EUROPEAN COUNTRIES (BILLION EUROS), 2022



Source: Compiled by the authors on the basis of Eurostat[16]

Finally, several studies have also assessed the indirect and induced contribution of the pharmaceutical sector in terms of value added and output. In the European Union, for each unit of value added produced directly, it is estimated that 0.46 additional units of value added are generated indirectly and 0.60 induced. These effects are significant, although they are lower than the tractor impacts on employment[7]. In Spain, similar to the situation with employment, the tractor effects on the sector's value added are more pronounced than the European average. For each unit of value added generated in our country, a further 2.09 units were produced in terms of indirect (0.81) and induced (1.28) effects (Figure 13)[9]. Other studies estimate similar figures for 2017, with an spillover effect for each euro of output in the pharmaceutical sector of around €0.8 in the economy as a whole, taking into account only the direct and indirect effect, and €1.1 if the induced effect is added[10]. In other words, if the pharmaceutical sector were to stop purchasing its intermediate inputs in Spain, production in the Spanish economy would fall by 0.76% (carryover capacity), a fall greater in absolute value than the sector's weight in the economy. On the other hand, if the rest of the sectors stopped acquiring inputs from the pharmaceutical sector, the fall in production in the Spanish economy would be 0.31% (carrying capacity)[10].

FIGURE 13. GENERATION OF INDIRECT AND INDUCED ADDED VALUE BY EACH UNIT OF VALUE ADDED DIRECTLY BY THE PHARMACEUTICAL SECTOR. EUROPEAN UNION AND SPAIN. MULTIPLIER, 2016



Source Own elaboration from EFPIA (2019)[9]

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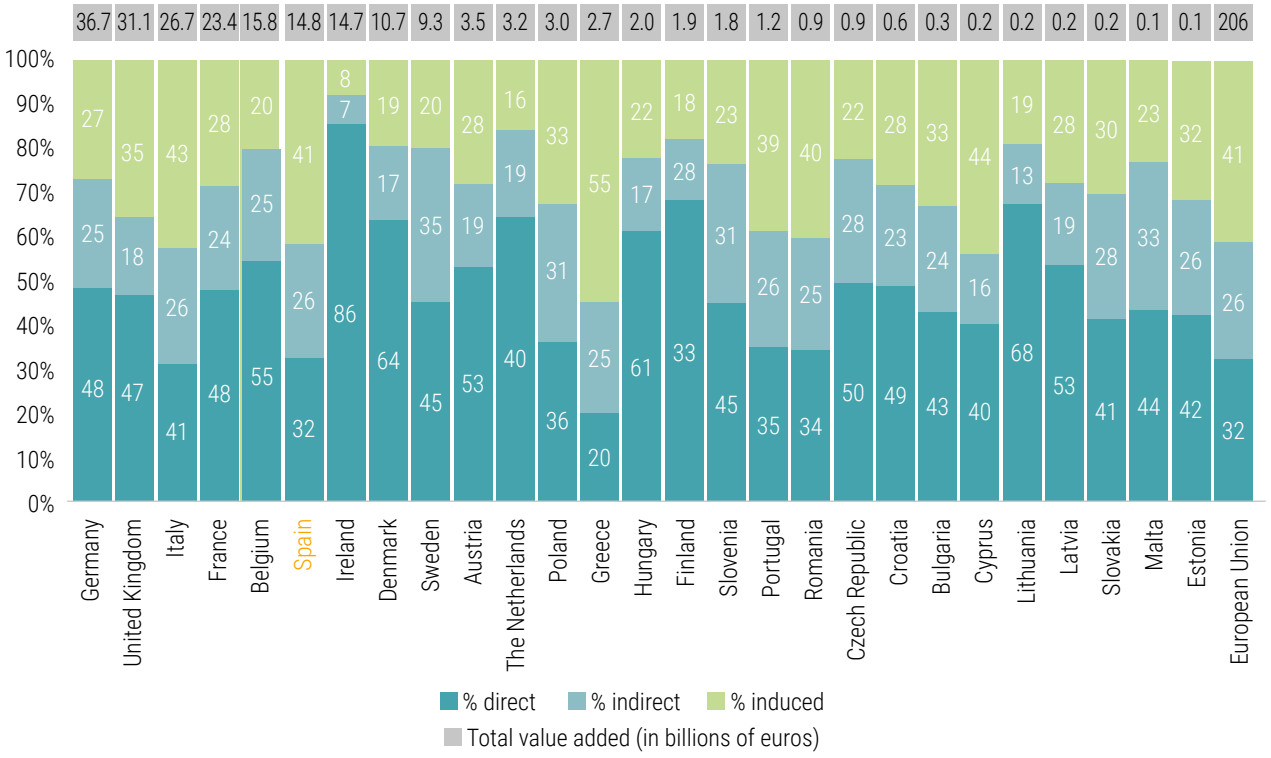
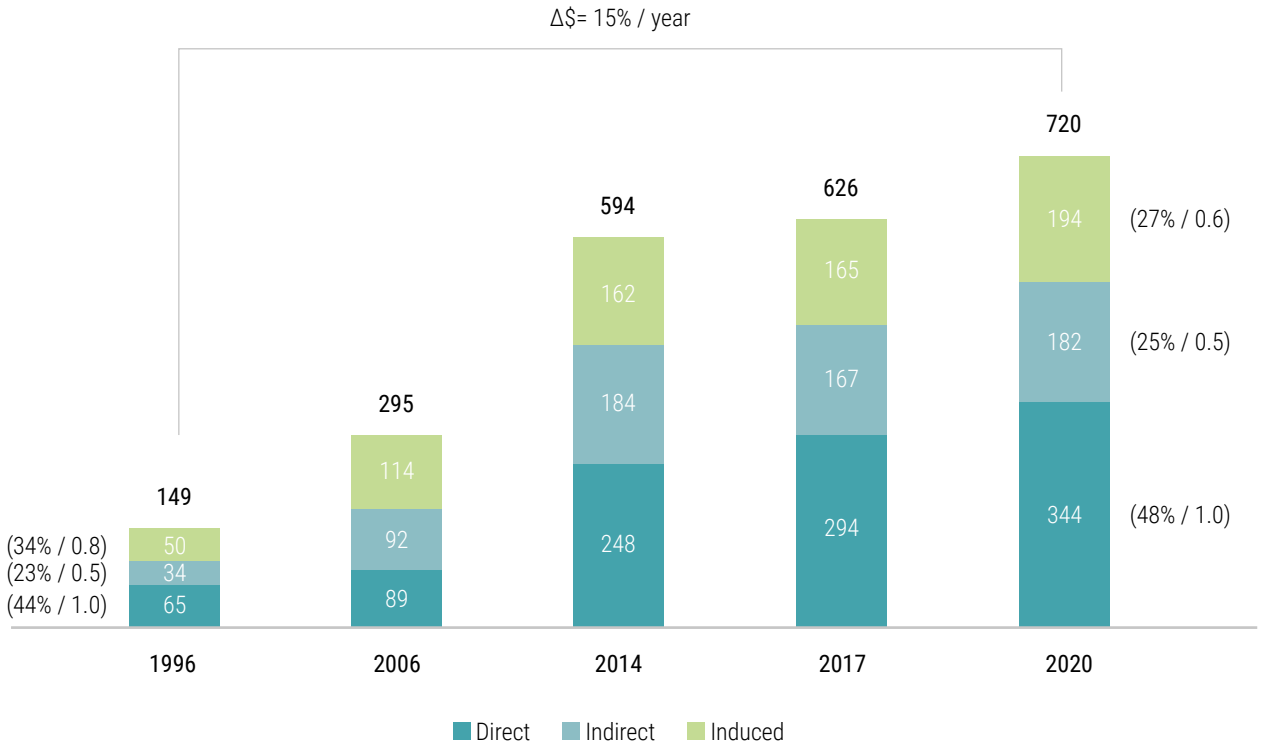
FIGURE 14. DISTRIBUTION OF DIRECT, INDIRECT AND INDUCED VALUE ADDED GENERATED BY THE PHARMACEUTICAL INDUSTRY IN THE EUROPEAN UNION, 2016



Source: Own elaboration based on EFPIA (2019)[7]

In the United States, the direct value added by the biopharmaceutical industry accounted for 1.6 per cent of its GDP in 2020. The total value added generated by the industry, beyond the biopharmaceutical industry itself, amounted to more than USD 720 billion or 3.4 per cent of total US GDP, with 25 per cent being indirect effects (with a multiplier of 0.5) and 27 per cent induced (multiplier of 0.6). Both the total multiplier effect and the percentage of value added generated indirectly and induced in 2020 are similar to those of 1996, although the induced effect in 2020 is slightly reduced compared to 1996. Value added shows an exponential increase, having increased considerably compared to 1996 and 2006 (Figure 15).

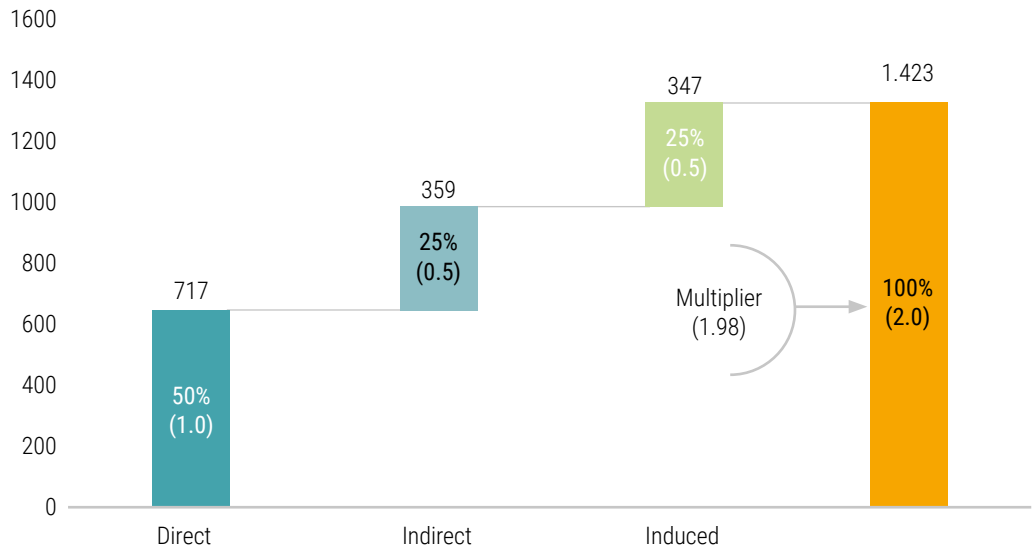
FIGURE 15. VALUE ADDED GENERATED DIRECTLY, INDIRECTLY AND INDUCED BY THE BIOPHARMACEUTICAL INDUSTRY. BILLIONS OF $ (MULTIPLIER /%). UNITED STATES, 1996-2020



Source: Own elaboration based on Archstone Consulting (2009)[12], PhRMA (2016)[17], PhRMA (2019)[13] and PhRMA (2022)[18]

Finally, in terms of output, the total contribution of the US biopharmaceutical industry in 2020 was $1,423 billion, compared to $1,149 billion in 2017[13]; i.e. there was a 24% increase between 2017 and 2020. In both years, half of the output was generated indirectly and induced (26% and 25% in 2020 and 26% and 25% in 2017, respectively). For every dollar produced directly, another dollar was generated indirectly and induced in both years (Figure 16)[18].

FIGURE 16. VALUE OF PRODUCTION GENERATED DIRECTLY, INDIRECTLY, AND INDUCED BY THE BIOPHARMACEUTICAL INDUSTRY IN THE UNITED STATES (BILLION EURO OF $, % / MULTIPLIER), 2020



Source: Own elaboration based on PhRMA (2022)[18]

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The pharmaceutical industry in Spain stands out for its high added value and productivity by employee. Between 2009 and 2021, it experienced steady growth, reaching a productivity of 116 thousand euros per employee in 2021, almost double the industry average.

In addition, it contributed significantly to the national economy, through the effects of the tractors on other economic sectors. It is estimated that for every euro produced in the pharmaceutical sector, another 0.8 euros are generated indirectly and 1.3 euros indirectly.

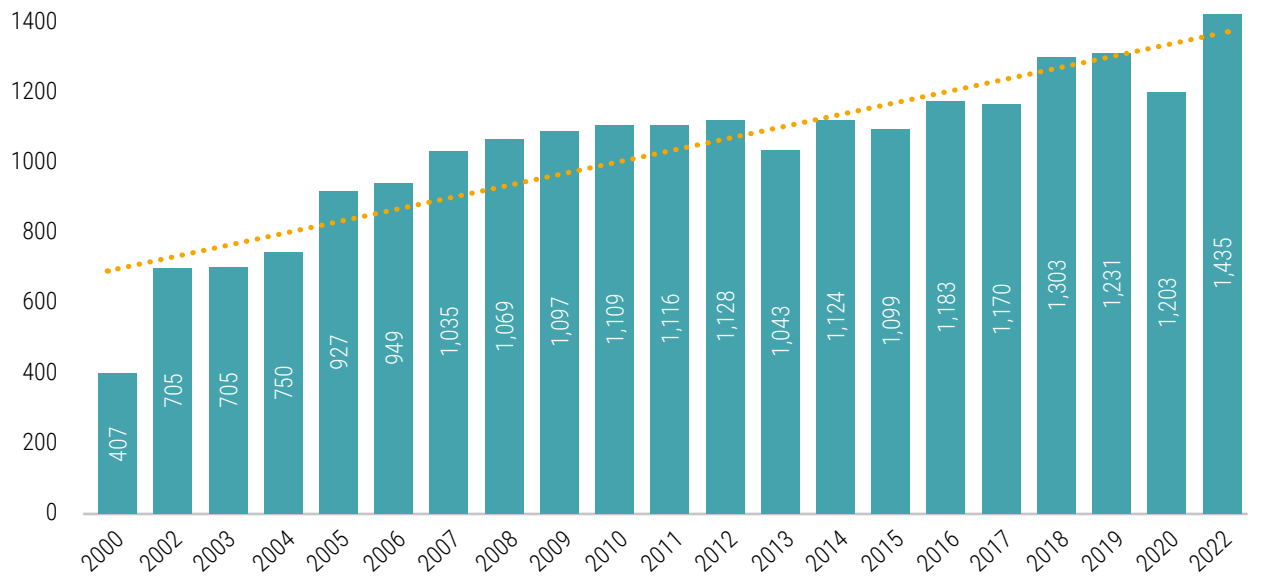
Eurostat (2024)[15] , Eurostat (2024)[16] , PhRMA (2019)[13] and PhRMA (2022)[18]

RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry also stands out as an R&D-intensive sector, as the introduction of new drugs requires considerable prior investment in research. In this context, the pharmaceutical sector is also the sector with the highest ratio of R&D investment to net sales.

The pharmaceutical industry is positioned as the industrial sector with the highest investment in R&D&I in Spain, allocating 1,435 million euros in 2022. The pharmaceutical sector's investment in this area increased by 23% compared to 2018, continuing the positive trend started since 2000. Over these 22 years, the pharmaceutical sector's investment in R&D&I has experienced an average annual growth of 6%, a significantly higher growth rate than that of the industrial sector as a whole, which only increased by 1% on average per year (Figure 17)[19].

FIGURE 17. EVOLUTION OF R&D+I EXPENDITURE IN THE PHARMACEUTICAL SECTOR, SPAIN 2000-2022

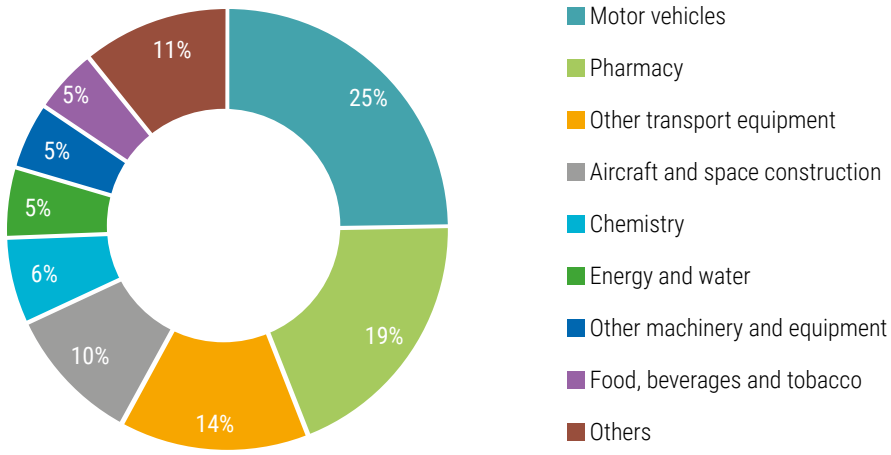


Note: The INE did not publish the survey on innovation in enterprises in 2021.

Source: Own elaboration based on the Survey on Innovation in Companies, INE (2024)[19]

Considering R&D expenditure, the pharmaceutical sector allocated 1,206 million in 2022, representing 19.3% of the industrial sector's R&D investment, ranking second only to the automotive sector (Figure 18)[19].

FIGURE 18. PERCENTAGE OF INDUSTRIAL SECTORS' R&D EXPENDITURE AS A PERCENTAGE OF TOTAL INDUSTRY. SPAIN, 2022

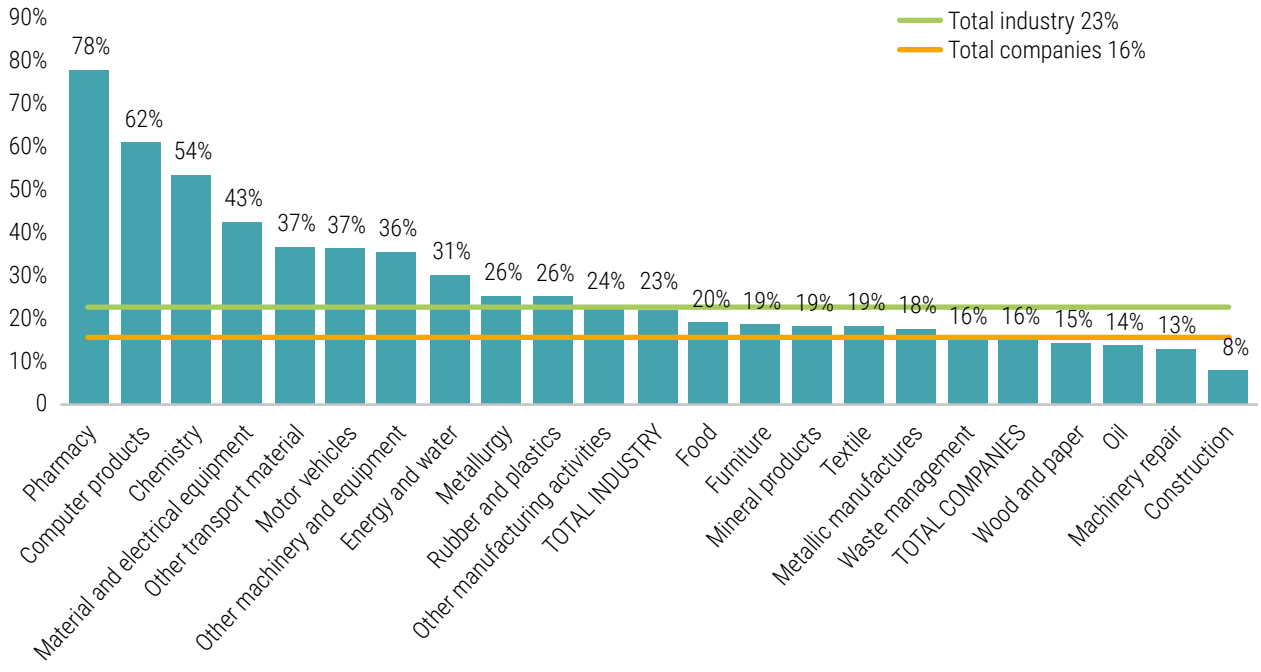


Note: the group "Others" is made up of those sectors with less than 5% weight in the industry

Source: Prepared by the authors based on the Survey on R&D Activities, INE (2024)[19]

In terms of the number of companies that carry out innovation activities, the importance of research in the pharmaceutical industry is particularly noteworthy, with 78% of companies investing in R&D&I, well above the 23% in the industrial sector and 16% in Spanish companies as a whole (Figure 19)[19].

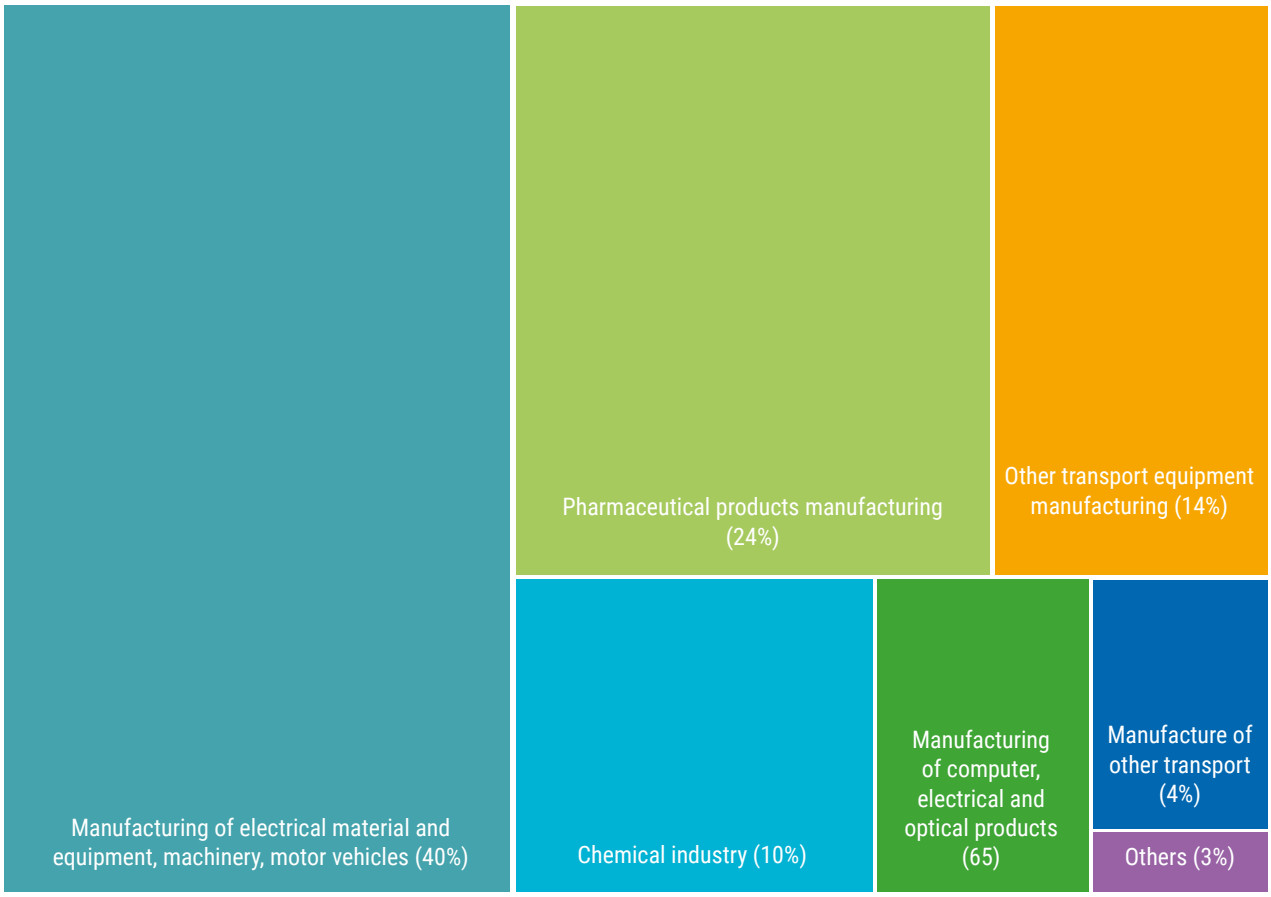
FIGURE 19. PERCENTAGE OF FIRMS ENGAGED IN INNOVATION ACTIVITIES, BY SECTOR OF ACTIVITY (%), SPAIN, 2022



Source: Own elaboration based on the Survey on Innovation in Companies, INE (2024)[19]

Moreover, the pharmaceutical industry is positioned as the industry with the second highest expenditure on internal R&D within the high-tech sectors, only behind the electrical equipment and machinery manufacturing sector, with 24% of the total expenditure of this group of companies. This implies that, in 2021, the pharmaceutical industry invested around 782 million euros, exceeding the average for high-tech sectors, which stood at 735 million euros (Figure 20)[20].

FIGURE 20. DOMESTIC SPENDING ON R&D IN HIGH-TECH SECTORS, BY INDUSTRY, SPAIN, 2021

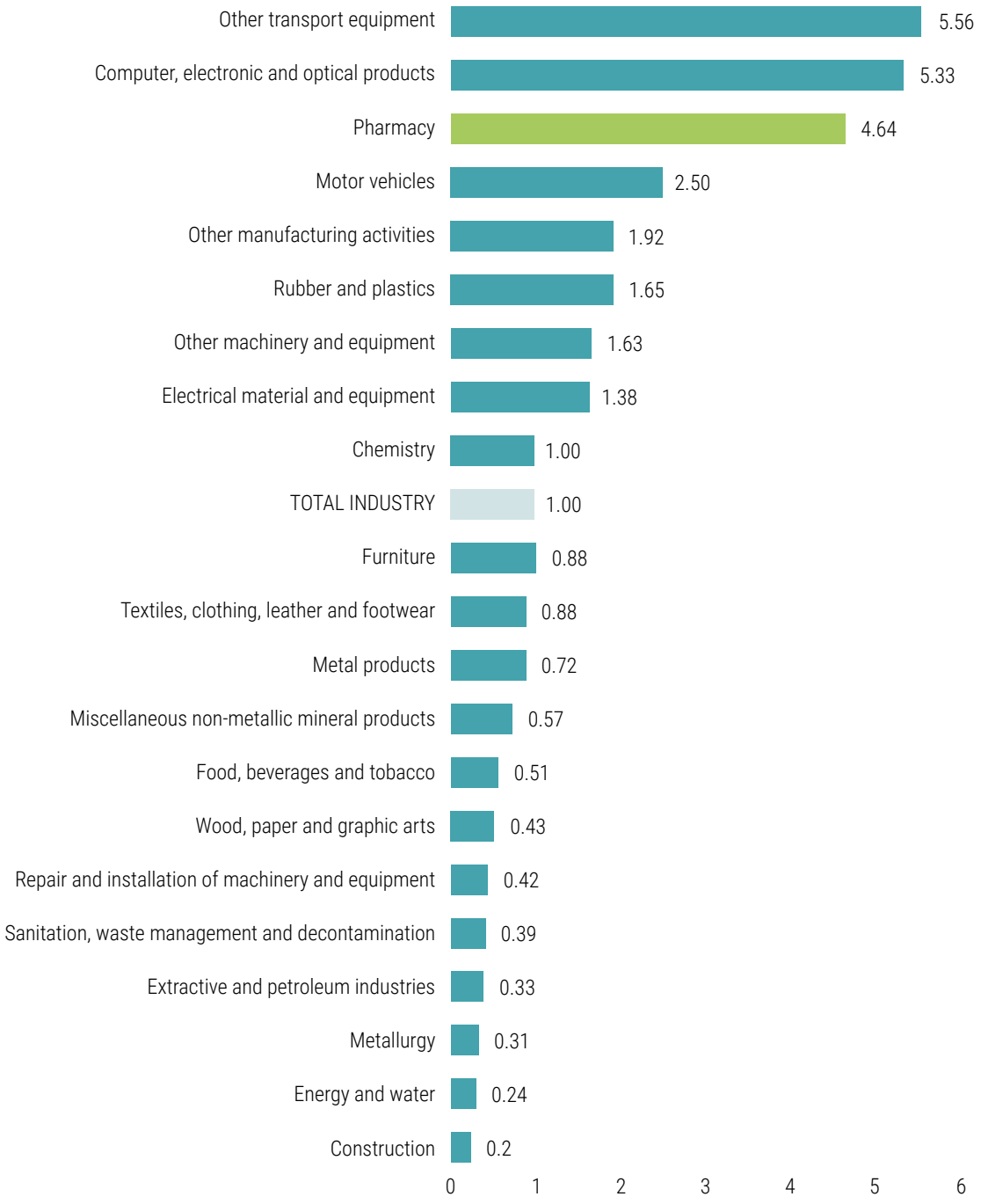


Note: The group "Others" is made up of those sectors with less than 2% of industry weight.

Source: Own elaboration based on High Technology Indicators, INE (2024)[20]

Likewise, the pharmaceutical industry is a sector with a high innovative intensity, ranking third among industrial sectors with the highest proportion of its turnover allocated to innovative activities (4.64%), only behind the sector dedicated to other transport materials (5.56%) and computer, electronic and optical products (5.33%), and far exceeding the average for the industrial sector as a whole (1.00%) (Figure 21)[19].

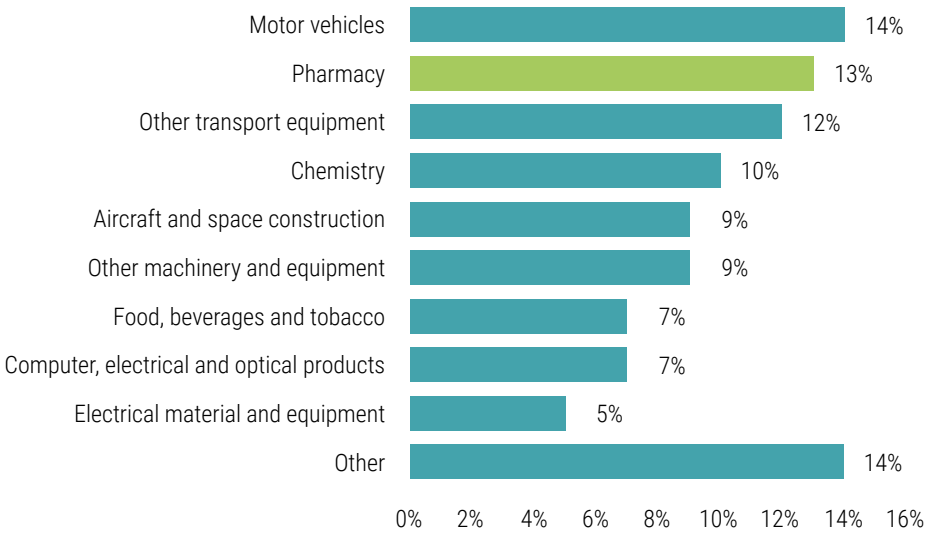
FIGURE 21. INNOVATION INTENSITY (EXPENDITURE ON INNOVATIVE ACTIVITIES/TURNOVER*100) OF COMPANIES, BY INDUSTRIAL SECTOR, SPAIN 2022



Source: Own elaboration based on the Survey on Innovation in Companies, INE (2022)[19]

In terms of full-time R&D staff, the pharmaceutical industry directly employs 6,037 full-time equivalents (5,453 in 2021), ranking second among industrial sectors (13%), close behind the automotive sector (14%). In terms of the number of people (full-time and part-time), the pharmaceutical sector also ranks second among industrial activities (Figure 22)[19].

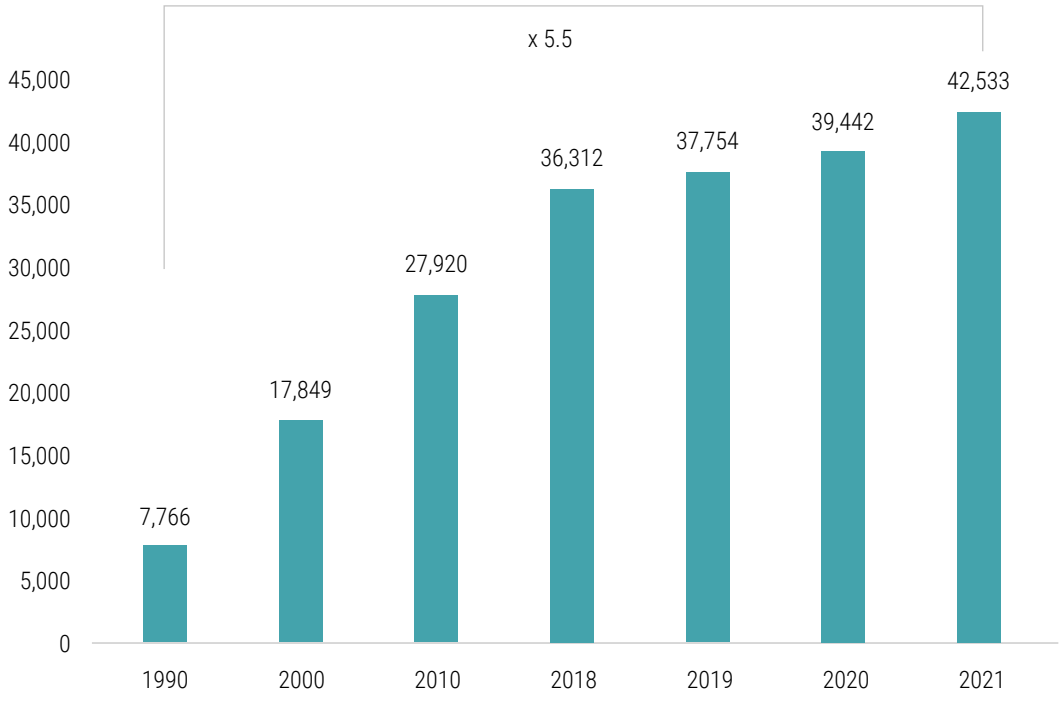
FULL-TIME R&D PERSONNEL AS A PERCENTAGE OF TOTAL INDUSTRY BY ACTIVITY SECTOR



Source: Prepared by the authors based on the Survey on R&D Activities, INE (2022)[19]

At the European level, the pharmaceutical sector also stands out as one of the leading sectors in R&D investment. In 2022, the pharmaceutical industry spent more than 44.5 billion euros on R&D activities, an increase of 1.1% over the previous year. In terms of average annual growth, R&D investment increased by an average of 5.5% per year between 1990 and 2021, more than multiplying total investment by 5 over the period (Figure 23)[4].

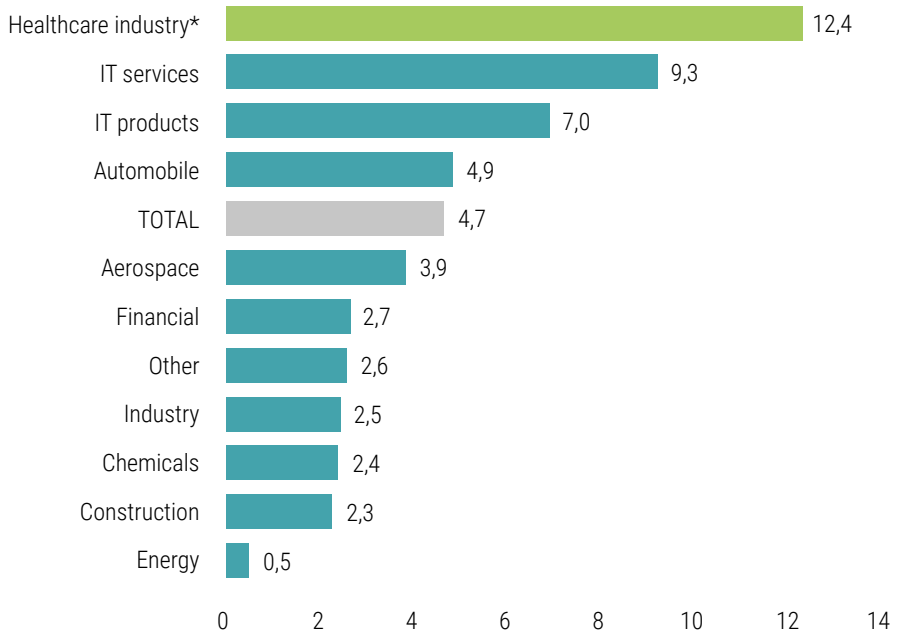
FIGURE 23. EVOLUTION OF PHARMACEUTICAL INDUSTRY R&D EXPENDITURE IN EUROPE (MILLIONS OF EUROS PER YEAR), 1990-2021



Source: Own elaboration based on EFPIA (2024)[4]

Meanwhile, the healthcare (biopharmaceutical) industries globally invested around €235.3 billion in R&D in 2021, representing 21.5% of total business R&D expenditure. This positions the sector as the most R&D intensive, investing 12% of its sales in R&D, followed by computer services (9%) and computer products (7%), and considerably distanced from the rest (Figure 24). In addition, this sector exhibits a significant drag effect on other interrelated economic sectors[4].

FIGURE 24. R&D INTENSITY BY SECTOR (PERCENTAGE OF R&D EXPENDITURE TO TOTAL SALES), WORLD, 2021



* The healthcare industry includes biotechnology, healthcare providers, medical equipment, medical supplies and pharmaceuticals

Source: Own elaboration based on EFPIA (2024)[4]

The pharmaceutical industry stands out for its intensive investment in research and development (R&D), being the sector with the highest ratio between R&D investment and net sales. In 2022, R&D investment in Spain reached €1,435 million, 23% more than in 2018. The sector represents 19% of total R&D investment in the industrial sector, ranking second only to the automotive sector.

INE (2024)[19], Nindl (2024)[21]

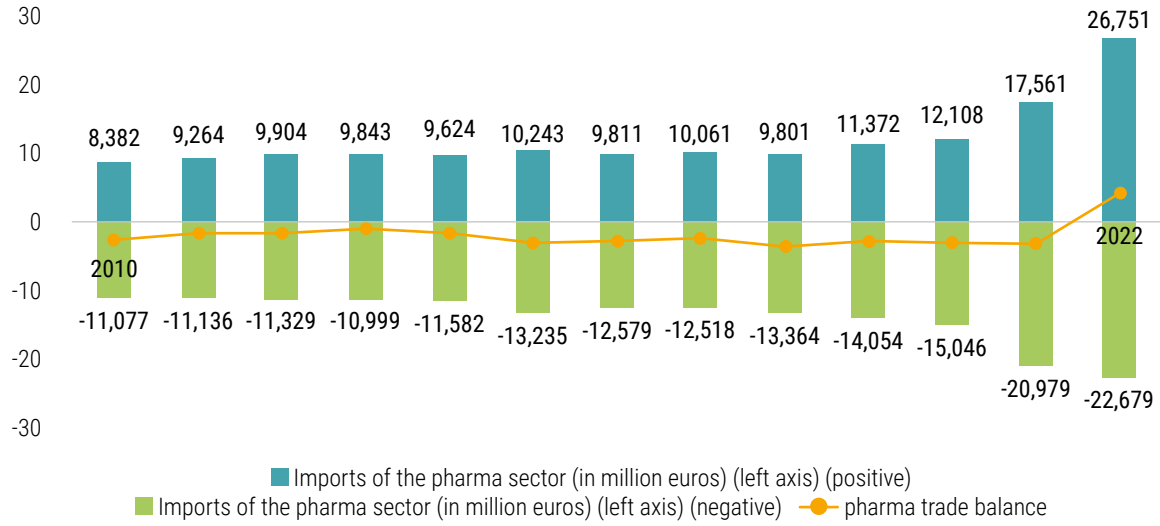
OTHER ECONOMIC INDICATORS OF THE PHARMACEUTICAL INDUSTRY

In addition to its contribution to job creation, wealth generation and R&D development, the pharmaceutical industry fosters external competitiveness through exports and imports. It also contributes to the maintenance of the welfare state through the payment of taxes and the generation of taxable activities.

FOREIGN TRADE

Since 2010, exports of the pharmaceutical industry in the country have experienced an upward trend, strengthening the Spanish pharmaceutical industrial sector, and there has been exponential growth since the pandemic caused by the coronavirus disease 2019 (COVID-19), reaching 26,750 million euros in 2022[22]. The relative share of exports in total foreign trade has risen from 4% in 2010 to 7% in 2022. On the other side of the external sector, imports of the pharmaceutical sector have increased in the last year available, reaching a figure of 22,679 million euros in 2022. The share of imports in total foreign trade has ranged from 4% to 6% between 2010 and 2022 (Figure 25)[23].

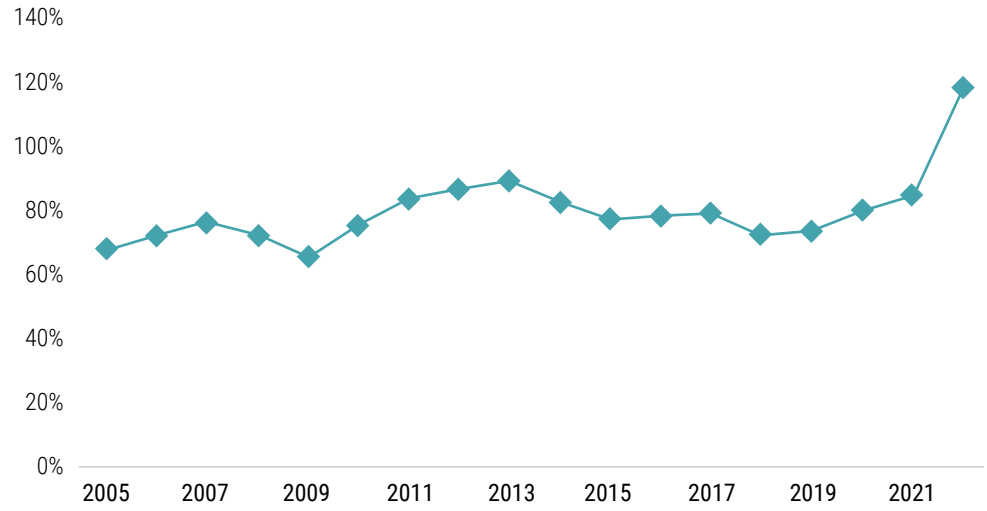
FIGURE 25. EVOLUTION OF THE VALUE OF IMPORTS AND EXPORTS OF THE PHARMACEUTICAL INDUSTRY (M€) AND WEIGHT IN THE TOTAL MANUFACTURING SECTOR (%), SPAIN 2010-2022



Source: Own elaboration based on data from the Secretariat of State for Trade[23]

Despite the growth in recent years of exports by Spanish pharmaceutical companies, Spain's industry has traditionally been an importer of pharmaceutical products, with a foreign trade coverage rate of between 60% and 85%, with the exception of 2022, when there were 18% more exports than imports, rising from a rate of 84% in 2021 to 118% in 2022. Medicines became Spain's third most exported product, behind only automobiles and fuels, probably marked by the exceptional situation of the COVID-19 pandemic and the vaccines developed to stop it (Figure 26)[23].

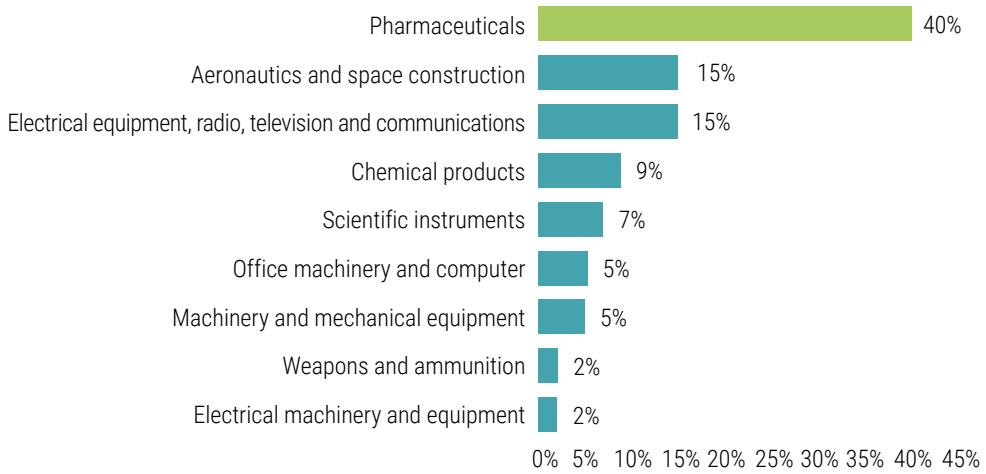
FIGURE 26. EVOLUTION OF THE FOREIGN TRADE COVERAGE RATE OF THE PHARMACEUTICAL INDUSTRY, SPAIN 2005-2022



Source: Own elaboration based on data from the Secretary of State for Trade[23]

Within the scope of high-tech exporting companies, in 2021, the pharmaceutical industry ranked first, accounting for 40% of exports of high-tech products, having represented an increase since 2017 (of 23%) (Figure 27)[24] . As mentioned in the previous paragraphs, Spain has experienced an upward trend in its exports, which has led to a strengthening of the Spanish pharmaceutical industrial sector.

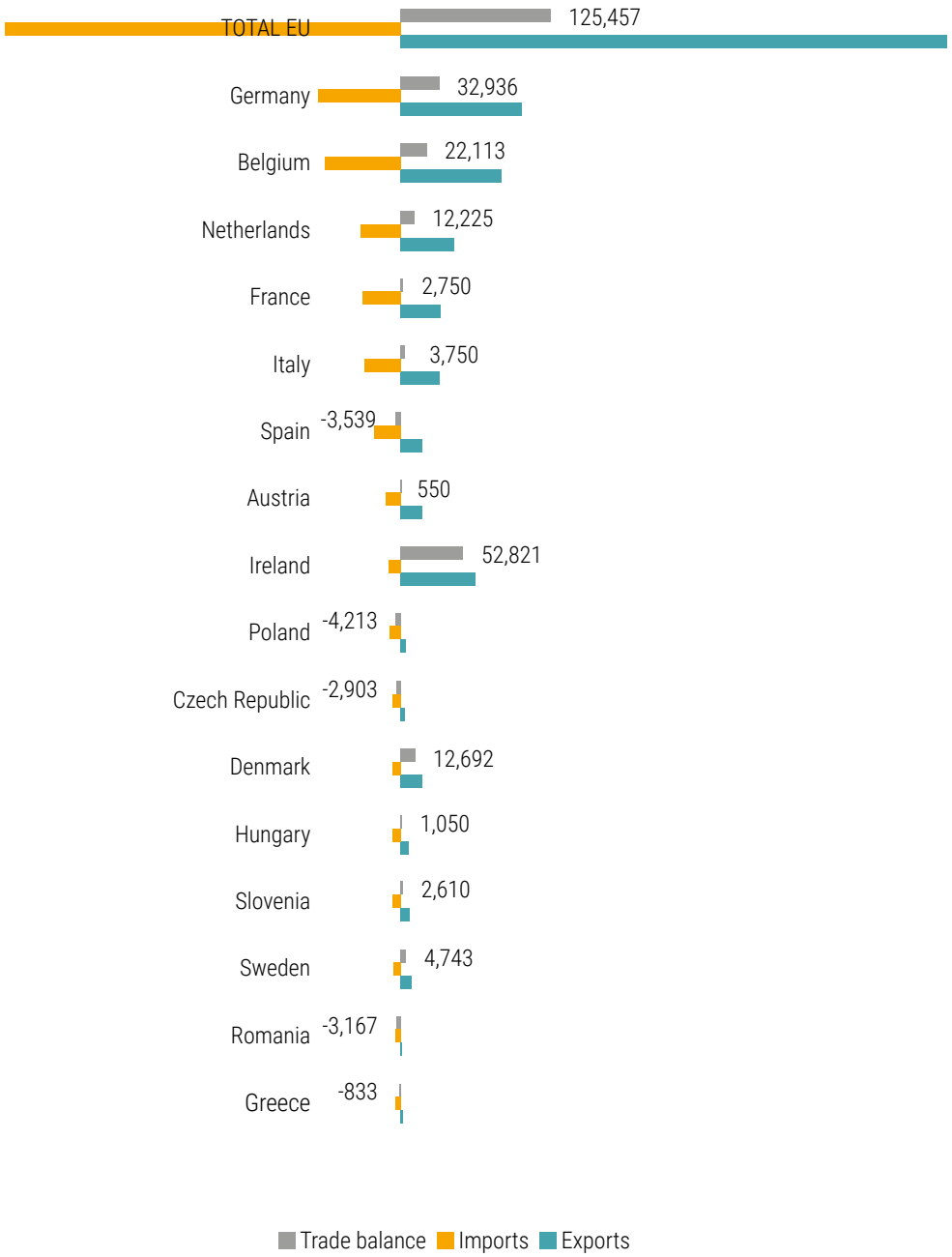
FIGURE 27. DISTRIBUTION OF THE VALUE OF EXPORTS OF HIGH-TECH PRODUCTS, BY VALUE OF PRODUCT GROUPS, SPAIN 2021



Source Own elaboration based on INE, High Technology Indicators (2022)[24]

In the European context, the pharmaceutical industry's trade balance amounted to 125,457 million euros in 2021, indicating that Europe is predominantly an exporting continent. When analysing this information by country, Spain was, together with others such as Poland and the Czech Republic, among the nations with a negative trade balance, while Germany, Belgium and the Netherlands led the ranking as exporters with notable surpluses (Figure 28)[4] .

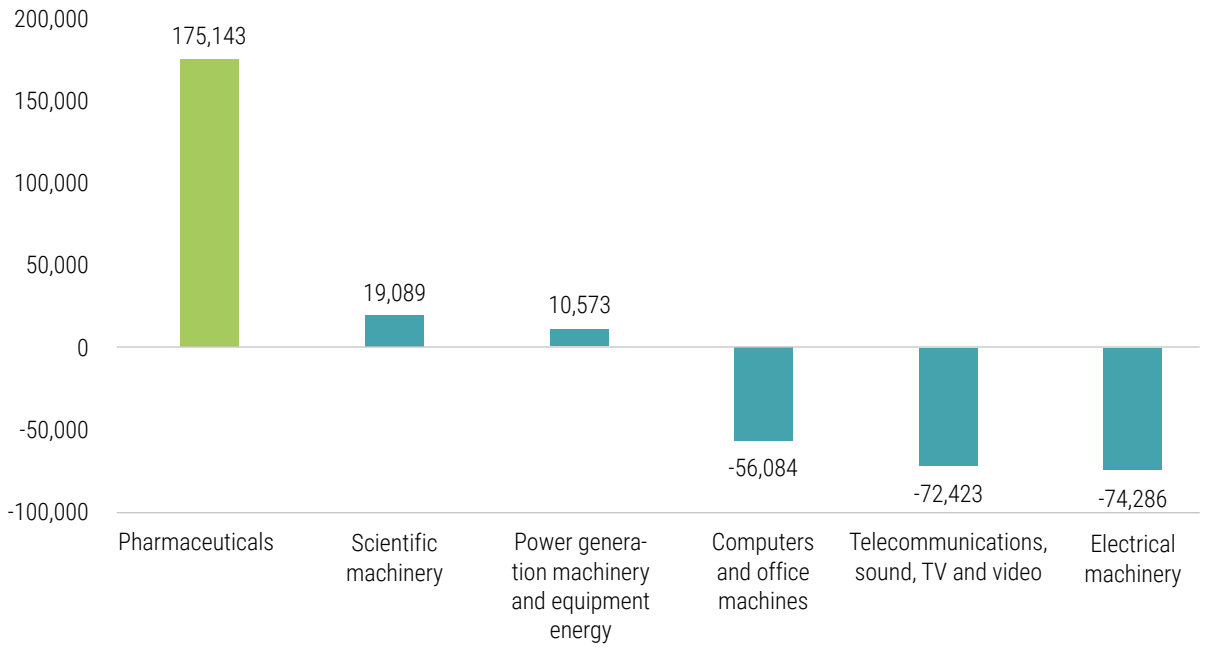
FIGURE 28. EXPORTS, IMPORTS AND TRADE BALANCE OF THE PHARMACEUTICAL INDUSTRY IN EUROPE, BY COUNTRY, 2021 (MILLION €)



Source: Own elaboration based on EFPIA (2024)[4]

In an analysis by branch of activity at the European level, the pharmaceutical sector stands out as the main contributor to the trade balance of the European area, registering a positive balance of 175,143 million euros in 2022. This figure significantly exceeds other sectors, such as scientific machinery and power generation machinery (Figure 29)[4]. The EU's largest trading partners are the United States (recipient of 32.5% of EU exports and exporter of 35.3% of EU imports) and Switzerland (EU exports 12.9% and imports 33.9%).

FIGURE 29. TRADE BALANCE OF HIGH-TECH SECTORS, EU 2022 (M€)



Source: EFPIA (2024)[4]

PUBLIC FINANCES

In addition to its prominent role in external competitiveness, the pharmaceutical sector also makes a significant contribution to public finances through tax payments. According to data from the Iberian Balance Sheet Analysis System (SABI), pharmaceutical companies based in Spain contributed a total of €611 million in 2022 in corporate income tax, representing 21.5% of the sector's results[25]. Likewise, according to the 2020 National Accounts, the pharmaceutical sector contributed 543.9 million euros through net taxes on production, as well as social contributions (50.6 and 493.3 respectively)[5]. On the other hand, the activity generated by the pharmaceutical sector directly, indirectly and induced brings in tax revenues via taxes (VAT, personal income tax and corporate income tax) and social security contributions of 3,978 million euros[10].

On the other hand, in the US, the biopharmaceutical industry generated a total of $359.36 billion in wages, two-thirds of which were generated indirectly and induced. In addition, it generated a total of $76.38 billion, of which almost 90% went to federal taxes (Table 1)[18].

TABLE 1. WAGES AND TAXES GENERATED BY THE BIOPHARMACEUTICAL INDUSTRY (BILLION $), USA 2020

	WAGES AND LABOUR	FEDERAL TAXES	REGIONAL TAXES
Direct effect	131.27	24.38	3.89
Indirect effect	117.73	21.52	3.26
Induced effect	110.36	20.25	3.07
TOTAL Effect	**359.36**	**66.16**	**10.22**

Source: PhRMA (2022)[18]

The pharmaceutical industry also has a significant influence on the Spanish economy in terms of external competitiveness and tax collection. Although the sector in Spain has historically been a net importer, in 2022 the value of exports exceeded that of imports by 18%.

In addition, the pharmaceutical industry contributes considerably to public finances through taxes, as pharmaceutical companies in Spain contribute more than 1 billion euros in terms of production taxes and social contributions.

State Secretariat for Trade[23], SABI[25], INE[5]

In short, the pharmaceutical industry is a fundamental economic pillar. It stands out not only for its capacity to generate quality employment and high productivity, but also for its investment in R&D, its contribution to external competitiveness and its spill-over effect on the rest of the economy.

Table 2 summarises the structural data on the pharmaceutical industry in Spain and its evolution since 2000, highlighting its relative importance within the total industrial landscape. Although pharmaceutical companies represent only 0.2% of industrial companies in the country, they contribute 2.2% of employment, 2.8% of turnover, 3.5% of value added, 5.6% of exports and 18.9% of R&D expenditure in the industrial sectors.

TABLE 2. SUMMARY OF THE MAIN STRUCTURAL DATA OF THE PHARMACEUTICAL INDUSTRY, SPAIN 2000-2021

	2000	2010	2015	2019	2020	2021	AVERAGE ANNUAL INCREASE 2015-2021	% OF TOTAL INDUSTRY 2021
Number of companies	340	300	343	337	360	369	1.2%	0.2%
Turnover (M€)	9,048	14,895	13,672	15,629	16,504	20,753	7.2%	2.8%
Production (M€)	7,952	12,743	13,043	15,034	16,024	20,250	7.6%	3.1%
Value added (VAT) (M€)	3,490	4,091	4,595	5,325	6,110	5,959	4.4%	3.5%
R&D expenditure (M€)	297	966	917	1,029	965	1,007	1.6%	18.9%
Nº. of employed	36,995	39,932	37,121	48,791	50,984	51,310	5.5%	2.2%
Nº of employees in R&D	2,917	4,665	4,859	5,217	5,266	5,453	1.9%	12.5%
VA per employee (€)	94,300	128,100	117,461	108,960	119,848	116,138	-0.2%	-
Exports (M€)	2,438	9,106	10,645	11,378	12,108	17,561	8.7%	5.6%
Imports (M€)	4,372	12,097	13,690	14,054	15,046	20,979	7.4%	6.1%
Trade balance (M€)	-1,934	-2,991	-3,044	-2,682	-2,938	-3,418	2.0%	-

Source: INE, Eurostat, State Secretariat for Trade[19,23,26,27]

2

SAVINGS IN DIRECT AND INDIRECT COSTS OF MEDICINES

In this chapter, we turn our attention to another aspect of value associated with medicines, namely the potential economic savings they bring. We examine several examples where the introduction of new drug therapies has resulted in the release of resources for other purposes, demonstrating how the additional expenditure associated with pharmaceutical innovations could result in net or partial savings in total costs by reducing both direct and indirect outlays.

To provide context for this chapter on costs, it is important to clarify the nature of direct and indirect costs. Direct costs cover both health and non-health aspects. Direct healthcare costs refer to outlays for medication, medical consultations, visits to emergency services, diagnostic tests, hospitalisations, home care and specialised transport, among others. Direct non-healthcare costs include, on the other hand, expenses related to personal assistance dedicated to individuals with limitations in their autonomy, either through paid professional services or through informal support provided by the patient's affective environment. Indirect costs comprise the loss of labour productivity suffered by society as a result of morbidity and/or premature mortality associated with the disease.

The first section of this chapter presents examples of direct health and non-healthcare cost savings from the use of medicines. Various treatments have the potential to generate partial or net savings in direct healthcare costs by preventing relapses, mitigating symptoms and adverse events, as well as reducing medication side effects, leading to a reduction in medical consultations, emergency room visits and hospitalisations, among other things. Examples from the scientific literature will be presented, both at a general level and in specific therapeutic areas. A second section will explore how pharmaceutical innovations can contribute to reducing the degree of disability in the patients for whom they are intended, thereby reducing the need for personal care and also generating savings in direct non-health care costs.

In addition, it is common for newly introduced medicines to improve adherence to treatment, which not only leads to better health outcomes, but also to a decrease in the frequency of health service use by non-adherent patients, which in turn reduces the associated health care costs. A specific boxed section is reserved to address this issue, where concrete examples are presented to illustrate how adherence to treatment can contribute to contain net health care costs.

The third section of this chapter is devoted to examining how new drugs can mitigate work losses by reducing absenteeism, which refers to absence from work due to illness, and presenteeism, which refers to being at work despite being ill, often resulting in reduced productivity. By addressing these issues, new drugs can increase work productivity. Finally, a special section highlights the specific case of vaccines as a paradigmatic example of pharmaceutical innovation that, through prevention, has helped to boost cost savings and labour productivity gains.

Finally, it is important to note that health and social cost savings can also be achieved through innovations in other health technologies, such as medical and surgical procedures, medical devices, medical imaging systems, and organisational and management systems, among others, used in the treatment, prevention, diagnosis and monitoring of diseases[28]. In this analysis, however, we will concentrate exclusively on the effects generated by medicines.

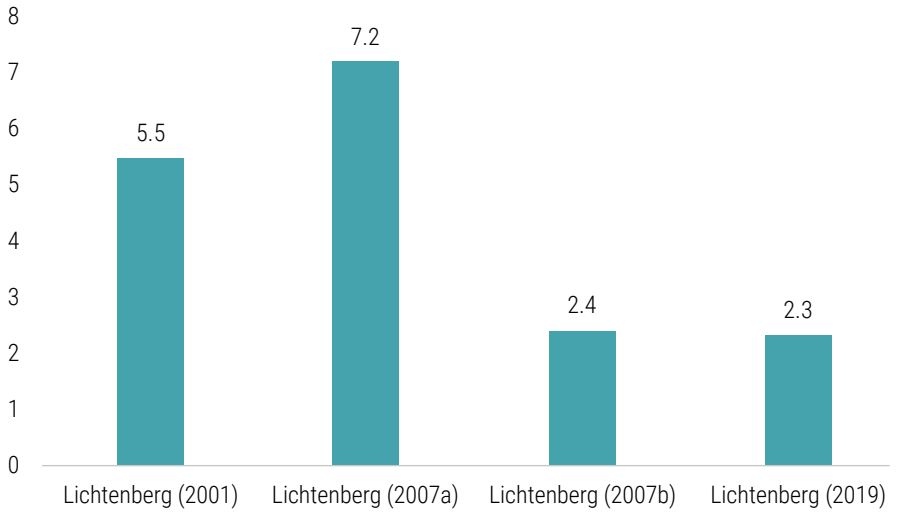
SAVINGS IN DIRECT HEALTHCARE COSTS

OFFSETTING EFFECT OF PHARMACEUTICALS ON DIRECT HEALTHCARE EXPENDITURE

Although new medicines generally tend to be more expensive than those they replace, their efficacy is often superior. This principle applies to both conventional and biotechnological medicines[29]. In addition, they can replace more costly surgical procedures and, through the improved health status they bring to patients, can prevent hospitalisations and reduce the need for other medical resources, leading to potential net cost savings for the health care system. Thus, several studies have been carried out to analyse the potential offsetting effect (offset effect) of new medicines, showing evidence in both directions[30]. The compensation effect is based on the premise that prescribed medicines can replace (fully or partially, depending on the case) the need for medical services such as consultations and hospitalisations[31]. This concept implies that the cost savings (both direct and indirect) that may arise from pharmaceutical innovations may outweigh the additional expense of purchasing them, resulting in net savings for the health system and society.

Frank R. Lichtenberg, professor at Columbia University, is one of the most prolific authors in the analysis of the costs and savings associated with new drugs. Using a variety of methodological approaches and a wide range of data, some of his studies focus on estimating the impact on the healthcare system of the absence of these new drugs on the market. In research prior to 2020, this author has confirmed the presence of the offsetting effect of new medicines in developed countries, observing net savings ratios in direct healthcare costs ranging from 2.3 to 7.2 times the additional expenditure associated with these pharmaceutical innovations[32,33,34,35] (Figura 30).

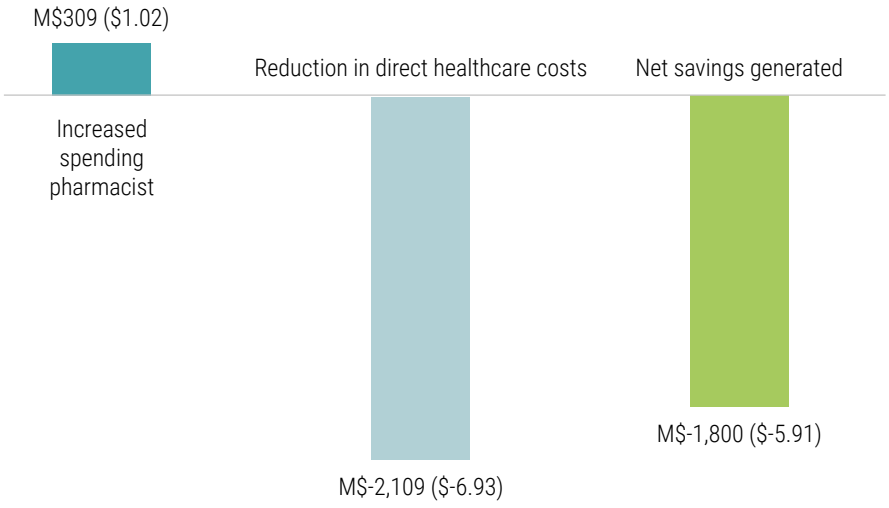
FIGURE 30. RATIO OF NET SAVINGS TO SPENDING ON PHARMACEUTICAL INNOVATION (IN TIMES)



Sources: Lichtenberg (2001)[32], Lichtenberg (2007a)[33], Lichtenberg (2007b)[34], Lichtenberg (2019)[35]

Santerre (2011) also analysed the offsetting effect of pharmaceutical innovation in the United States, and his findings are consistent with those of Lichtenberg. In 2007, in the US, the introduction of a new drug increased drug spending by $1.02 per person, amounting to a total of $309 million nationally. However, there was a net savings in medical services of $5.91 per person, generating an overall savings in medical costs of approximately $1.8 billion (Figure 31)[31].

FIGURE 31. OFFSETTING EFFECT OF THE INTRODUCTION OF EACH INNOVATIVE DRUG IN THE UNITED STATES, 2007 (NATIONALLY, IN MILLION DOLLARS / DOLLARS PER CAPITA)

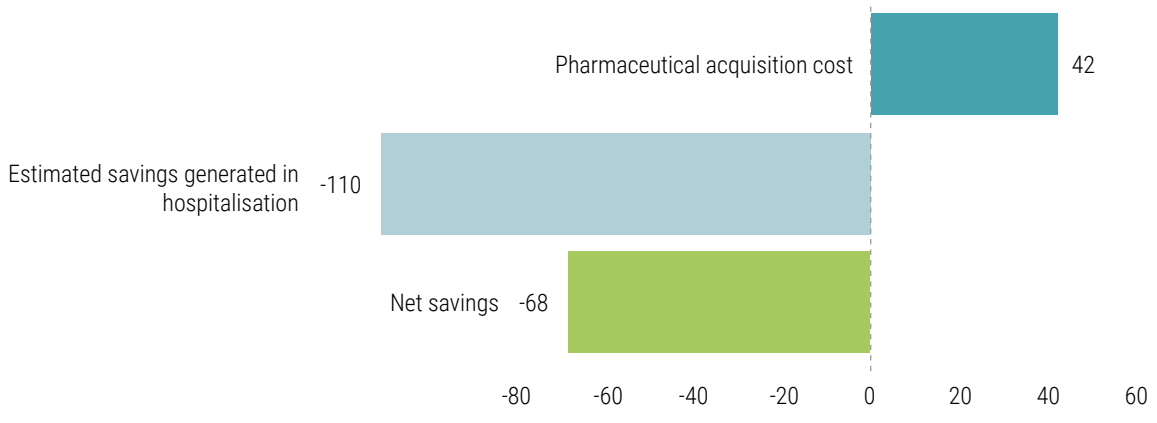


Fuente: Santerre (2011)[31]

In Spain, a similar study conducted by Farmaindustria estimated that the growth in hospital pharmaceutical spending observed between 1999 and 2005 led to a more pronounced decline in other areas of hospital spending, resulting in net hospital cost savings. Specifically, it is estimated that for every 10% increase in average hospital drug spending per outpatient, spending in this specific area rose by 2.5 euros per person, while other hospital spending items decreased by 3.6 euros, thus generating a net saving of 1.1 euros per patient in overall hospital spending[36].

In more recent studies, we also find evidence of a possible offsetting effect of drugs. One such example is found in Lichtenberg (2023), which indicates that innovative medicines approved in the period 1984-1997 in the United States (investment of $42 million) were responsible for a reduction of $110 billion in hospitalisation costs in the country in 2014, resulting in a net saving in this cost line alone of approximately $68 billion (Figure 32)[37].

FIGURE 32. OFFSETTING EFFECT OF THE INTRODUCTION OF INNOVATIVE DRUGS APPROVED BETWEEN 1984 AND 1997 IN THE UNITED STATES, MILLIONS OF DOLLARS, 2014



Source: Lichtenberg (2023)[37]

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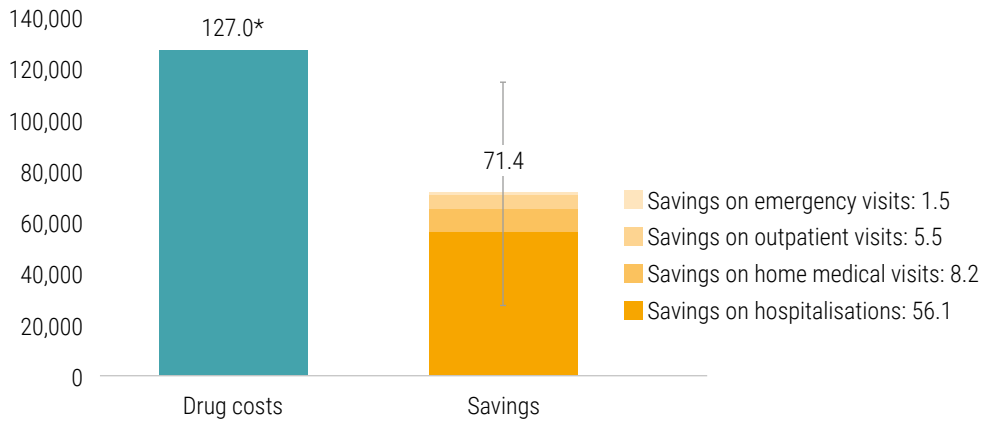
Other studies have focused on analysing the compensation effect in certain subgroups of the US population, such as those benefiting from the Medicare or Medicaid programmes, as well as residents of assisted living communities ("Community Residences"[i]).

With respect to the first subgroup, the Medicare/Medicaid-covered population, Shang (2007)[38] observed that for those in the worst health on Medicare and with drug coverage, each dollar spent on pharmaceuticals translated into reductions of $2.06 in hospitalisations and $0.44 in doctor visits. Civan (2010)[39] concluded that a one-year decrease in the average age of a prescription drug correlates with an $8.2 increase in per capita pharmaceutical spending, and a $45.4 reduction in out-of-pocket health expenditures, of which 40% is attributed to decreases in hospital spending. In addition, Lakdawalla (2017)[40] estimated that, for each additional prescription of medicines under the Medicare programme during the period 1996-2013, associated health costs were reduced by $94 per year.

A study by Lichtenberg (2021) sought to analyse the overall impact that biotechnology innovation has had on the use of medical services in residents of assisted living communities in the United States in the period 1998 to 2015. It found that direct cost savings were $71.4 billion (95%CI: 28.3-115.7), compared to a drug acquisition cost of $127 billion, with an offsetting effect of 56%[41]. The sum of the savings over the period was broken down by different categories, with the reduction in hospitalisation cost being the main factor, responsible for almost 80% (56.1 billion; 95%CI CI: 21.4-91.9) of the total savings, followed by home medical visits (8.2 billion; 95%CI: 4.7-11.8), outpatient visits (5.5 billion; 95%CI: 1.5-9.5) and emergency visits (1.5 billion; 95%CI: 0.6-2.5)[41] (Figure 33).

FIGURE 33. PARTIAL COMPENSATION EFFECT OF THE INTRODUCTION OF THE INNOVATION BIOTECHNOLOGY, IN THE USE OF MEDICAL SERVICES BY RESIDENTS OF ASSISTED COMMUNITIES IN THE UNITED STATES, 1998-2015, IN BILLION DOLLARS



Source: Lichtenberg (2021)[41]

i To be a community residence, a facility must provide food and accommodation. In addition, it must offer some other services, such as social services; help with personal activities of daily living; training in socialisation and life skills; or provide occasional or incidental medical care

In recent years, evidence on the potential offsetting effect of medicines has accumulated in several developed countries, confirming previous findings since the early 2000s. The direct cost savings, especially in hospitalisation, from investment in new drugs may be greater than the additional investment required to purchase them.

Lichtenberg (2001)[32], Farmaindustria (2009)[36], Santerre (2011)[31], Lakdawalla (2017)[40], Lichtenberg (2023)[37]

PARTIAL OFFSETTING EFFECT: EFFICIENCY IN THE GENERATION OF HEALTH OUTCOMES

In certain circumstances, the phenomenon known as the compensatory effect of pharmaceuticals may manifest itself in a partial way. Such a situation can be observed both from the perspective of the health care system and from a broader societal perspective. In both cases, it is imperative to assess the efficiency, measured in terms of cost-effectiveness, of these pharmaceuticals in relation to the production of health outcomes.

According to Bertram et al. (2016), researchers representing the World Health Organization (WHO) project "Selecting cost-effective interventions (WHO-CHOICE[ii]), in 2005 suggested that interventions that avert a disability-adjusted life year (DALY), a quality-adjusted life year (QALY) or a life-year gained (YLL)[iii] for a cost less than the average per capita income of a given nation or region are considered highly cost-effective. Likewise, interventions whose costs are less than three times the average per capita income per DALY, QALY or QALY averted are still considered cost-effective[44].

Thus, a stream of work quantifies the return on investment in medicines in terms of health. For example, the study by Miller et al. (2000), conducted in several OECD countries, developed an econometric model to estimate the effects of drug consumption on the health production function. The researchers concluded that expenditure on pharmaceuticals is positively and statistically significantly correlated with life expectancy, both at intermediate (age 40) and advanced (age 60) stages. According to their estimates, for every additional dollar spent on pharmaceuticals, the life expectancy of a 40-year-old man would increase by an average of 1.2 days, and that of a 60-year-old man by 1.5 days[45].

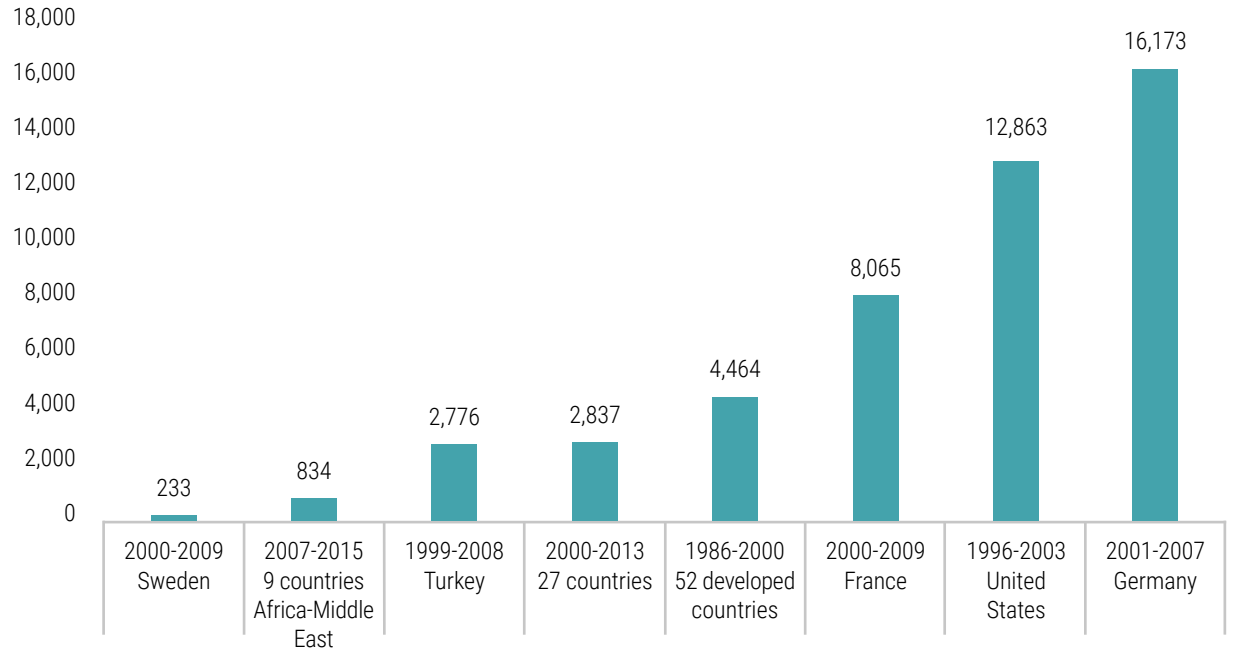
Shaw et al. (2002) conducted a similar analysis, modelling a health production function for 29 OECD countries, concluding that increases in per capita pharmaceutical spending would increase the life expectancy of the population. According to their results, doubling per capita pharmaceutical spending would increase life expectancy by about 1 year for men aged 40 and by less than 1 year for women aged 65. This study provides specific data for Spain. A $1 increase in per capita drug spending in 1985 would translate into an increase in life expectancy at age 60 (in the year 1997) of 1.28 days for men and 1.58 days for women, and 1.15 days and 1.44 days, respectively, at age 65[46].

Ultimately, according to research conducted before 2020, the introduction of new medicines appears to be a highly cost-effective health intervention, with costs per life-year gained ranging from $233 in Sweden to $16,200 in Germany (Figure 34)[47,48,49,50,51,52,53,54].

ii *WHO-CHOICE (World Health Organization CHOosing Interventions that are Cost-Effective)*

iii *For the general population, one year of life gained is on average equivalent to between 0.79 and 0.94 QALYs[42,43]*

FIGURE 34. COST-EFFECTIVENESS RATIO OF PHARMACEUTICAL INNOVATION PER LIFE-YEAR GAINED ($), ACROSS COUNTRIES AND TIME PERIODS



Note: OM: Middle East. Data for Sweden includes hospitalisations only. Data for Africa includes persons aged less than 75 years.

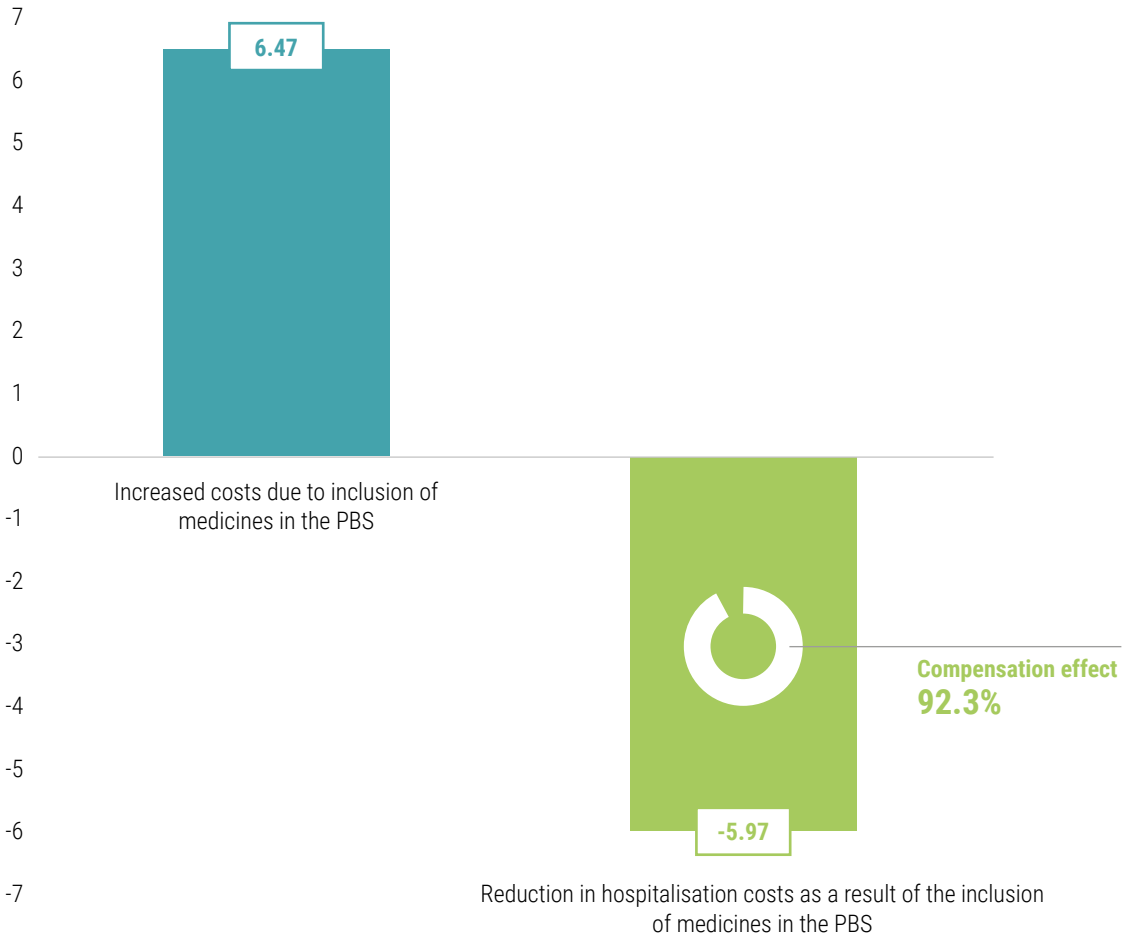
Source: Own elaboration based on Lichtenberg (2003[52], 2012a[47], 2012b[54], 2013[53], 2014a[50], 2014b[48], 2018[49], 2019[51])

Furthermore, a 2020 study in the context of Canada found that the absence of the drugs marketed between 1986 and 2001 would have resulted in a 26% higher incidence of DALYs lost, equivalent to a loss of 2.31 million DALYs in 2016 in Canada. Based on the study's findings, which are based on the analysis of pharmaceutical spending, a cost-effectiveness ratio of $2,842 per DALY is estimated, suggesting that these interventions are highly cost-effective[55].

Similarly, in Australia, the inclusion of medicines in the Pharmaceutical Benefits Scheme (PBS[iv]) between 1994 and 2011 resulted in an increase of 6.47 billion Australian dollars (~3.92 billion euros) in costs by 2019, compared to a hypothetical scenario where these drugs had not been included in the PBS. Savings associated with reduced hospitalisations over the same period reached A$5.97 billion (~3.62 billion euros). Consequently, savings from a single cost category, specifically those related to hospitalisations, offset 92% of the additional costs attributable to the inclusion of medicines in the English-speaking country's PBS (Figure 35)[56].

iv *The PBS in Australia is a government programme that helps reduce the cost of prescription drugs for the population. The government negotiates prices with pharmaceutical companies for a range of medicines, making them more affordable. Patients pay a subsidised price when they purchase medicines included in the PBS, and the government covers the rest of the cost.*

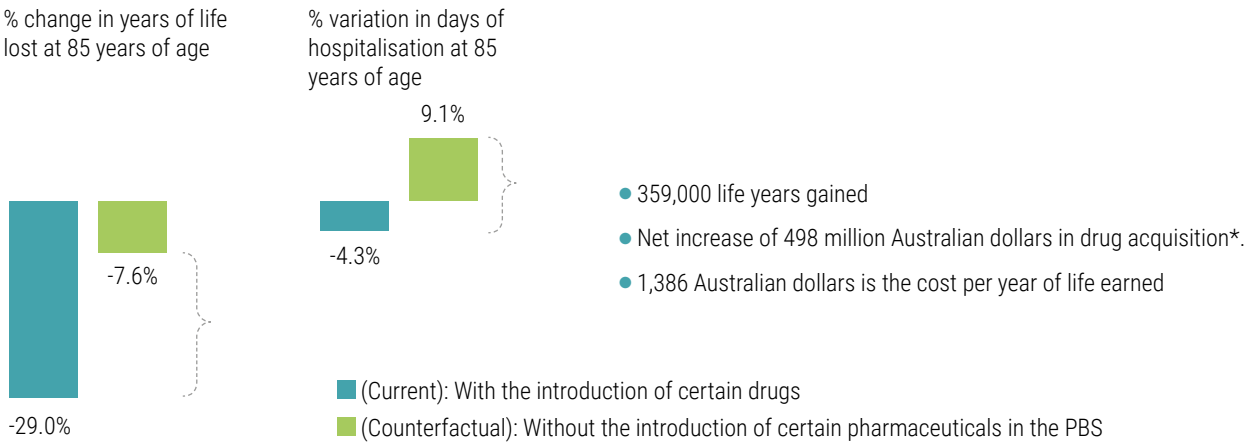
FFIGURE 35. PARTIAL COMPENSATION EFFECT OF THE INTRODUCTION OF NEW MEDICINES BETWEEN 1994 AND 2001 IN THE AUSTRALIAN PHARMACEUTICAL BENEFITS SCHEME (PBS), YEAR 2019, IN BILLION AUSTRALIAN DOLLARS



Source: Lichtenberg (2023)[56]

The authors of the same study also calculated that the increase in the number of medicines included in the PBS correlated with a reduction in the number of years of life lost before the age of 85 in 2019, which amounted to 359,026 years. Thus, a rough estimate of the cost per year of life gained before the age of 85 in 2019, resulting from the prior inclusion of medicines in the PBS, was Australian dollars. In 2019, Australia's gross domestic product per capita reached A$78,092, suggesting that the addition of these drugs to the PBS was a highly cost-effective intervention (Figure 36)[56].

FFIGURE 36. EFFICIENCY OF MEDICINES INCLUDED IN THE AUSTRALIAN PHARMACEUTICAL BENEFITS SCHEME, AS A RESULT OF REDUCED YEARS OF LIFE LOST AND HOSPITALISATIONS



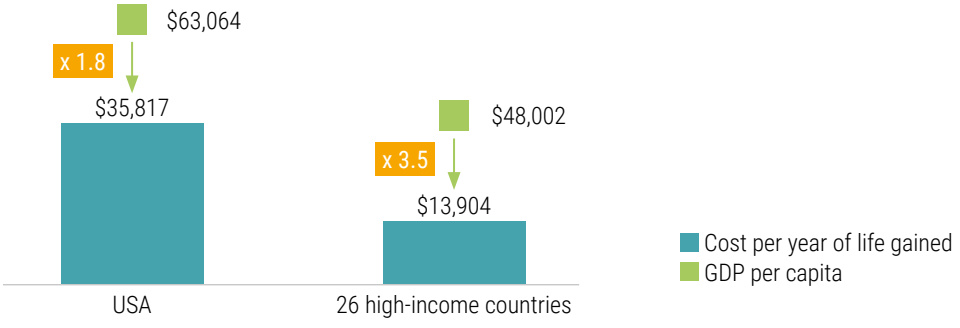
Note: *this increase was only possible due to reductions in hospitalisations, which generated 5.97 billion in savings, compared to a total cost of 6.47 billion.

Source: Lichtenberg (2023)[56]

Recently, an analysis of the cost per life-year gained has been conducted in the United States and 26 other high-income nations for the introduction of innovative drugs during the period between 2006 and 2018, and 2006 and 2016, respectively. The longevity metric examined was mean age at death, which correlates with life expectancy at birth. To assess pharmaceutical innovation, the average age (year of initial global launch) of drugs used to treat each disease in each country was used. Changes in the distribution of drug age are due to both the introduction of new therapies and the obsolescence of existing ones. Data analysis reveals that as the average age of medicines decreases, the average age at death increases. The reduction in drug age between 2006 and 2018 led to an increase in the average age at death of US citizens by approximately 6 months. On the other hand, the decrease in the age of medicines led to an increase in the average age at death in the 26 high-income countries of 1.23 years between 2006 and 2016[57].

Estimates of the cost per life year gained for the United States and the 26 countries amount to $35,817 and $13,904, respectively. Both figures are significantly below the GDP per capita in the respective regions ($63,064 and $48,002, respectively), suggesting that, overall, pharmaceutical innovation has been cost-effective (Figure 37)[57].

FIGURE 37. COST PER LIFE-YEAR GAINED FROM REDUCING THE AVERAGE AGE OF MEDICINES IN THE UNITED STATES (2006-2018) AND 26 HIGH-INCOME COUNTRIES (2006-2016), IN DOLLARS VS. GDP PER CAPITA



Source: Lichtenberg (2022)[57]

Several studies support the idea that investing in reducing the average age of medicines can be cost-effective. According to the latest estimate for 27 high-income countries, the cost of new medicines per year of life gained ranges from $14-36,000, which is 2-4 times less than the GDP per capita in these regions, making them an efficient investment.

Miller (2000)[45], Bertram (2016)[44], Lichtenberg (2019)[51], Lichtenberg (2022)[57], Lichtenberg (2023)[56]

EVIDENCE OF COST SAVINGS IN DIFFERENT PATHOLOGIES

Moreover, an important area of research focuses on understanding how innovative medicines impact on overall healthcare spending, especially in the context of specific chronic diseases. Examples are presented below in the context of cardiovascular diseases and cancer, two of the leading causes of mortality in Europe, responsible for more than 50% of all deaths in 2020[58]. In addition, allusions are made to examples related to specific rare diseases, as well as examples found in other pathologies as a way to illustrate the scope and applicability of the concepts discussed. In all these scenarios, new treatments have been shown to generate significant savings in hospital costs, which, in several instances, exceed the observed increase in pharmacological costs.

Cardiovascular diseases

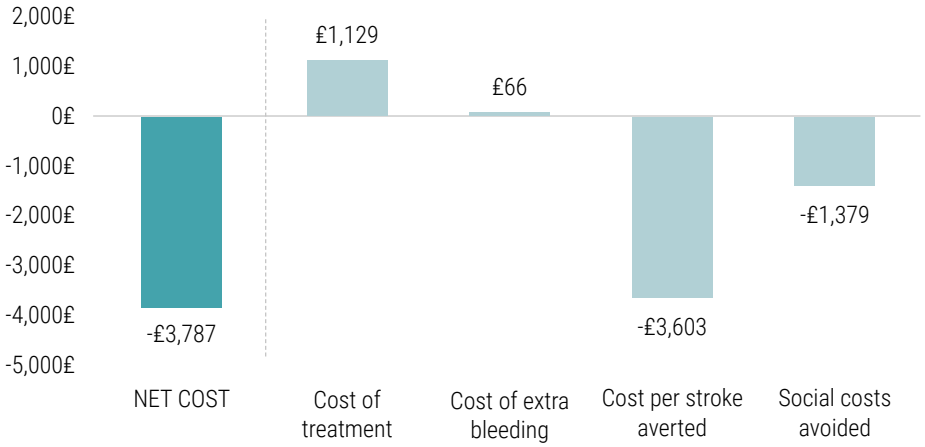
In the field of cardiovascular diseases, Lichtenberg (2009) notes that the introduction of new medicines in OECD countries in the period 1995-2004 increased the average pharmaceutical expenditure per capita by $24, but managed to decrease both the average hospitalisation rate and the average length of stay, generating savings of $89 per capita in hospitalisations, resulting in a net savings ratio of 3.7 times59 . In later work for Switzerland, the author estimated that cardiovascular drug innovation between 2003 and 2012 was responsible for a quarter of the increase in longevity of patients over 75 with cardiovascular disease, and that these drugs have been highly cost-effective, with an associated ratio of $9,544 per life-year gained[60].

A US trial (Air Force/Texas Coronary Atherosclerosis Prevention Study) found that statin use resulted in a benefit-cost (social) ratio of 4 in the period 1987-2008, when associated with an average annual treatment cost of $11,231 per capita, resulting in survival gains equivalent to an average annual social value of $46,157 per patient. According to another study, statin use in the United States (US) averted hospitalisation costs of $4.4 billion for heart attacks and $400 million for strokes in 2008[61].

According to a cost-effectiveness study by Nguyen et al. (2018) on the use of statins in patients with acute myocardial infarction in Finland, these drugs were not only cost-effective in the period 1998-2011 (with a ratio of between 800 and 15,000 €/AVG), but in the period 2008-2011 they generated a net saving in healthcare costs of between 1,800 and 2,400 € per person62[62].

Another study analysed the impact of the introduction of antithrombotic drugs by the UK National Health Service on healthcare costs63. According to estimates, providing anticoagulation treatment to patients with atrial fibrillation is associated with a net per capita saving to the health system of £412 in the short term and £2,408 over the patient's lifetime, in addition to savings to society of £94 and £1,379, respectively (Figure 38)[63].

FIGURE 38. ESTIMATED LIFETIME COSTS PER PATIENT OF ANTITHROMBOTIC THERAPY IN PATIENTS WITH ATRIAL FIBRILLATION, UK



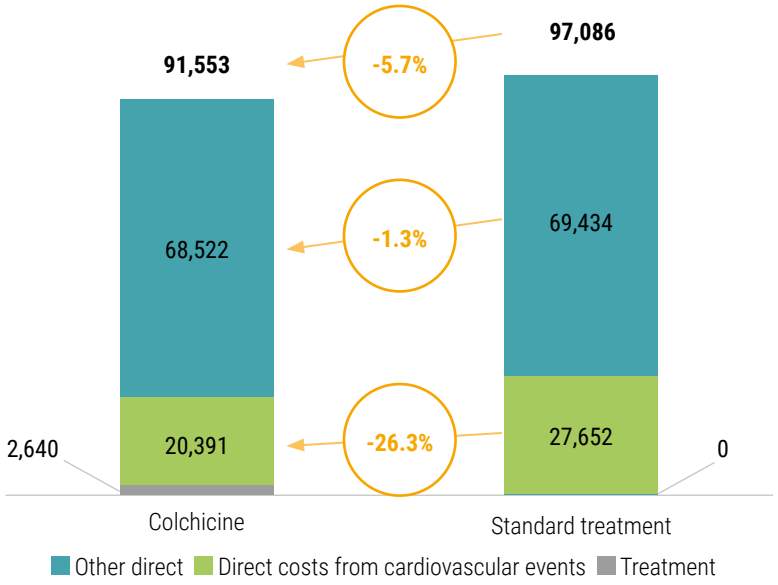
Source: Kerr (2014)[63]

Some studies, such as Masbah (2016) conclude that the new oral anticoagulants are better alternatives to warfarin, preventing the risk of stroke in atrial fibrillation and thus generating net healthcare cost savings. This paper, which looks at hospitalisations over 5 years for a group of Scottish patients with atrial fibrillation, counts the cases of heart failure avoided in each treatment group and concludes that the total direct healthcare costs associated with oral anticoagulants are 17% lower than the control group[64].

The use of antihypertensive drugs has not only had a significant impact on population health, but also on the healthcare costs associated with this risk factor by reducing the likelihood of vascular accidents. It is estimated that during the 1990s in the United States, the use of antihypertensives in 2002 prevented a direct health care cost of $16.5 billion for myocardial infarction and stroke, 70% of which were hospital costs[65]. This saving alone is already greater than the annual expenditure on antihypertensives in the United States, which in 1998 was about USD 8.8 billion[66]. Other studies corroborate the favourable cost-effectiveness of the use of antihypertensive drugs for the treatment of hypertension[67].

In more recent studies, colchicine, an anti-inflammatory agent with a long history of use, has been evaluated for the treatment of various inflammatory conditions such as gout, pericarditis, and juvenile idiopathic arthritis. Multiple large-scale clinical trials have shown that colchicine offers benefits in cardiovascular outcomes compared to standard treatment. In a recent study conducted by Boczar (2023) in the Canadian context, it was found that prolonged use of colchicine is associated with a reduction in the lifetime incidence of events such as myocardial infarction, revascularization, stroke, and gout flare-ups. The accumulated QALYs over a lifetime were 19.92 in the prolonged colchicine treatment group, compared to 19.80 in the standard treatment group. Additionally, the authors demonstrated that, due to the reductions in costs associated with these cardiovascular events, the total lifetime cost of colchicine treatment amounted to 91,553 Canadian dollars, compared to 97,086 Canadian dollars for standard treatment. In other words, this medication not only led to an improvement in quality of life but also resulted in a reduction in total costs due to a decrease in the number of cardiovascular events (Figure 39)[68].

FIGURE 39. LIFETIME COST PER PATIENT FOR TREATMENT OF THE DISEASE ATHEROSCLEROTIC CARDIOVASCULAR DISEASE, COLCHICINE VS. STANDARD TREATMENT, CANADIAN DOLLARS



Source: Boczar (2023)[68]

Cancer

It has been estimated that **cancer** drugs marketed during 1980-1997 have averted about 1.72 million hospital days per year in Canada alone[69]. In monetary terms, this equates to a reduction in hospital expenditure of 4.7 billion Canadian dollars in 2012, which is more than the expenditure attributable to cancer drugs (old and new) at that date (3.8 billion Canadian dollars), thus resulting in a net cost saving.

In 2020, Lichtenberg published estimates from new models applied to cancer drugs in the United States[70]. According to his calculations, drugs marketed between 1989 and 2005 are associated with a 13.3% reduction in the number of hospital days for cancer and a reduction in hospital costs of $4.8 billion. For their part, drugs marketed between 2000 and 2014 are associated with a gain of 719,133 life years (before age 75) in 2014, resulting in a cost-effectiveness ratio of $7,853 per life year gained. This figure is higher than that estimated for other countries, such as Russia (ratio of $2,170 per GALY for 14 oncology drugs at ages below 75 years[71]), but is still well below GDP per capita, and thus gives an idea of the favourable cost-effectiveness of this type of pharmaceutical intervention.

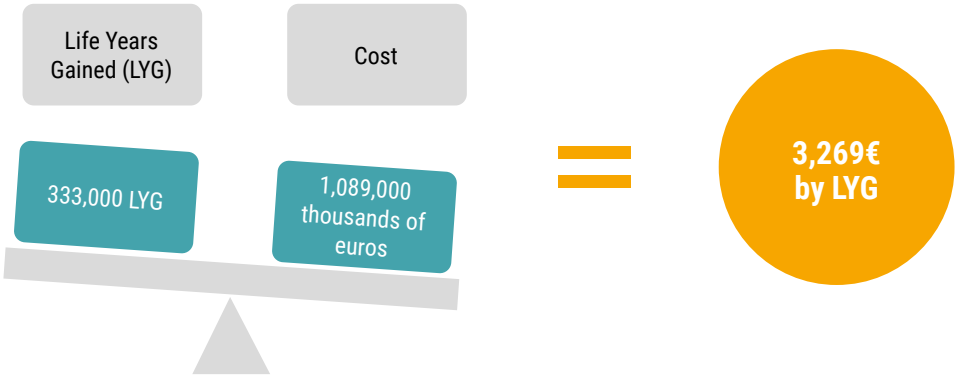
A more recent study by Lichtenberg (2023) illustrates the impact that oncologic drugs approved in New Zealand between 1985 and 2001 have had, reducing Potential Years of Life Lost at 85 (PYLL85) by 67% (i.e. 244,876 PYL85) in 2017. In the absence of these approvals, the APVP85s would have been 3.02 times higher compared to those recorded in 2017. In economic terms, in 2011, the Ministry of Health estimated that the annual cost to the New Zealand public health system related to cancer was NZ$511 million. This figure included a range of costs, such as hospitalisation, outpatient consultations and medicines, for patients from one year before diagnosis to five years after. This cost was projected to rise to NZ$628 million by 2021, representing an increase of 23%. Therefore, the cost per year of life gained before the age of 85 in 2017 from drug approvals would not exceed NZ$2,566[v] or $1,719 USD americans[vi], even if the projected cost for 2021 were to be considered. It is worth noting that New Zealand's GDP per capita in 2017 was USD 42,260[72].

v Calculated as 628 million New Zealanders divided by 244,876 years of life.
vi Considering an exchange rate of 0.67 US dollar to 1 New Zealand dollar

Let us turn to an example in our country. Despite the increase in the incidence of cancer, mortality from this disease has experienced a notable decrease in Spain over the course of the 21st century. However, the extent of this reduction has varied according to the different typesvii of cancer. For example, the average age at death due to three specific types of cancer, including lymphoblastic leukaemia, has increased by more than 6 years, while the average age at death due to two other types of cancer, such as liver cancer, has increased by less than 1.4 years[73].

Lichtenberg (2023) recently conducted research to determine the incremental cost-effectiveness ratio of cancer drug innovation in Spain. The author concluded that the increase in mean age at death between 1999 and 2016 tended to be greater for tumour types that experienced greater innovation. Furthermore, the authorisation of new drugs over the previous 17 years correlated with a decrease in the number of years of life lost before the age of 75 in 2016, estimated at 333,000, with an associated cost of €1,089,000. Thus, the pharmaceutical expenditure per year of life gained before the age of 75 in 2016 from new cancer drugs authorised between 2000 and 2016 was estimated to be €3,269 (Figura 40)[73].

FIGURE 40. YEARS OF LIFE GAINED AT AGE 75 AND COSTS OF DRUG INTRODUCTION BETWEEN 2000 AND 2016 IN SPAIN, ESTIMATES IN EUROS, 2016



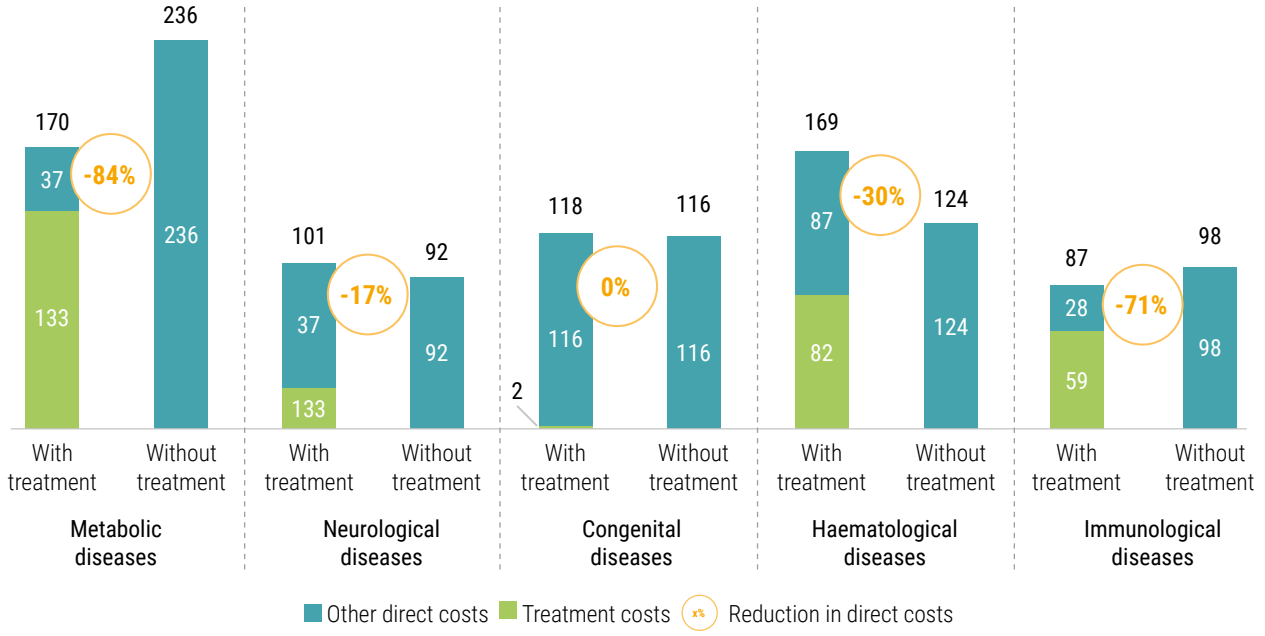
Source: Lichtenberg (2023)[73]

In summary, analysis of various studies over several decades and in different countries suggests that cancer drugs have proven to be highly cost-effective. These treatments have led to significant reductions in hospitalisation and associated costs, and have extended patients' lives with a favourable ratio between costs incurred and benefits in terms of life years gained, underlining the economic efficiency and positive impact of pharmaceutical innovation in oncology.

Rare diseases

Targeted medicines for rare diseases (RDs) not only improve patients' quality of life, but can also reduce associated healthcare costs. A study in the US analysed the impact of treatments in 227 RDs, selecting 24 relevant ones. Direct, indirect and mortality-related costs were assessed, showing that the introduction of specific treatments can significantly reduce costs, especially in metabolic and immunological diseases, where direct costs were reduced by 71% to 84%, partially offsetting the increased costs of drug procurement (Figure 41)[74].

FIGURE 41. COMPARATIVE ANALYSIS OF ANNUAL DIRECT COSTS PER PATIENT IN A SAMPLE OF UP TO 24 RARE DISEASES IN THE UNITED STATES, WITH AND WITHOUT PHARMACOLOGICAL TREATMENT



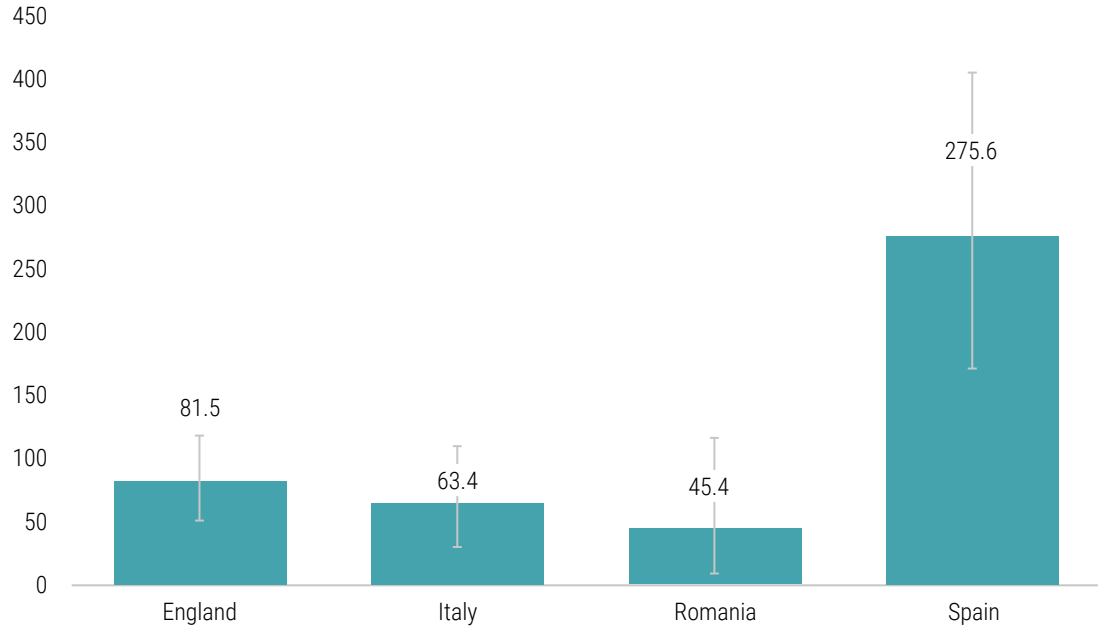
Source: Andreu (2022)[74]

Hepatitis C

An analysis based on a Markov model of **hepatitis C** virus progression examined the clinical and economic impact of direct-acting antiviral therapy (DAA) in the settings of England, Italy, Romania and Spain. This model integrated considerations of DAA eligibility, as well as demographic and epidemiological data for the period 2015-2019. The results of this research reveal that DAAs offer significant clinical benefits and have the potential to generate substantial economic savings over a 20-year time horizon. Based on the model estimates, the projected number of avoided cases of hepatocarcinoma, decompensated cirrhosis and liver transplantation over this period was as follows: 1,057 in England, 1,221 in Italy, 1,211 in Romania and 1,103 in Spain for patients treated between 2015 and 2016; and 640 in England, 626 in Italy, 739 in Romania and 643 in Spain for patients treated between 2017 and 2019[75].

In terms of the economic benefits of expanding access to direct-acting antiviral treatment over a 20-year time horizon, England estimates savings of 81.5 million euros (95% CI 51.3-118.6). 63.4 million (95%CI: 30.4-108.6) is projected. 45.4 million in Romania (95%CI: 7.7-116.0). Finally, Spain anticipates savings of 275.6 million euros (95%CI: 170.9-404.9) (Figure 42)[75].

FIGURE 42. ECONOMIC OUTCOMES OF EXPANDING ACCESS TO DIRECT-ACTING ANTIVIRAL THERAPY OVER A 20-YEAR TIME HORIZON IN ENGLAND, ITALY, ROMANIA AND SPAIN (IN MILLIONS OF EUROS)



Source: Mennini (2021)[75]

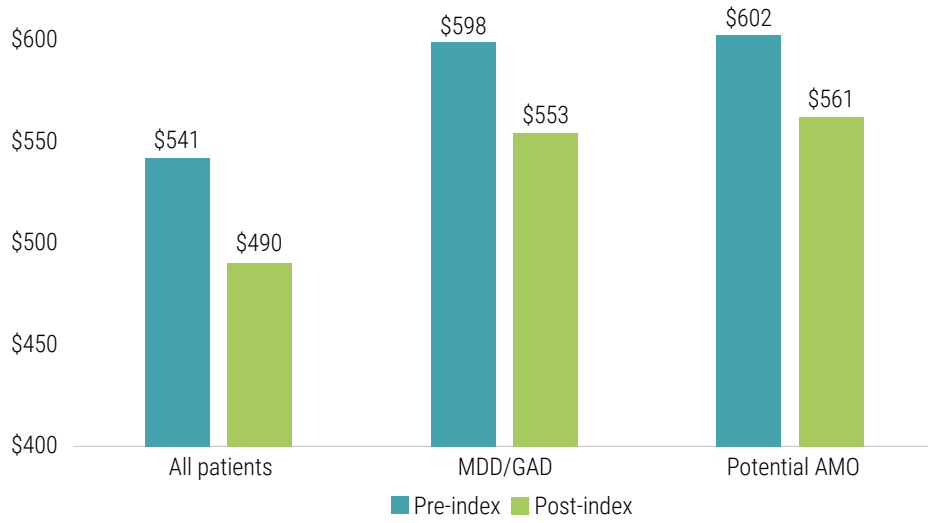
Migraine

Currently, preventive treatments for **migraine** are evolving with new therapeutic options that demonstrate efficacy in reducing the frequency and severity of migraine episodes. A humanised monoclonal antibody, specifically directed against the calcitonin gene-related peptide, has been shown to be an effective agent for the preventive treatment of migraine in adults. Based on real-world evidence, a comprehensive evaluation of the impact of this treatment on multiple relevant aspects, such as migraine-associated medication consumption, healthcare resource utilisation, and associated costs, has been conducted in patient populations characterised by the presence of comorbidities, acute medication overuse (UEMA), and/or unsatisfactory pre-migraine preventive response (RPIPM)[76].

The data used for this retrospective analysis were obtained from US administrative databases. The population of interest consisted of adults who met specific eligibility criteria, including the presence of pre-existing migraine-associated comorbidities (such as depression, anxiety and cardiovascular disease), as well as the possible manifestation of UEMA or RPIPM. In total, data from 3,193 patients who met the eligibility criteria were identified and analysed. It was observed that from the pre-index to post-index period, the mean number of migraine-related acute and preventive medication claims (with the exception of fremanezumab) per patient per month (PPPM) decreased significantly from 0.97 to 0.86 ($P < 0.001$), and from 0.94 to 0.81 ($P < 0.001$), respectively[76].

In addition, there was a significant decrease in migraine-related outpatient visits, neurological consultations, emergency department visits and other outpatient services in the post-index period compared to the pre-index period ($P < 0.001$ for all cases). This pattern of reduced healthcare resource utilisation translated into a decrease in the average total cost of medical care per patient per month from US$ 541 to US$ 490 ($P = 0.003$)[76] (Figure 43).

FIGURE 43. TOTAL MIGRAINE-RELATED HEALTH CARE COSTS (EXCLUDING FREMANEZUMAB), PER PATIENT PER MONTH, IN DOLLARS



Abbreviations: MDD: major depressive disorder; GAD: generalised anxiety disorder; AMO: acute medication overuse.

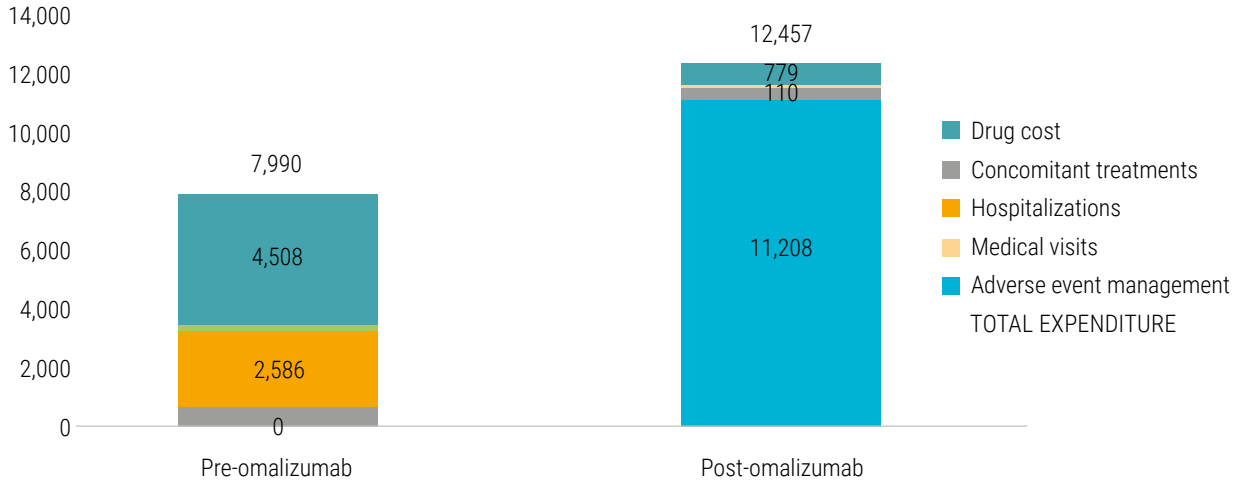
Source: Buse (2024)[76]

Asthma

Net savings associated with pharmacological treatment of **asthma** have also been found. For example, an Irish study concluded that treating patients with severe allergic asthma with a monoclonal antibody for 6 months reduces exacerbations, reducing the use of healthcare resources and leading to fewer lost workdays, resulting in net healthcare savings of more than 800 euros per patient and total societal savings of more than 2400 euros per patient[77].

In addition, a recent real-life study in Italy on patients with severe asthma showed that a biologic drug generated 84% savings in all other direct non-health costs, especially hospitalisations and management of adverse events, but no net savings (Figure 44)[78].

FIGURE 44. TOTAL DIRECT HEALTH CARE COSTS PER ASTHMA PATIENT IN THE 12 MONTHS BEFORE AND AFTER OMALIZUMAB TREATMENT, ITALY (EUROS)

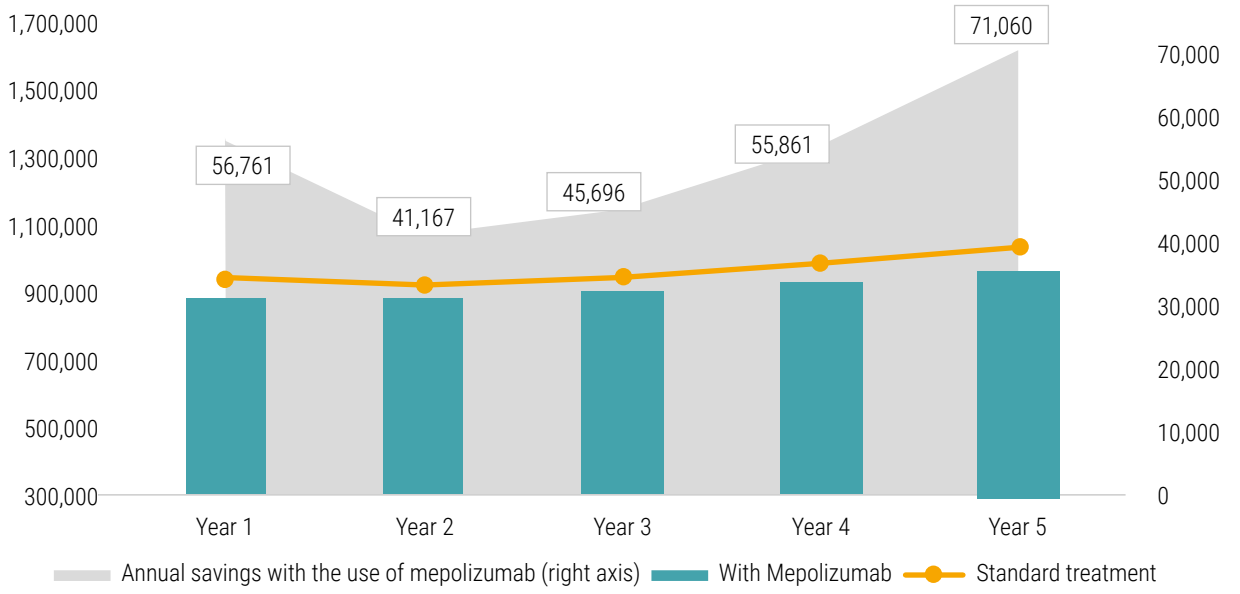


Source: Own elaboration based on Canonica (2020)[78]

A more recent study assessed the five-year budgetary impact of introducing a specific monoclonal antibody for patients with severe uncontrolled eosinophilic asthma, who were being treated in a tertiary care hospital centre within the domain of the Dubai Health Authority (DHA)[79].

Eligibility criteria for administration of the monoclonal antibody included experience of at least two asthma exacerbations during the preceding year and an eosinophil count equal to or greater than 150 cells/μL. The comparative analysis involved comparing the costs associated with treating patients in two alternative scenarios: one reflecting standard clinical practice and the other where access to this monoclonal antibody is fully facilitated for patients meeting the established criteria[79]. The results suggest that the implementation of this monoclonal antibody in eligible patients in the context of Rashid Hospital leads to an estimated total cost saving of £270,545 over a five-year period (Figure 45)[79].

FIGURE 45. PROJECTED BUDGETS IN THE SCENARIO WITH AND WITHOUT MEPOLIZUMAB, AS WELL AS THE OVERALL BUDGET IMPACT, IN ASTHMA PATIENTS, DUBAI HEALTH AUTHORITY, IN POUNDS STERLING

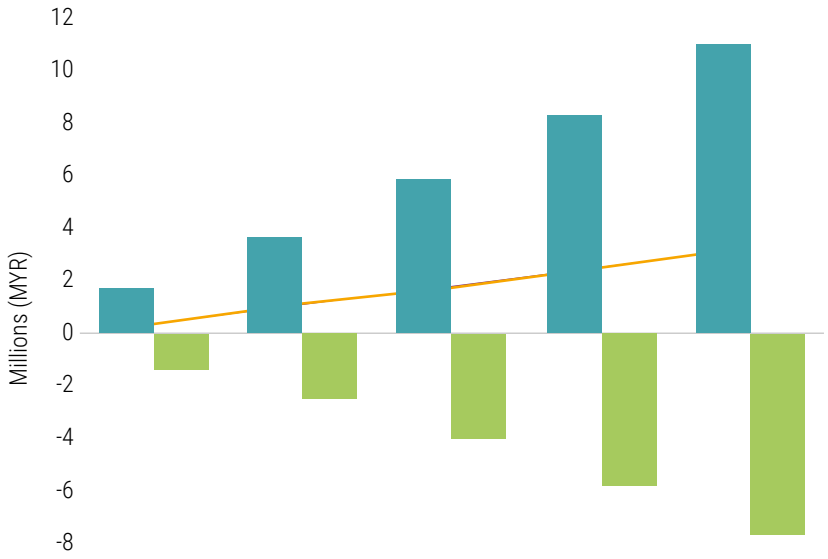


Source: Mahboub (2022)[79]

Osteoporosis

In another analysis, an assessment of the budgetary impact of increasing the uptake of denosumab for the management of postmenopausal **osteoporosis** over a 5-year period was conducted from the perspective of the healthcare provider in Malaysia. As a result, an increase in denosumab uptake of 8% per year over a 5-year time horizon would result in intervention cost increases of MYR10.9 million (USD2.6 million) in year 5; however, cost reductions associated with fracture treatments of MYR7.6 million (USD1.8 million) would be observed during the same year. This translates into a net budget impact of MYR 3.3 million (USD 0.8 million) in year 580 (Figure 46).

FIGURE 46. BUDGET IMPACT OF INCREASING UPTAKE OF DENOSUMAB FOR THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS IN MALAYSIA OVER A 5-YEAR TIME HORIZON



	Year 1	Year 2	Year 3	Year 4	Year 5
Intervention (MYR)	1,648.872	3,569,624	5,754,823	8,195,599	10,887,692
Fracture treatment (MYR)	1,384.934	3,500,954	4,041,556	5,792,304	7,636,896
Total budget impact (MYR)	263,938	1,068,670	1,713,267	2,404,295	3,250,708

Source: Choo (2023)[80]

Alzheimer's disease

Recent research in the field of **Alzheimer's disease** focused on the evaluation of donepezil and memantine using causal inference analysis. To do so, they implemented doubly robust estimators on one of the largest and most reliable medical databases available to estimate the impact of these treatments, both individually and in combination, on the average frequency of hospital or emergency room visits in patients diagnosed with Alzheimer's disease. According to the study findings, compared to no treatment, both memantine and donepezil monotherapy, as well as the combined use of both drugs, produce a statistically significant reduction in the average number of hospital or emergency visits per year, by 13.8%, 25.5% and 23.4%, respectively[81].

This decrease in the frequency of hospital or emergency visits is thus associated with a significant reduction in medical costs. If patients currently receiving no drug treatment or using only donepezil or memantine were to switch to the combined regimen of donepezil and memantine, it is estimated that the average number of hospital or emergency room visits could decrease by more than 613,000 per year in this country. This, in turn, would lead to a considerable reduction in the medical costs associated with the hospitalisation of patients with this disease, amounting to more than $940 million per year[81].

Evidence supports the (partial or net) savings that innovative medicines could generate in prevalent diseases, such as cardiovascular diseases and cancer, as well as in less common diseases such as rare diseases, asthma or hepatitis C. Even when the savings do not fully offset the costs, these drugs can still be cost-effective. For example, in Spain, the cost per year of life gained by innovative cancer drugs is estimated at €3,000, which would be considered a highly efficient intervention.

Mennini (2021)[75], Andreu (2022)[74], Boczar (2023)[68], Lichtenberg (2023)[73], Buse (2024)[76]

SAVINGS IN DIRECT NON-HEALTHCARE COSTS

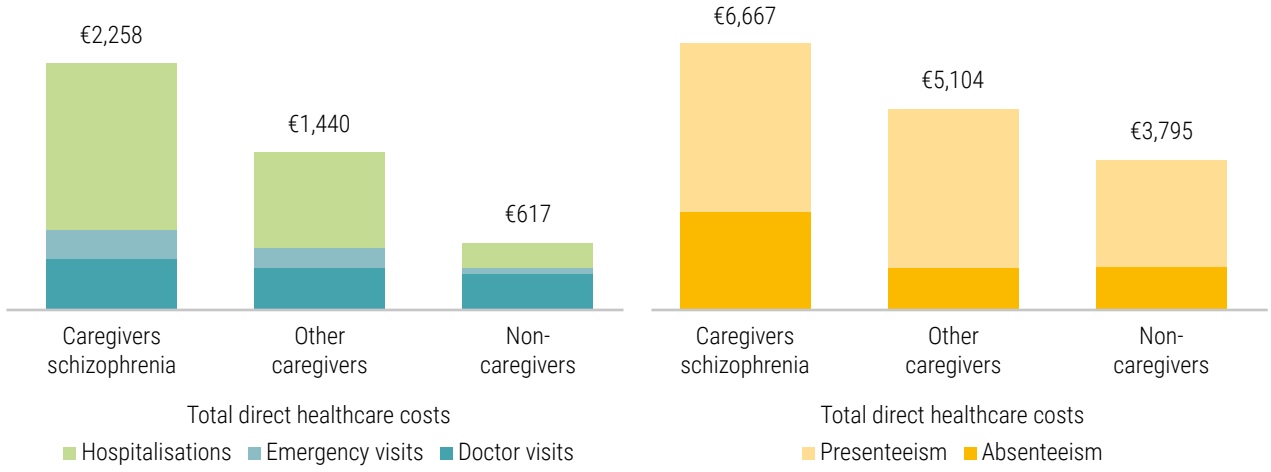
In addition to potential savings in the direct costs of medical care by reducing restrictions in carrying out daily activities, medicines also bring benefits in terms of direct non-medical costs. These include those associated with care provided by professionals or the patient's affective environment, as well as home adaptations required for patients with certain pathologies. Unfortunately, published empirical evidence in this area remains limited.

In any case, it is clear that the impact on direct non-medical costs is particularly significant in diseases involving greater functional dependency, either due to the physical or mental impairment they entail. The older age group is particularly vulnerable in this respect. In fact, numerous studies analyse the burden of illness experienced by carers, pointing to substantial **spillover effects** on their health, especially in terms of mental health, quality of life and working environment[82].

Some research suggests that the burden is more pronounced among carers of people with mental illness compared to those caring for people with chronic illness. Furthermore, the impact in terms of levels of depression, anxiety and lack of autonomy for carers increases as the patient's illness becomes more prolonged and their degree of dependency increases[83–86].

Thus, several studies have identified a positive correlation between the burden of care for people with schizophrenia and a deterioration in the health, especially mental health, of caregivers87,88 . These sequences are reflected in the health and work environment of carers, as evidenced by a study carried out in five European countries, including Spain. In this case, caregivers of people with schizophrenia consume more health resources compared to those caring for patients with other pathologies (with an average of €2,558 per person versus €1,440, due to a higher rate of hospitalisations) and experience a higher loss of work productivity (with an average of €6,667 versus €5,104, due to higher presenteeism) (Figure 47)[89].

FIGURE 47. COMPARISON OF DIRECT HEALTH CARE COSTS AND INDIRECT COSTS ASSOCIATED WITH CARERS OF PEOPLE WITH SCHIZOPHRENIA COMPARED TO CARERS WITH OTHER PATHOLOGIES AND TO NON-CAREGIVERS, EU5

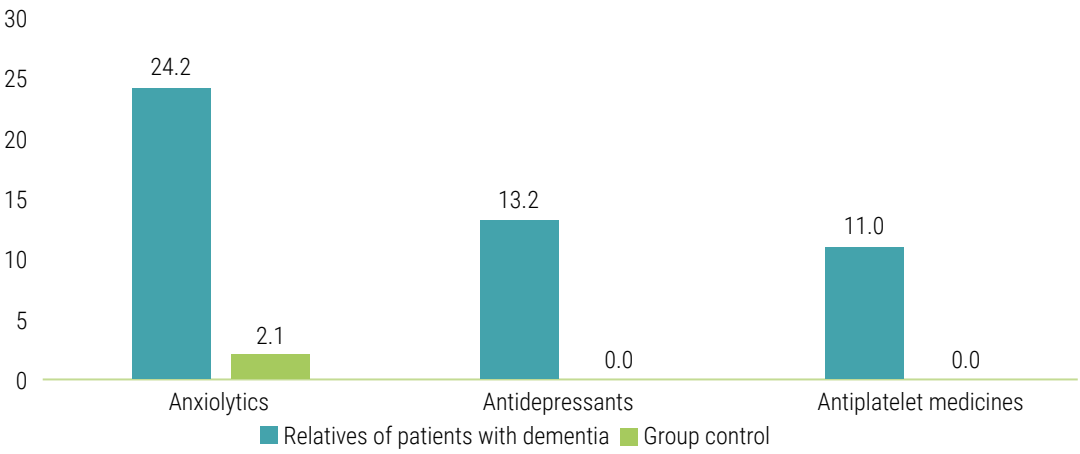


Source: Gupta (2015)[89]

Furthermore, the burden of care and, consequently, the direct non-health care costs associated with age-related conditions such as dementia, Alzheimer's disease and Parkinson's disease are of great relevance. In this regard, a systematic review of economic evaluations in the field of dementia and Alzheimer's revealed that most of the recently published evaluations do not take into account the costs of personal care provided to patients. If these costs were incorporated, 85% of the cost-effectiveness ratios obtained would tend to be more favourable or could even represent net cost savings[90].

Regarding the impact of dementia on caregiving, a study in Spain confirmed that caregivers of dementia patients consume more anxiolytics and antidepressants compared to caregivers of other patients (24.2% and 13.2% versus 2.1% and 0%, respectively)[91] . In addition, they require a higher proportion of socio-health services, such as psychologists, social workers or assistance from patient associations. On the other hand, a literature review on informal care among older people with dementia revealed that pharmacological treatment reduces both the burden of care and the time spent on care and supervision (Figure 48)[92].

FIGURE 48. PERCENTAGE OF CASES AND CONTROLS RECEIVING MEDICATION FROM EACH DRUG GROUP (CASES: CAREGIVERS OF DEMENTIA PATIENTS)



Source: Martín-García (2016)[92]

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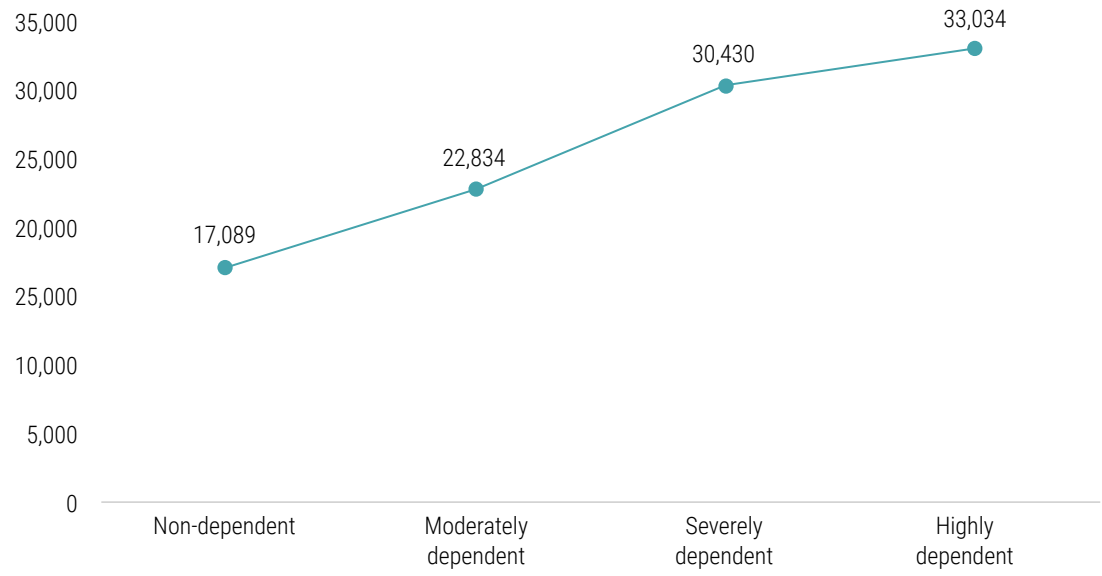
In addition, caregivers of people with Parkinson's disease have been shown to experience greater job losses than caregivers of people with other conditions. In the United States, it is estimated that over a 5-year period, caregivers of Parkinson's patients would have an average cumulative loss of income of $5,967 per year, compared to an average of $2,634 for other caregivers[93].

In the case of chronic conditions such as chronic obstructive pulmonary disease (COPD), the cost of informal care increases as the patient becomes more dependent. The annual cost in Spain varies between €17,089-28,319 if the patient is not dependent, and between €33,034-54,740 if the patient is highly dependent on the caregiver (Figure 49)[85].

FIGURE 49. COST OF INFORMAL CARE (MAIN CAREGIVERS) ACCORDING TO DEGREE OF DEPENDENCY, COPD PATIENTS (ANNUAL COST, IN EUROS)

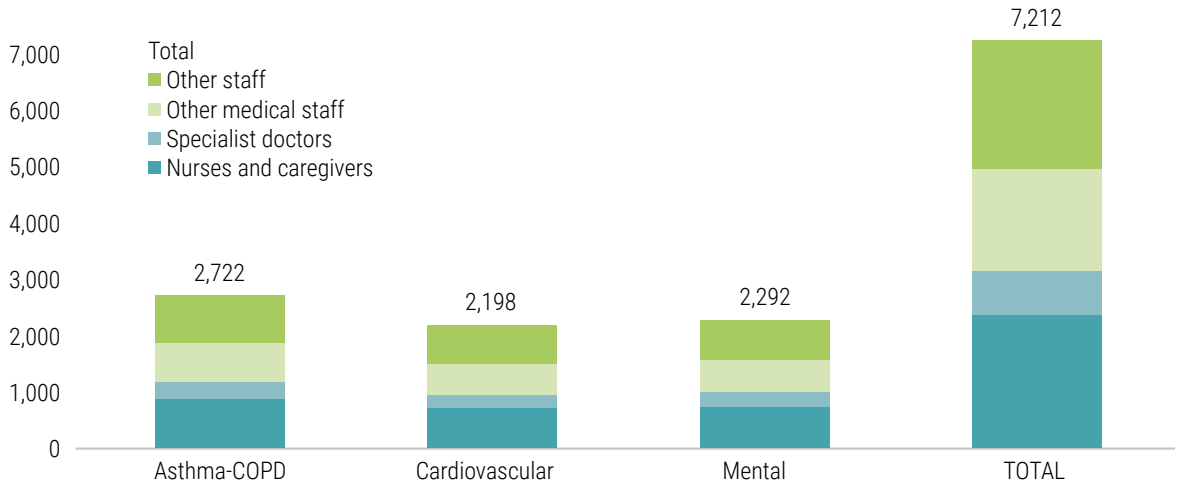


Source: Peña-Longobardo (2015)[85]

Furthermore, an observational study in Italy analysed the impact of biologics on moderate/severe psoriasis, highlighting how the improvement in symptoms and quality of life is reflected in patients' work, personal and care environments. The need for home care decreased from 28 days per year to just 10, associated with an average saving of 60% in these direct non-medical costs (or €1,021 per patient per year). In this case, carers reduced their absenteeism from 8 days per year to just 2 days[94].

On the other hand, another study has attempted to approximate the cost savings associated with integrated patient care (health and non-health costs) derived from the commercialisation of a group of ten pharmaceutical innovations (aimed at three groups of diseases) in the Netherlands[95]. According to this study, the pharmaceutical innovations marketed between 1995 and 2007 have generated annual savings equivalent to the labour costs of 7,212 full-time patient care staff, including 2,359 nurses and carers, 784 specialist doctors, 1,825 other medical staff and 2,244 other staff (Figure 50). The largest savings are observed in the group of asthmatic and pulmonary diseases, followed by mental illnesses and cardiovascular diseases.

FIGURE 50. ANNUAL COST SAVINGS IN INTEGRATED PATIENT CARE (FULL-TIME EQUIVALENT OF HEALTH AND NON-HEALTH STAFF) GENERATED BY 10 NEW MEDICINES, BY THERAPEUTIC AREA, THE NETHERLANDS, 2007

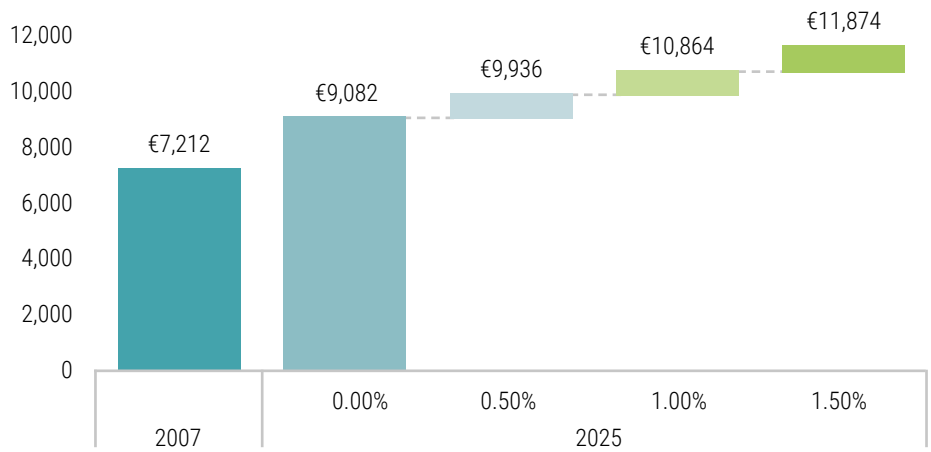


Fuente: Own elaboration based on Tsiachristas (2009)[95]

The author also makes a projection of the potential annual cost savings associated with integrated patient care that could materialise by 2025, considering various annual growth rates in medicine utilisation (Figure 51). It concludes that pharmaceutical innovations have the potential to increase savings in these costs, which would improve the financial sustainability of the healthcare system. This would be achieved by relieving healthcare professionals of the time burden of caring for these patients, allowing them to focus on other responsibilities. It would also reduce the burden on patients' families, who would be able to use these hours of care for other activities, such as work or leisure, instead of attending to the daily needs of those with limited daily activities[95].

Another example of savings in direct non-health care costs is shown by De Sequera et al. in which the use of patiromer in patients with chronic kidney disease or heart failure in Spain was linked to savings of 19.9% and 18.5%, respectively[96].

FIGURE 51. PROJECTED COST SAVINGS IN INTEGRATED PATIENT CARE TO 2025 (FULL-TIME EQUIVALENT OF HEALTH AND NON-HEALTH STAFF), BASED ON THE ANNUAL GROWTH RATE OF THE SHARE OF USE OF 10 NEW MEDICINES IN THE NETHERLANDS



Source: Own elaboration based on Tsiachristas (2009)[95]

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Medicines may also have benefits in terms of costs related to the personal care required by the patient. Although the published evidence is limited, the effect on these direct non-health care costs will be particularly relevant in pathologies involving greater functional dependence.

de Sequera (2023)[96], Siddiqui (2019)[86]

ADHERENCE TO TREATMENT AND COST SAVINGS

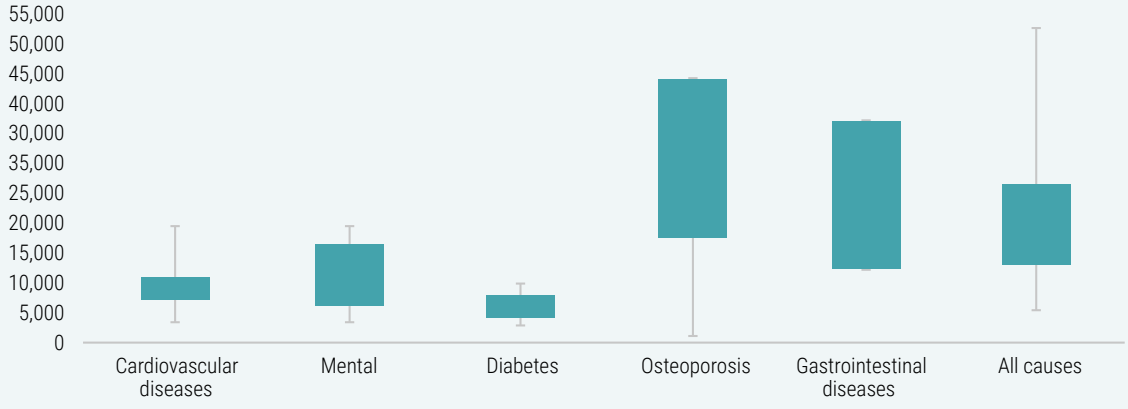
Adherence to treatment can be crucial in terms of cost savings, especially for patients with chronic diseases where medication is essential. It is estimated that around 50% of these patients are non-adherent. For example, in the United States, hospitalisations related to poor adherence account for approximately $100 billion[97].

In general, adequate adherence to treatment favours its success, while in other cases it also reduces the risk of relapse. In the White Paper on Adherence, three measures are mentioned as the most relevant when it comes to improving adherence to treatment: reviewing active prescriptions before prescribing a new drug in order to avoid duplication, multidisciplinary care and detecting the reasons for non-adherence[98].

In terms of costs, better disease control often translates into less use of emergency health services and hospitalisations, resulting in potential savings in healthcare costs compared to non-adherent patients. An example of this relates to the three most prevalent chronic conditions - diabetes, hypertension and hyperlipidaemia - which stand out as the diseases with the highest avoidable costs. Every additional dollar spent on medicines for compliant patients can generate between $3 and $13 in savings in avoidable emergency department visits and hospital admissions alone[99].

A systematic review analysed 79 studies (83% conducted in the US and 7.6% in Europe) and concluded that the annual cost of non-adherence ranged from $5,271 to $52,341 per person (Figure 52). The average annual costs per person of medication non-adherence were $6,310 for diabetes, $9,204 for cardiovascular disease, $11,052 for mental disorders, $23,317 for gastrointestinal disease and $32,866 for osteoporosis[100].

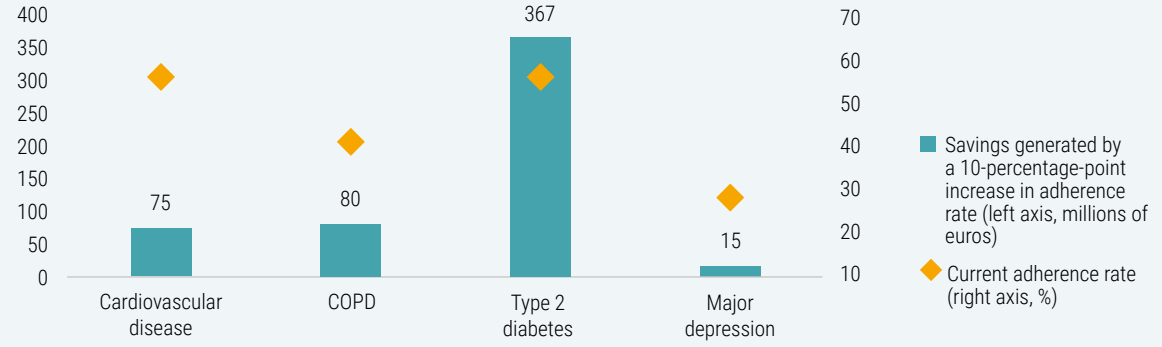
FIGURE 52. ADJUSTED ANNUAL COST OF NON-ADHERENCE TO MEDICATION, PER PATIENT, FOR DIFFERENT DISEASES ($). UNITED STATES



Source: Cutler (2018)[100]

In Spain, it is estimated that a 10% increase in adherence rates for four diseases could generate savings of more than 500 million euros in direct healthcare costs, as well as prevent 8,700 deaths from cardiovascular disease, more than 10,000 deaths and 190,000 exacerbations from COPD, 52,000 adverse events related to type 2 diabetes and 25,000 relapses from major depression (Figure 53)[101].

FIGURE 53. ESTIMATED IMPACT ON DIRECT HEALTH CARE COSTS OF A POTENTIAL 10 PP INCREASE IN THE ADHERENCE RATE. SPAIN (MILLIONS OF EUROS AND %)

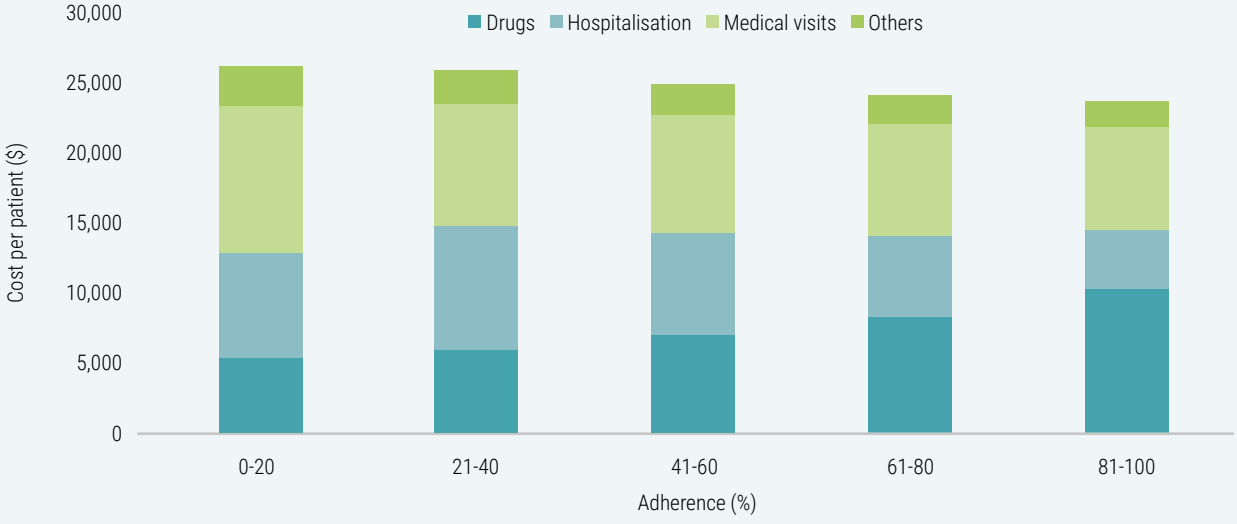


Notas: COPD: Chronic Obstructive Pulmonary Disease. Time horizon: The time horizons considered are 15 years for cardiovascular disease, 2 years for COPD, 20 years for type 2 diabetes, and 6 months for major depression.

Source Farmaindustria (2016)[101]

Several studies that disaggregate costs (in medicines, hospitalisations, medical consultations, absenteeism from work) have confirmed that increased adherence can be associated with net savings in healthcare costs, due to the offsetting effect[102, 103, 104–106, 107]. For example, a US study on diabetes involving 32,631 patients found that as patients' adherence increased, medication costs increased, but this was offset by a decrease in the costs of hospitalisation, physician consultations and other services (such as radiology, laboratory and emergency consultations), resulting in a reduction in total costs[106]. According to this analysis, a patient with 81-100% adherence costs USD 2,471 less (9.4%) than a patient with 0-20% adherence (Figure 54).

FIGURE 54. RELATIONSHIP BETWEEN ADHERENCE AND HEALTHCARE COSTS FOR PATIENTS TREATED WITH INSULIN PENS FOR DIABETES. UNITED STATES ($)

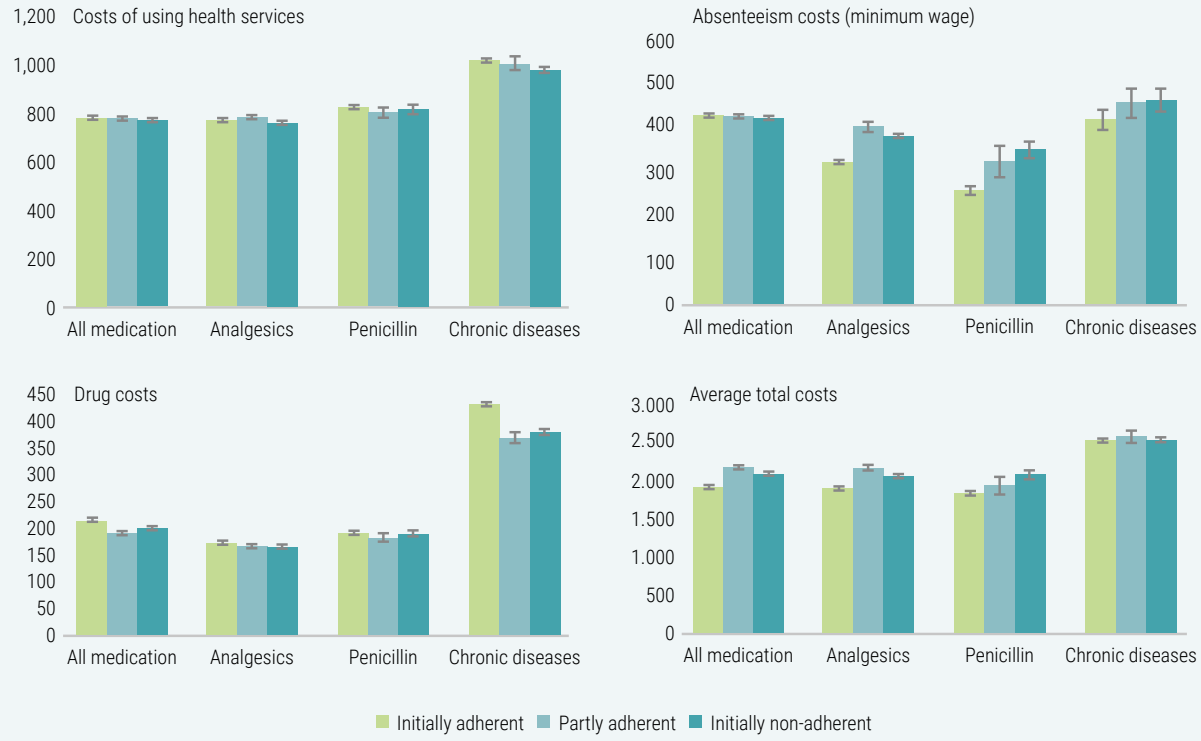


Source: Chandrau (2015)[106]

Meanwhile, another study using data from all patients over 14 years of age who received primary care in Catalonia in 2012 (a cohort of 1.7 million people) assessed the impact of initial non-adherence to treatment on the use of healthcare resources, days of absence from work and healthcare costs associated with 13 of the most prescribed medicines and/or with the highest cost associated with their use[107].

According to the results of this analysis, based on the volume of initially non-adherent patients (13%), non-adherence generated an impact of 89 million euros in total costs for the Catalan health system. Overall, although the costs of health services and medicines were higher in the group of adherent patients, this was compensated by a lower cost of work absenteeism. Therefore, on balance, total costs were lower in the adherent group, with a difference of 165 euros per patient in the non-adherent group and 242 euros compared to the partially adherent group (Figure 55)[107].

FIGURE 55. IMPACT OF NON-ADHERENCE ON AVERAGE COSTS PER PATIENT (€), BY TYPE OF MEDICATION/ DISEASE AND COST CATEGORY. CATALONIA, 2012

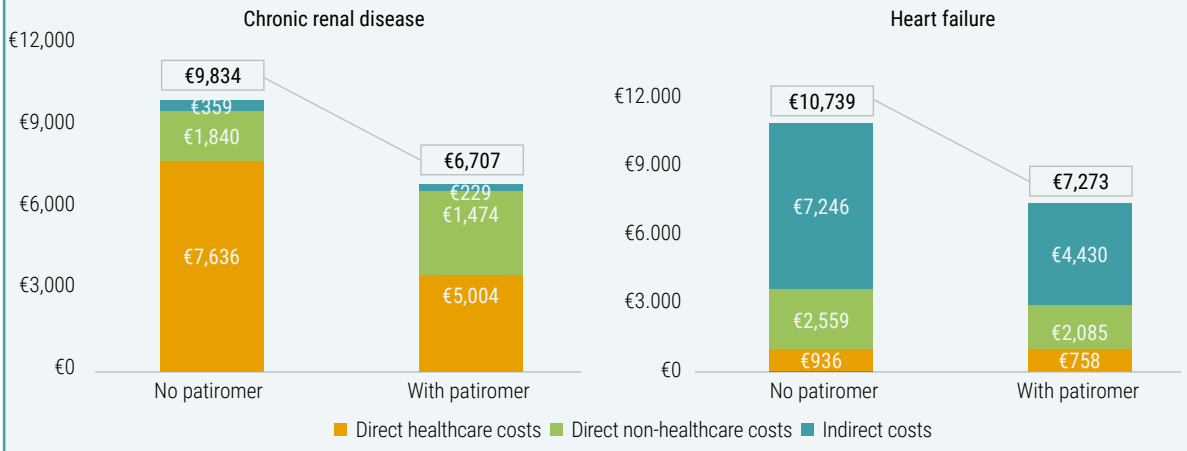


Note: Drugs included in chronic diseases: insulins and long-acting analogues (ATC A10AE); platelet aggregation inhibitors excluding heparin (B01AC); ACE inhibitors, monodrugs (C09AA); HMG-CoA reductase inhibitors (C10AA); other antiepileptics (N03AX); selective serotonin reuptake inhibitors (N06AB); adrenergics in combination with corticosteroids or other agents, excluding anticholinergics (R03AK); anticholinergics (R03BB).

Source: Own elaboration based on Aznar-Lou (2017)[107]

Another interesting recent example is found in the work of Sequera et al. (2023), who studied the economic impact of the use of patiromer in chronic kidney disease (CKD) or heart failure (HF) for the treatment of chronic hyperkalaemia in Spain. After use of the drug, a reduction of 11.7% in the need for informal care was observed in CKD and 13.7% in HF. Taking into account the reduced risk of cardiovascular events, patiromer treatment and thus maintenance of renin-angiotensin-aldosterone system inhibitors (RAASI) would have resulted in a 19.9% saving in informal care in HF and 18.5% in CKD (Figure 56)[96].

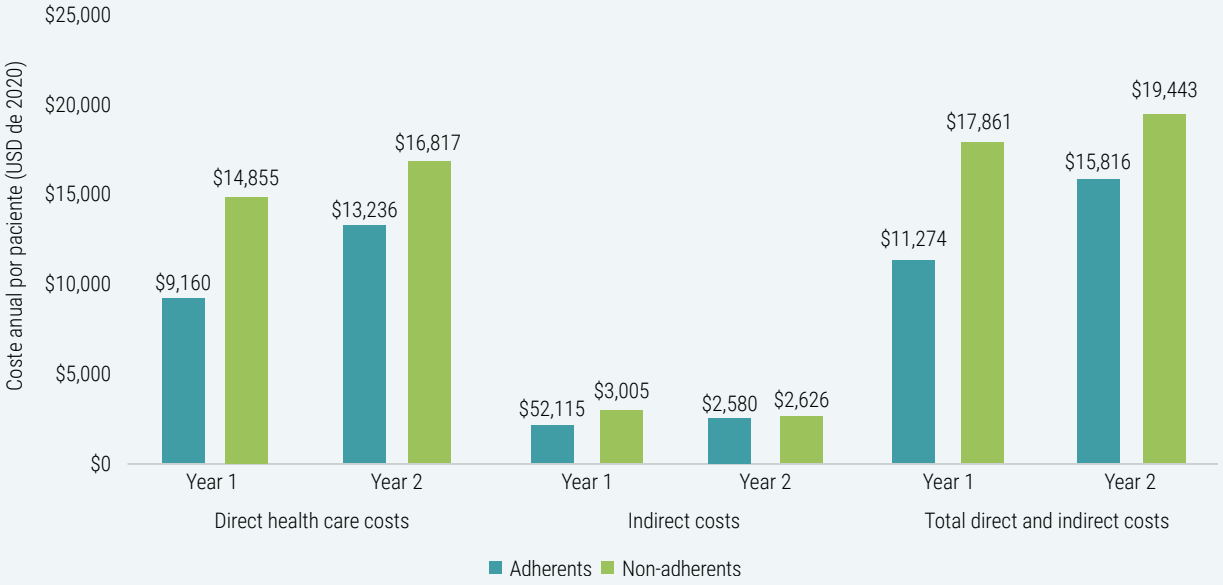
FIGURE 56. ECONOMIC IMPACT OF PATIROMER USE ON AVERAGE ANNUAL COSTS PER PATIENT WITH CHRONIC KIDNEY DISEASE OR HEART FAILURE, SPAIN, 2020



Source: Own elaboration based on de Sequera (2023)[96]

Adherence not only impacts on healthcare costs, but also on the costs associated with work productivity. Therefore, MIttal et al. (2021) studied medical and indirect costs of US patients treated with adalimumab (treatment of 10 autoimmune indications) over two years according to their adherence. Adherent patients were found to have $10,214 less expenditure on medical and indirect costs, as a result of lower health-care resource utilisation, fewer days of absenteeism and lower rates of work loss events (Figure 57)[108].

FIGURE 57. HEALTH CARE COSTS AMONG PATIENTS WITH HIGH VERSUS LOW ADHERENCE TO ADALIMUMAB, $ PER PATIENT PER YEAR, UNITED STATES, 2007-2017



Source: Own elaboration based on Mittal (2021)[108]

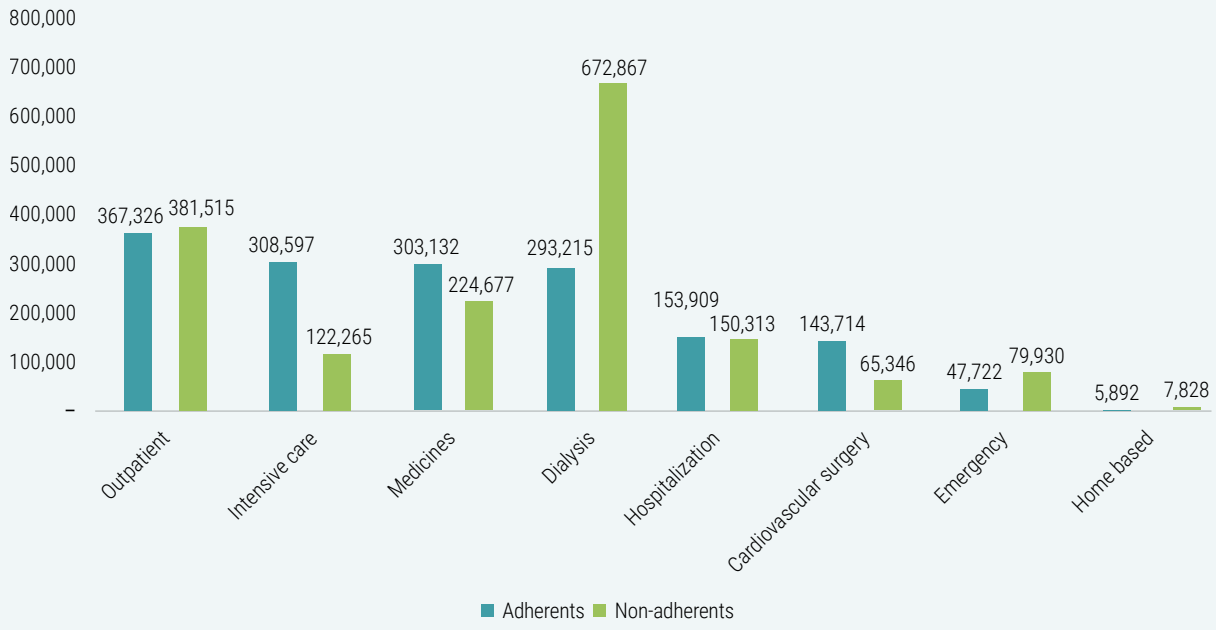
Also in the United States, Axon et al. (2020) studied for one year the costs incurred by Medicare supplement beneficiaries with cholesterol who use statins (adherence ≥ 80%). These beneficiaries had fewer outpatient and inpatient visits, compared to beneficiaries with statins.

with adherence of less than 80%. This resulted in outpatient appointment savings of $43.49/month, inpatient appointment savings of $127.57/month, and increased drug spending of $12.69/month, resulting in total savings of $157.32/month per member[109].

Continuing in the United States, Qiao et al. (2020) examined the effects of medication adherence on health care costs among low-income Medicare beneficiaries with diabetes, hypertension and/or heart failure. Among patients with a single disease, such as diabetes, patients with the lowest adherence (< 25%) had higher Medicare costs $3,125/year than patients with higher adherence (≥ 95%)[110].

Another study in diabetes also examined the costs of non-adherence to treatment in patients with type 2 diabetes mellitus between 2015 and 2016. Healthcare costs associated with drug adherence decreased by 5%, amounting to $81,144 ($1,623,597 costs with adherence and $1,704,741 without adherence), with the largest impact being on drug spending with an increase of 56% (Figure 58)[111].

FIGURE 58. AVERAGE COST PER USER OF PATIENTS WITH TYPE 2 DIABETES MELLITUS BY ADHERENCE, COLOMBIA IN DOLLARS, 2015 AND 2016



Fuente: Own elaboration based on Hoyos (2020)[111]

Continuing with diabetes, among other diseases, Qiu et al. (2021)[112] associated a reduction in medical and pharmacy costs between different adherence in diabetes, cholesterol and hypertension (based on adherence below 50%) (Table 3). If we compare adherence costs below 50% and above 99%:

- *High blood pressure medications (renin angiotensin system agents) were associated with potential savings of $2,901 per person per year*
- *High cholesterol (statins) was associated with potential savings of $1,563 per year*
- *Diabetes medicines were associated with potential savings of $3,365 per year*

In addition, each one percentage point increase in the number of days of medication adherence was associated with a decrease in the cost of health care from $21 to $46.

TABLE 3. AVERAGE MEDICAL AND PHARMACY EXPENSES IN DIABETES, CHOLESTEROL, AND HYPERTENSION BY ADHERENCE (DOLLARS), UNITED STATES, 2017-2018

ADHERENCE	DIABETES	HIGH CHOLESTEROL	HYPERTENSION
<50% (reference group)	14,643	12,895	15,837
50% – <80%	-888	-262	-421
80% – <95%	-2,164	-676	-1,575
95% – <99%	-2,910	-1,236	-2,799
99% – 100%	-3,365	-1,563	-2,901

Source: Qiu (2021)[112]

Finally, a study of inhalers and adherence has also been published. Miravitlles et al. (2020) analysed the economic impact of switching from multiple daily inhaler therapy to a single daily inhaler. The results of the study showed that a 20% increase in once-daily inhaler use boosted adherence by 52%. In addition to the clinical and quality of life improvements resulting from this change, the total savings to the NHS over a 3-year time horizon would amount to €7,082,105, of which €4,378,201 would be linked to the reduction in exacerbations due to improved adherence to treatment[113].

Adherence to pharmacological treatment can also translate into a reduction in healthcare costs, stemming from lower resource utilization. Various studies have quantified this relationship across different diseases, highlighting the importance of promoting adherence to improve both health outcomes and efficiency in medical care.

Mittal (2021)[108], Axon (2020)[109], Qiao (2020)[110], Hoyos (2020)[111] and Qiu (2021)[112]

IMPROVEMENTS IN LABOUR PRODUCTIVITY

From a societal perspective, the value of the medicine would also address the potential impact it could have on the indirect costs associated with achieving better health, such as gains in labour productivity.

Labour productivity depends on both the output generated per hour worked and the number of hours worked per employee and the number of people employed. Thus, new medicines can influence a country's economic prosperity in three ways: by increasing labour supply, by enabling more people to be able to work; by increasing the number of hours worked per person, by preventing absences from work; and by improving productivity per hour worked, since, by improving the patient's health and quality of life, higher work output is achieved.

On the other hand, labor productivity can be quantified primarily through two approaches: mortality avoidance or morbidity reduction. On one hand, numerous medications have succeeded in reducing premature mortality associated with diseases, preventing the deaths of a significant number of individuals of working age who can continue contributing to society from a labor perspective.

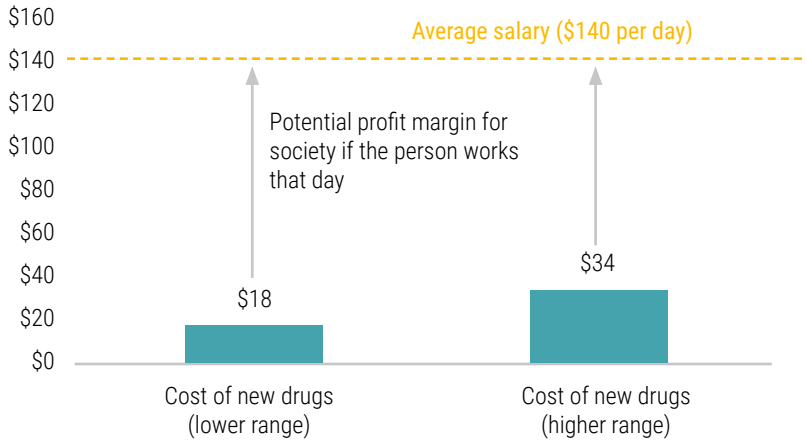
Likewise medications have made significant advancements in curing diseases, reducing symptoms, minimizing adverse effects, and lowering comorbidities, which positively impacts patient morbidity. These improvements can directly translate into a lower incidence of absenteeism (workdays lost due to illness, temporary or permanent leaves) and presenteeism (reduced workplace performance due to illness), both of which can be economically quantified.

Work losses are a substantial part of the economic burden of diseases, especially when they are chronic or involve a high degree of physical and/or mental disability. At an aggregate level, it has been estimated that, for 25 different pathologies, for every dollar of health expenditure (medical and pharmaceutical) there is an average of 2.3 dollars of work losses due to absenteeism and presenteeism in the United States[114].

In addition, several studies have tried to approximate the magnitude of the effect that new drugs have had on the labour productivity lost by society as a whole. One example is the work of Bui (2010), who estimates that each new medicine introduced on the market has reduced the average number of working years lost due to early retirement and premature mortality in Germany by 200 per year in the period 1988-2004. The cumulative gain in working years associated with the use of the medicines in that period would account for about 10% of the country's total work loss in 2004[115].

For his part, Lichtenberg included in several of his studies the impact of new drugs on labour productivity. In one of them, he estimated that each additional year of drug innovation reduces lost workdays by an average of 1% and inability to work by 1.2%. Thus, he states that, on average, reducing lost work days by 1 day between 1970 and 1998 would imply an average drug cost ranging from $18 to $34 (Figure 59)[116] . If these figures are compared with the average wage in the United States in that period ($140 per day at that time), they are 4 times lower, inferring that it is worthwhile for society to invest in new drugs to avoid lost workdays.

FIGURE 59. AVERAGE DAILY COST ASSOCIATED WITH NEW MEDICINES (LOWER AND UPPER RANGE) REQUIRED TO REDUCE LOST WORKDAYS BY 1, COMPARED TO THE AVERAGE COST OF NEW MEDICINES (LOWER AND UPPER RANGE) REQUIRED TO REDUCE LOST WORK DAYS BY 1, COMPARED TO THE AVERAGE COST OF NEW MEDICINES (LOWER AND UPPER RANGE). AVERAGE DAILY WAGE. USA 1970-1998

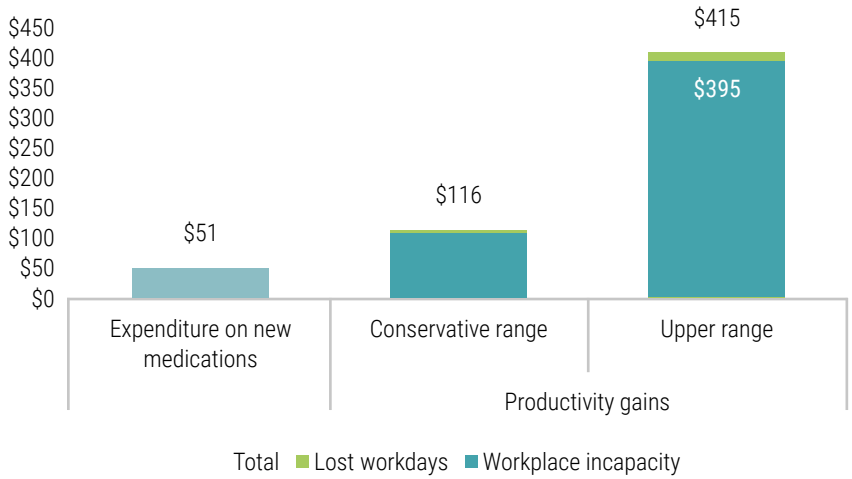


Source: Own elaboration based on Lichtenberg (2002)[116]

In later work, Lichtenberg (2005) estimated that the value of the increased ability to work in the United States attributable to new drugs is between 2.3 and 8.1 times higher than the expenditure on these new drugs. While the average annual expenditure on new drugs (for the 47 pathological conditions) is about 2.3 to 8.1 times higher than the expenditure on these new drugs.

While the estimated effect of the new medicines on the ability to work between 1982 and 1996 is about $51 per person, the author quantifies the reduced probability of being unable to work and missing work as a result of this stock of medicines at about $415 per year per employee (Figure 60)[117]. The most conservative quantification assumes that only 28% of the estimated effect on the ability to work is attributable to new medicines (the same proportion as pharmaceutical R&D investment over industry health R&D investment), with the remaining 72% attributable to other medical innovations. This would reduce annual productivity savings to $116 per employee, which would still be much higher (2.3 times) than spending on new medicines.

FIGURE 60. ANNUAL PER CAPITA COST OF DRUGS APPROVED BETWEEN 1982 AND 1996 FOR 47 CHRONIC CONDITIONS AND DERIVED ANNUAL LABOUR PRODUCTIVITY SAVINGS, USA 1996



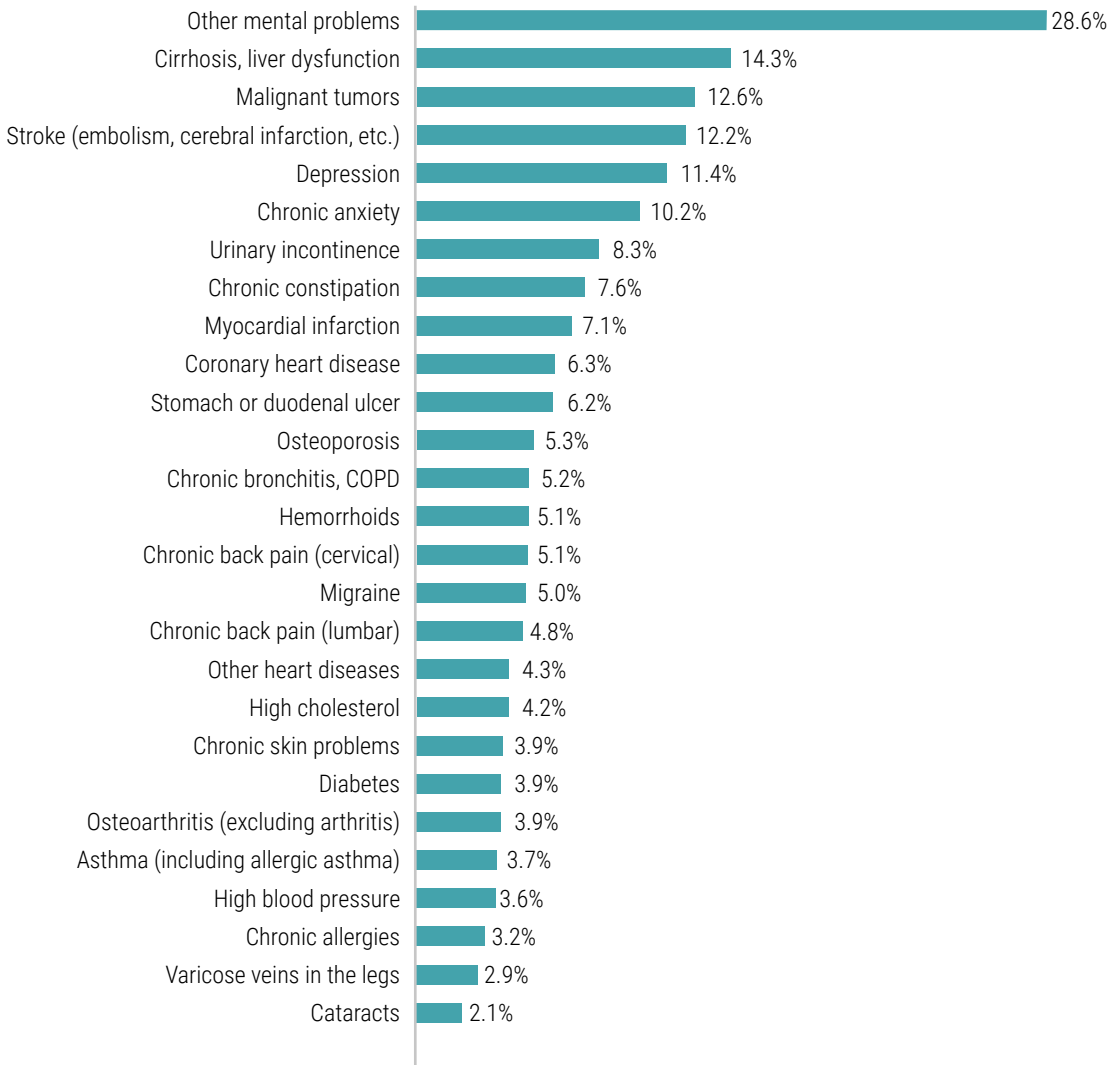
Source: Own elaboration based on Lichtenberg (2005)[117]

At the aggregate level, the above results mean that, if no new drugs had been approved for these 47 pathologies after 1983, there would have been 1.4 million more people unable to work in the United States in 1996, which in monetary terms would have translated into a loss of labour productivity for the country of about $43 billion per year ($61.5 billion in current 2015 dollars)[118].

Finally, in a 2014 paper, the author notes that the increase in the use of new medicines in the US between 1997-2000 and 2006-2010 reduced the proportion of illnesses causing work losses and the number of work days lost by 6.3% (or 0.6% per year on average)[119]. This implies that pharmaceutical innovation would be responsible for a reduction of 36.9 million lost work days, and for one-third of the reduction in the average annual rate of lost work days over the period.

Likewise, the type of chronic disease suffered influences the magnitude of lost productivity as much or more than comorbidities. According to the Spanish National Health Survey, the chronic diseases with the highest rates of work incapacity are mental illness (other mental problems 29%; depression 11%; chronic anxiety 10%), liver disease (14%), cerebrovascular diseases (stroke-stroke 12%, heart attack 7%), cancer (13%) and urinary incontinence (8%) (Figura 61)[120].

FIGURE 61. PERCENTAGE OF PEOPLE UNABLE TO WORK BY TYPE OF CHRONIC DISEASE. SPAIN 2017



Source: Own elaboration based on the National Health Survey 2017, INE[120].

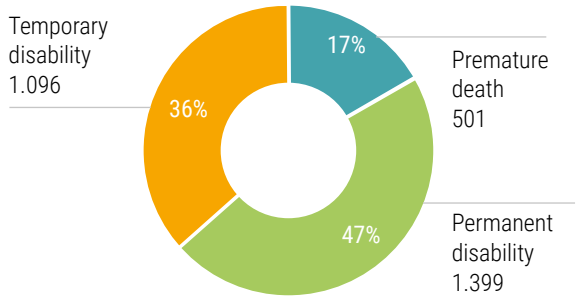
The following are some published examples of the impact of medicines on the work productivity of people with specific pathologies.

In the field of **cancer**, recent Canadian research concluded that pharmaceutical innovation increases the likelihood that cancer patients will remain in employment for 5 years after diagnosis of the disease. Innovation was measured by the number of drugs and patents approved in this period[121]. Specifically, in prostate cancer, the number of drugs marketed and patents approved during the period 1992-2010 would be associated with a reduction of 20-52% and 20-46%, respectively, in the decrease in employment income of these patients. This suggests an average wage gain of $13,500 per year associated with treatment innovation for these tumours. In breast cancer, the average gain would be $5,800 per year.

Depression is one of the illnesses that generates most productivity losses. Empirical evidence shows a high prevalence of this chronic mental illness among the working population and significant associated work losses. In the United States, workers with diagnosed depression have an average of 1.5 to 3.2 more days of sick leave per month than workers without depression, which is associated with a productivity loss of between $182 and $395 per month per person[122].

A review of the literature reveals that, in developed countries, major depression generates direct costs of between €500 and €24,000 per patient on average, and indirect costs ranging from €1,960 to €27,400, considering suicides and lost productivity due to absenteeism and absenteeism[123]. In Spain, it is estimated that mental illness as a whole is associated with work productivity losses of around €2,997 million per year, 47% due to permanent disability, 36% due to temporary disability and the remaining 17% due to premature mortality[124] (Figure 62).

FIGURE 62. COSTS OF PRODUCTIVITY LOSS ASSOCIATED WITH MENTAL DISEASES IN SPAIN IN 2002, IN MILLIONS OF EUROS

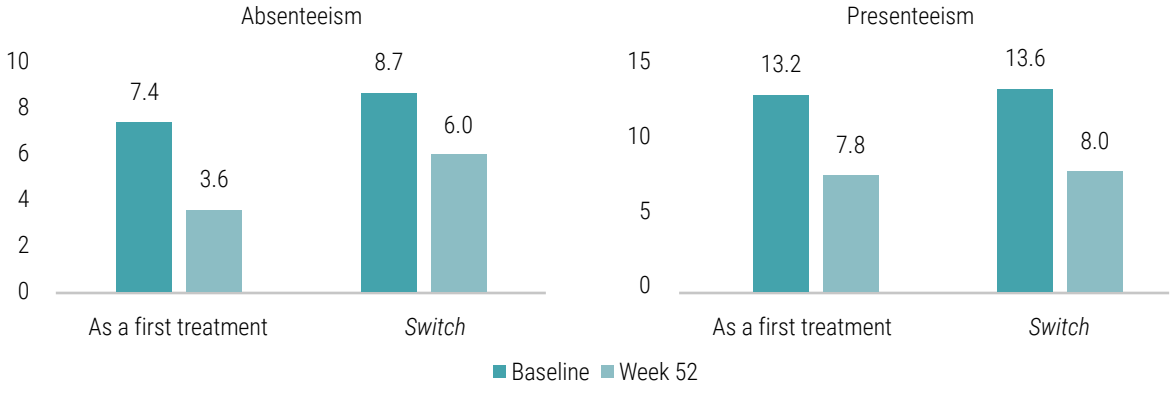


Source: Oliva-Moreno (2009)[124]

Also, in the field of depression, it has been noted that new drug treatments may have reduced the labour costs associated with the disease. It is estimated that, in the United States, In the United States, the productivity losses of people with depression were reduced by $522 per person between 1990 and 2000, mainly due to reduced absenteeism costs. That is, for every dollar invested in pharmacological treatment for depression, work losses were reduced by 0.56% dollars[125].

More recent research in Canada found that the use of a treatment for major depression over 52 weeks significantly reduced absenteeism and presenteeism, both as a first treatment and as a switch therapy (Figure 63)[126]. This translated into an economic impact from increased productivity of $111 on average ($140 if the antidepressant was the first treatment and $82 if it was a switch) per week. This translated into an economic impact from increased productivity of $111 on average ($140 if the antidepressant was the first treatment and $82 if it was a switch) per week. Cumulatively, the use of the antidepressant led to an average productivity gain of $5,681 per patient treated, generating a net saving on drug costs (which was $1,130) estimated at between $3,780 and $5,329 (Figure 64)[126].

FIGURE 63. CHANGE IN ABSENTEEISM AND PRESENTEEISM FOLLOWING 52-WEEK USE OF VORTIOXETINE FOR DEPRESSION (DAYS). CANADA, 2017



Source: Own elaboration based on Lachaine (2019)[126]

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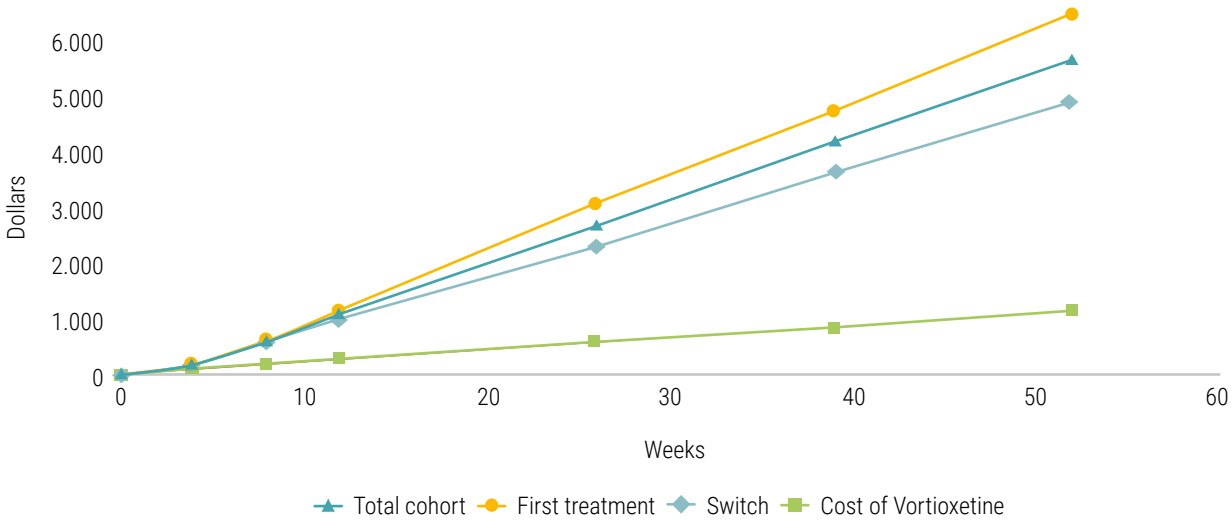
FIGURE 64. NET INDIRECT COST SAVINGS GENERATED BY THE 52-WEEK USE OF VOR- THIOXETINE FOR DEPRESSION (CUMULATIVE ECONOMIC IMPACT). CANADA, 2017



Source: Own elaboration based onLachaine (2019)[126]

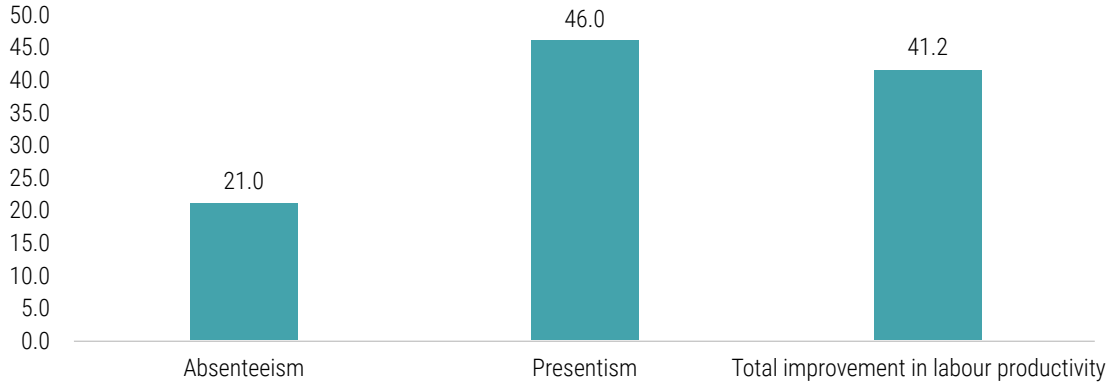
In the field of **urinary incontinence** in the United States, another study concluded that pharmacological treatment for this health problem has reduced the rate of activity limitation by 5.7 percentage points and reduced work productivity losses due to absenteeism and presenteeism by 8.9%[127].

Taking **psoriasis** as an example, an observational study in Italy estimated that the improvement in the health and quality of life of patients on biologic therapy resulted in a 71.4% reduction in the indirect costs of the disease for these patients by reducing absenteeism and presenteeism[94].

In **rheumatoid arthritis**, some studies have found that the introduction of new biologic treatments has increased drug costs, but this has been partially offset by decreases in other costs, such as hospitalisation and work loss costs. A German study found that between 2002 and 2011, indirect costs associated with RA patients decreased by 8% and 9%, depending on whether the human capital or frictional cost approach is used, respectively[128].

A recent systematic literature review and meta-analysis reported an improvement in work productivity in patients with **psoriatic arthritis** treated with specific biologic or synthetic medications at week 24, estimated at 21.0% improvement in absenteeism, 46.0% improvement in presenteeism and 41.2% improvement in work productivity (Figure 65). Based on analysis of change from baseline among patients treated with synthetic drugs, and without adjusting for placebo response, the estimated mean absolute decrease in psoriatic arthritis-related indirect costs linked to productivity was 10,688 euros per year per patient[129].

FIGURE 65. IMPROVEMENT IN WORK PRODUCTIVITY IN PATIENTS WITH PSORIATIC ARTHRITIS TREATED WITH BIOLOGIC DRUGS, WEEK 24

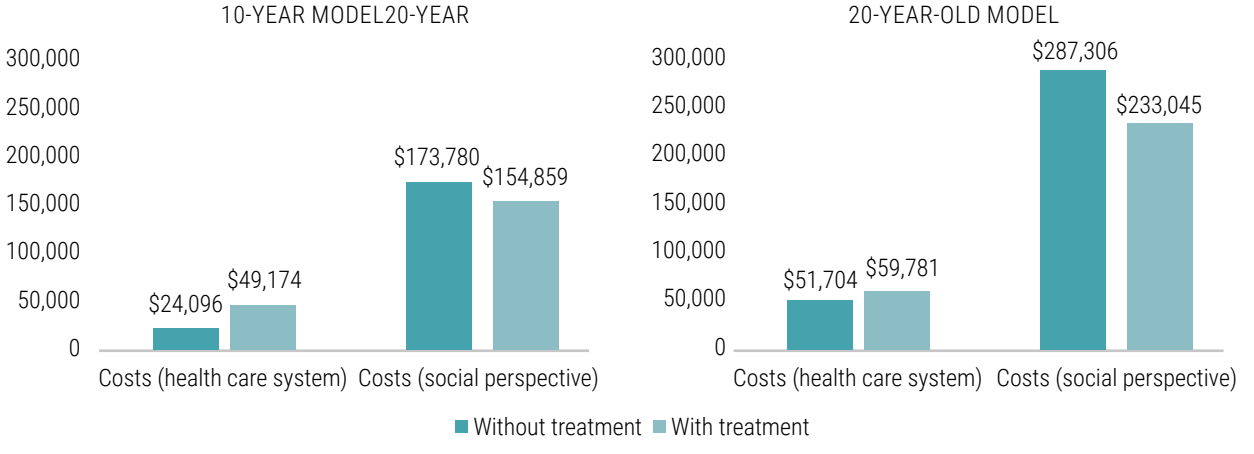


Source: Gossec (2024)[129]

On the other hand, an economic model developed to simulate the course of **Parkinson's** disease over 25 years estimated the cost savings from delaying disease progression under different scenarios. For example, delaying progression by 20% would translate into a total net monetary benefit of more than $75,000 per patient in the US, of which $15,200 is in labour productivity gains, $22,700 in monetisation of the expected QALY gain (0.45) and $38,000 in net direct cost savings[130].

In the field of **hepatitis C**, considering the social perspective, treatment would move from being cost-effective to a net cost-saving option, thanks to the lost work days avoided over the period considered, which in the 10-year model amount to 35 days and in the 20-year model to 64 days. Under treatment, social costs would be reduced by 11% and 19% compared to the no-treatment scenario in the 10- and 20-year models, respectively (Figure 66)[131].

FIGURE 66. HEPATITIS C TREATMENT COSTS FROM A HEALTH SYSTEM PERSPECTIVE AND A SOCIETAL PERSPECTIVE, 10 AND 20 YEARS, IN THE USA

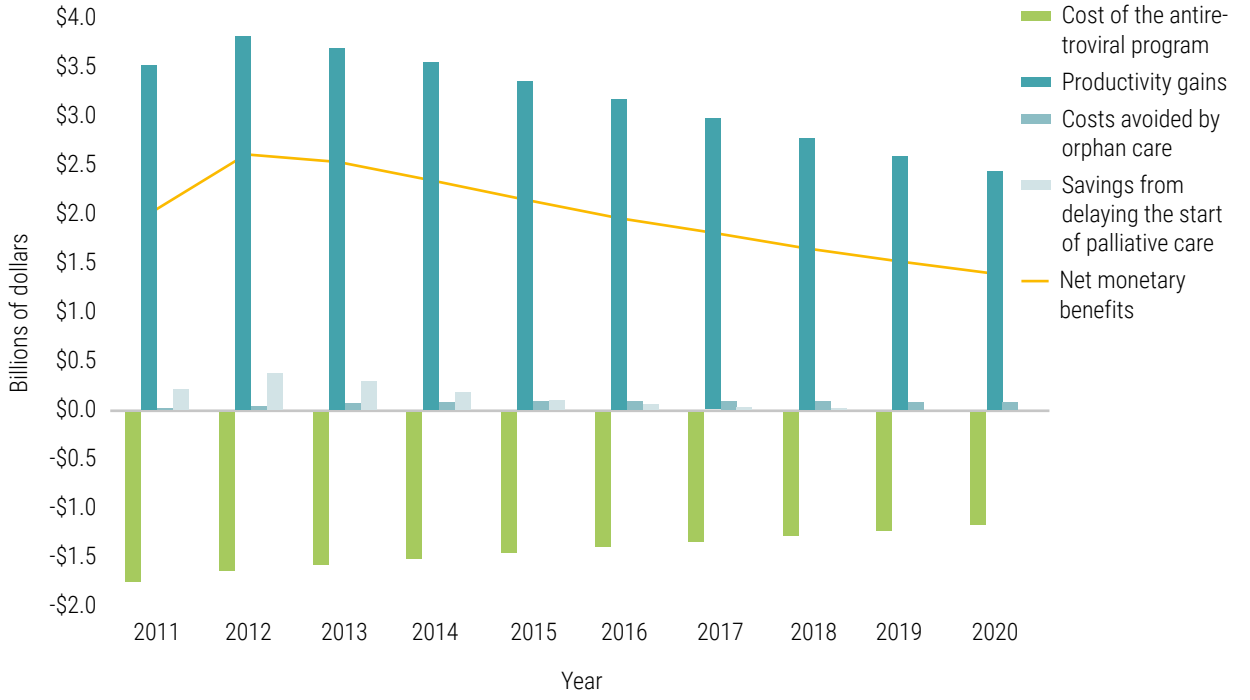


Source: Mattingly (2020)[131]

Another illustrative example of the benefit of pharmaceutical innovation on patients' work productivity can be found in the field of **HIV/AIDS**. If not properly treated, HIV/AIDS patients develop infections and other symptoms that limit their health and ability to work. In contrast, antiretroviral therapy restores physical function and extends life expectancy, allowing the patient to retain their employment and maintain their productivity[132,133]. Some studies put the return in developing countries at 1.4 times the investment in ART in the period 2011-2020

(Figure 67)[134]. In this case, treating a cohort of 3.5 million people with antiretrovirals would involve a cumulative investment of US$ 14.2 billion, but would gain US$ 31.8 billion in labour productivity, as well as avoid end-of-life costs (US$ 1.4 billion) and costs for other medication (US$ 830 million), resulting in a net saving of EUR 19.8 billion.

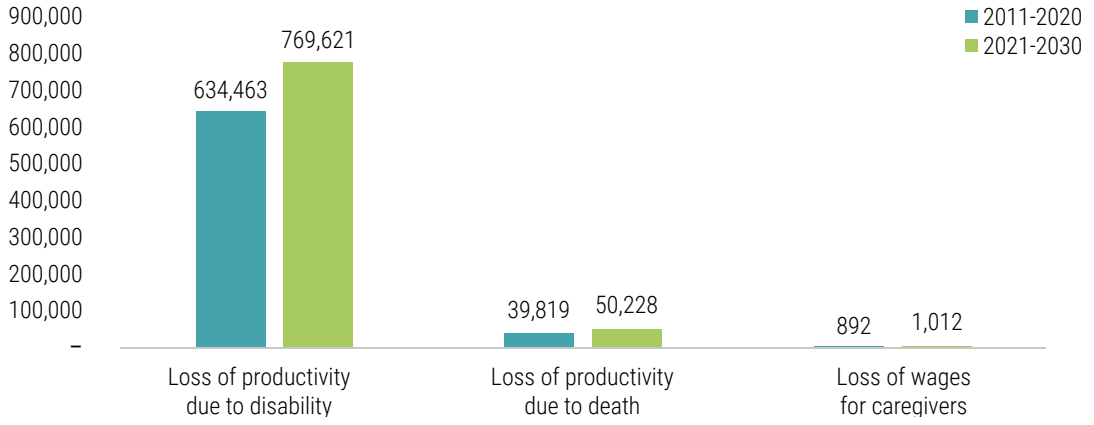
FIGURE 67. COSTS AND BENEFITS OF THE ANTIRETROVIRAL PROGRAMME APPLIED TO THE GLOBAL FUND PATIENT COHORT, 2011-2020



Source: Resch (2011)[134]

For vaccines, in low- and middle-income countries, vaccines against 10 pathogens are estimated to have averted an economic burden of US$675.175 billion in 94 low- and middle-income countries between 2011 and 2020 and US$820.861 billion between 2021 and 2030 (Figure 68)[135].

FIGURE 68. DISEASE COSTS AVOIDED IN THE VACCINATION PROGRAM AGAINST 10 PATHOGENS IN 94 LOW-AND MIDDLE-INCOME COUNTRIES, BETWEEN 2011 AND 2030 (IN MILLIONS OF EUROS)



Source: Own elaboration based on Sim (2020)[135]

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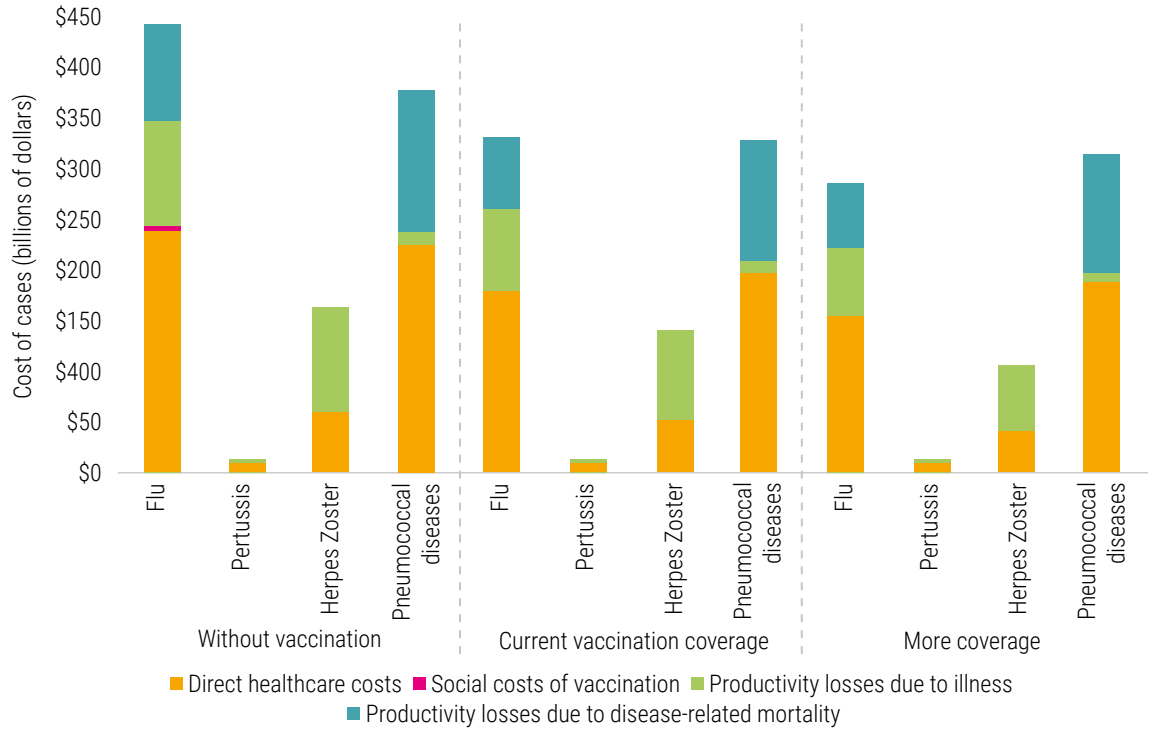
In another study in a high-income country such as the United States, it was estimated that adult vaccination could prevent 65 million cases of disease over 30 years, and that the social costs avoided by the cases would exceed the costs of vaccination by approximately US$49 billion. As can be seen in Figure 69, the higher the coverage, the lower the productivity costs for all diseases[136].

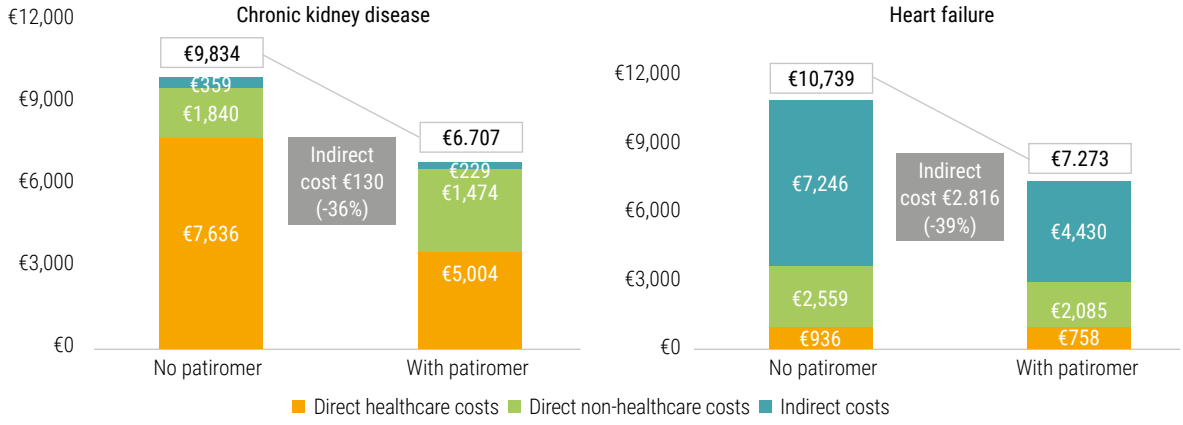
FIGURE 69. COSTS OF DISEASE AVERTED BY 30-YEAR VACCINATION PROGRAMME BY DISEASE, UNITED STATES



Source: Carrico (2021)[136]

Another example is found in De Sequera et. al. (2023), who studied the economic impact of the use of a drug (the patiromer) in patients with **chronic kidney disease or heart failure** in Spain, observing an average reduction of €130 in indirect costs (associated with premature mortality) per patient in chronic kidney disease and €2,816 in heart failure (Figure 70)[96].

FIGURE 70. ECONOMIC IMPACT OF THE USE OF PATIROMER IN CHRONIC KIDNEY DISEASE OR HEART FAILURE (AVERAGE ANNUAL COSTS PER PATIENT), SPAIN



Source: Own elaboration based on de Sequera (2023)[96]

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The results of a study simulating the incremental benefits of a **migraine** treatment (erenumab) versus standard treatment have also recently been published. The results show that prescribing the drug to the indicated population in Germany could lead to a reduction of 166 million migraine days per year and consequently reduce productivity losses by around €27 billion[137].

On the other hand, other studies have calculated that for every £1 invested in OTC medicines in the UK (a £3.3 billion market), there is a social return of £8.4, of which £1 in contributions in wages and exports, £5.4 in cost savings from avoided absence from work, and £1.9 in savings in prescription and appointment costs (Figure 71). To this should be added savings in direct health costs[138].

Finally, the economic impact of pharmaceutical innovations can also be approached from a more global point of view, taking into account the effect on the tax burden. For example, according to recent work in the cardiovascular field, the uptake of four classes of innovative medicines (direct-acting oral anticoagulants, sodium-glucose cotransporter type 2 inhibitors, severe asthma biologics, and non-peptide vasopressin antagonists) would yield an estimated productivity gain of £17.9 billion in the UK, 16.7 billion of which £16.7 billion would come from wage labour. This gain would in turn generate an estimated £5.5 billion in additional tax payments to the exchequer (assuming a 33% national tax rate on these productivity gains)[139]. This additional tax revenue would offset approximately 42% of the incremental costs, representing a return on investment.

FIGURE 71. ECONOMIC AND SOCIAL IMPACT OF NON-PRESCRIPTION MEDICINES PRESCRIPTION, UNITED KINGDOM

Source: Own elaboration based on Frontier Economics (2023)[138]

From a societal perspective, the value of a medicine is also associated with its impact on indirect costs, such as patients' labour productivity gains resulting from their improved health status. New medicines can influence a country's economic prosperity by increasing labour supply, increasing hours worked per person and improving productivity per hour worked. Recent studies have exemplified the positive economic impact of specific medicines on various diseases, which can offset or even exceed the costs of investment in medicines.

Gossec (2024)[129], Frontier Economics (2023)[138], de Sequera (2023)[96], Sim (2020)[135], PwC (2020)[139], Carrico (2021)[136], Seddik (2021)[137]

THE POWER OF VACCINES

Vaccines are considered one of the most cost-effective public health interventions in the world[140,141]. Their benefits typically far outweigh their development and implementation costs, especially when considering their long-term economic and social impact[142].

The impact of vaccines can be measured not only in health terms, such as morbidity and mortality avoided through disease eradication or symptom reduction, but also in economic terms, through savings in direct health costs, labour productivity gains and other positive externalities generated in the short and long term, which in turn contribute to social and economic development[143–145]. Globally, vaccination programmes generate savings 5 times greater than other preventive measures such as water chlorination[146].

More than 40 vaccines are currently available for the prevention of 25 preventable diseases. There is evidence that traditional vaccines (polio, smallpox, measles, etc.) generated significant net savings, sparing the health system and society as a whole both direct and indirect resources. In contrast, vaccines that appeared later (hepatitis, human papilloma, etc.) emerged from more complex processes and are therefore more costly, although most of them remain cost-effective[147].

Vaccination in children and adults, including at older ages and for certain risk groups, is especially relevant to reduce the burden of disease and mortality from different diseases in an efficient manner[148,149]. The pandemic caused by COVID-19 has highlighted the importance of safe and efficient vaccination as the most effective and efficient measure for disease control[150].

The following are examples of published results on childhood and adult vaccines in general and for specific diseases:

- *A study has estimated the long-term economic cost-effectiveness of current vaccination programmes and increased coverage against four preventable diseases in older adults in the United States. Vaccination is expected to prevent 65 million cases of disease over 30 years, and the social costs of averted cases would exceed the costs of vaccination by about US$49 billion (social CBR of 1.4). If vaccination coverage for four diseases were increased, an additional 33 million cases of disease could be prevented, leading to additional social savings of $13 billion over the same time horizon136[136].*

Regarding childhood vaccination:

- *Routine childhood vaccination against 13 preventable diseases in the 2017 US birth cohort was associated with $55.1 billion in avoided healthcare payer costs, which translates to a benefit-cost ratio (BCR) of 7.5 and also generated $13.7 billion (BCR of 2.8) in avoided costs from a societal perspective[151].*
- *For every $1 invested in the United States in an infant immunisation programme with diphtheria, tetanus and pertussis vaccine, a total of $27 is saved in the long run, of which $9 is direct health cost savings to the system[152].*
- *In Spain, it is estimated that for every euro invested in childhood vaccination, 22 euros are saved in direct and indirect costs. Thus, the savings generated by the 94 million euros invested in vaccination by the NHS in 2016 are estimated at 2,068 million euros[153].*
- *The use of hexavalent vaccine offering protection against six childhood diseases, including diphtheria, tetanus, pertussis, polio, Haemophilus influenzae type b and hepatitis B (DTaP-IPV-Hib-HepB) over pentavalent induces a cost reduction of US$36.22 per infant or $9,236,417 in total for the entire birth cohort of 260,500 children in Korea [154].*

- *A study in Catalonia showed that childhood pertussis vaccination generated average savings of 107.9 euros per case averted, and that the average direct costs of a vaccinated patient (191 euros) were significantly lower than the average costs of an unvaccinated patient (3,551 euros)[155].*
- *Vaccination with the combined diphtheria, tetanus and pertussis (Tdap) vaccine was cost-effective at $7,601/QALY in pregnant women in the United States, resulting in a decrease of 22 infant deaths, 11 cases of infant encephalopathy, 2,018 infant hospitalisations, 6,164 infant pertussis infections and 8,585 maternal pertussis infections, with an increase of 19,489 QALYs[156].*

Regarding vaccination against measles and rubella:

- *Measles and rubella vaccination yields enormous benefits. In fact, measles is the most cost-effective vaccine: it is estimated that every dollar invested in measles vaccine yields a return on investment of $58[157].*
- *A recent study showed that increasing coverage above the reported trend in 2018 is a cost-effective vaccination strategy in most low- and middle-income countries for both measles and rubella[158].*

Regarding vaccination against chickenpox:

- *In Aragon, it is estimated that vaccinating children under 1 year of age and the entire population affected by chickenpox would have resulted in savings of 1.3 million euros between 2004 and 2014[159].*
- *A study in Slovenia considered different strategies for childhood varicella vaccination versus non-vaccination over a 50-year period. All strategies proved to be efficient at the incremental cost-effectiveness ratio (ICER) threshold for Slovenia (€25,000/ QALY), with ICERs ranging from €11,608 per QALY to €15,284 per QALY compared to non-vaccination. From a societal point of view, all vaccination strategies resulted in savings compared to the non-vaccination strategy, providing more QALYs at a lower cost[160].*

Regarding smallpox eradication and polio eradication efforts:

- *Smallpox eradication has prevented 40 million deaths worldwide and saved $2 billion annually[161]. Recently, the positive impact of historical smallpox vaccination on longevity and economic well-being in terms of disability and occupational attainment of three generations in Sweden has been demonstrated. Specifically, smallpox vaccination increases the total and disability-free life expectancy of the first generation by 11 years and improves their occupational attainment by 10%[162].*
- *Polio eradication efforts have saved the world more than $27 billion in health costs since 1988. In addition, sustained polio eradication over time is projected to generate an additional $14 billion in savings through 2050, compared to the cost to countries of indefinitely controlling the virus[163].*

Regarding vaccination against meningococcus and pneumococcus:

- *A cost-effectiveness analysis of childhood vaccination with the four-component meningococcal B vaccine (4CmenB) in England has shown that, when the overall burden of invasive serogroup B meningococcal disease is considered comprehensively, childhood 4CMenB vaccination can be cost-effective[164].*
- *Pneumococcal vaccination in adults over 50 years of age in Finland is estimated to have generated savings of €218 million in the period 2012-2016[165].*
- *The results of a cost-utility analysis showed that the vaccination strategy with the pneumococcal*

conjugate 20-valent vaccine (PCV20) is a dominant option compared to the sequential regimen (PCV15 + PPSV23) in the Spanish adult population over 60 years of age, resulting in direct cost savings of 85.7 million euros over 10 years[166].

Regarding hepatitis vaccination:

- *The implementation of a universal hepatitis A vaccination system in the USA in 2006, compared to the previous coverage of high-risk individuals, resulted in total cost reductions by half, preventing 259,776 infections, 4,781 hospitalisations and 228 deaths each year*[167].
- *Hepatitis B vaccine avoids long-term costs. According to a study in Italy, during the first 20 years of vaccination, the costs of vaccination are similar to the net savings generated for the system. However, over a period of 60 years, a saving of 2.78 euros is generated for every euro invested in vaccines*[168].

Regarding rotavirus vaccination:

- *The introduction of universal rotavirus vaccination in 2013 in a region in southern Italy has generated annual savings of €1.1 million, and reductions of 45% in hospitalisations for gastroenteritis caused by rotavirus*[169]*. In Finland, the same action in children under 5 years of age resulted in annual net benefits of 2.2 million euros (33 euros per vaccine) and 93% reductions in hospitalisations for gastroenteritis over a 5-year period*[170].
- *Prevention of rotavirus gastroenteritis has a marked positive impact on parental wages and government tax revenues, with benefits extending throughout the economy. In addition, universal mass vaccination against rotavirus can help reduce health service utilisation during and after the SARS-CoV-2 pandemic*[171].
- *From a societal perspective, it was estimated that in the United States, the rotavirus vaccination programme for all children under 5 years of age from 2011 to 2015 saved approximately $2 billion primarily related to hospitalisations averted, followed by outpatient visits for acute gastroenteritis from all causes and physician visits averted*[172].

Regarding Hib vaccination:

- *Vaccinating one million people against Hib, in middle-income countries, would prevent 5,494 deaths at an incremental cost of between US$91 and US$369 per disability-adjusted life-years (it would therefore be highly cost-effective)*[173].
- *A study evaluating Hib vaccination has reported that, between 2011 and 2020, Hib vaccination has averted $53.6 billion in disease costs, $6.4 billion in life years of disability averted, estimating the global economic and social value of Hib vaccination at $820 billion*[174].

Regarding vaccination against human papillomavirus (HPV):

- *HPV vaccination of 58 million women under 12 (universal coverage) in 179 countries would prevent 690,000 cases of cervical cancer and 420,000 deaths over time and is cost-effective in 87% of countries (156 out of 179)*[175].
- *In Spain, the vaccination strategy with gender-neutral non-avalent HPV vaccine was compared with vaccination for females only, resulting in an ICER of 34,040 euros/QALY*[176].

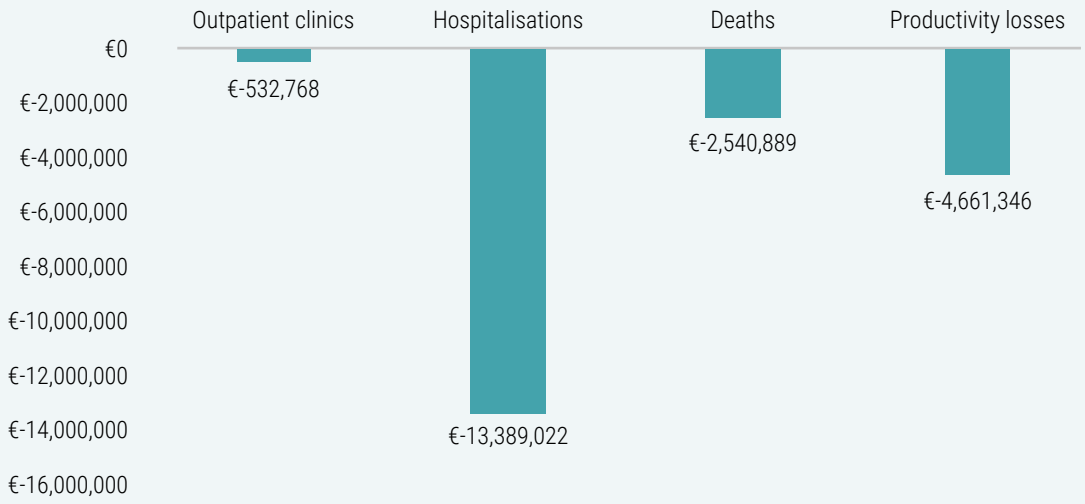
Regarding influenza vaccination in adults:

- *In 5 countries in Europe, replacing trivalent influenza vaccines with quadrivalent vaccines would generate savings of €242 million over 10 years, through reduced hospitalisations and doctor visits, and increased labour productivity*[177]*. In Spain, this would result in 40,000 QALYs gained over a patient's lifetime, and would avoid 76,375 cases, 1,674 hospitalisations and 745 deaths, at an in-*

cremental cost of 8,748 euros per QALY from a societal perspective, representing a cost-effective option[178].

- *It has been estimated that replacing trivalent influenza vaccines with quadrivalent vaccines in all eligible patients with current vaccination coverage in Spain could save €532,768 in outpatient visit costs, €13 million in hospitalisation costs and €3 million in costs of influenza-related deaths per year. From a societal point of view, a further €5 million per year could be saved in costs associated with lost productivity (Figure 72)[179].*

FIGURE 72. IMPACT OF THE REPLACEMENT OF TRIVALENT INFLUENZA VACCINES WITH QUADRIVALENT VACCINES, SPAIN



Source: Crépey (2021)[179]

- *The use of influenza vaccine with MF59 adjuvant in the population over 65 years of age in Spain would generate savings of 82 million euros, with a benefit/cost ratio (BCR) of 12.83[180].*
- *When the relative efficacy of the adjuvanted versus standard flu vaccine is 34.6% in the Spanish adult population, the incremental cost per QALY gained was €2,240 for the MF59 adjuvanted vaccine on the payer side, while from society's perspective, the MF59 adjuvanted vaccine was cost saving compared to the standard[181].*
- *High-dose tetravalent inactivated influenza vaccine compared to an adjuvanted trivalent inactivated vaccine strategy in the 65+ population in Spain is associated with an ICER of €24,353/QALY. In addition, high-dose inactivated trivalent influenza vaccine could save €28 million per year through averted cardiorespiratory events[182].*

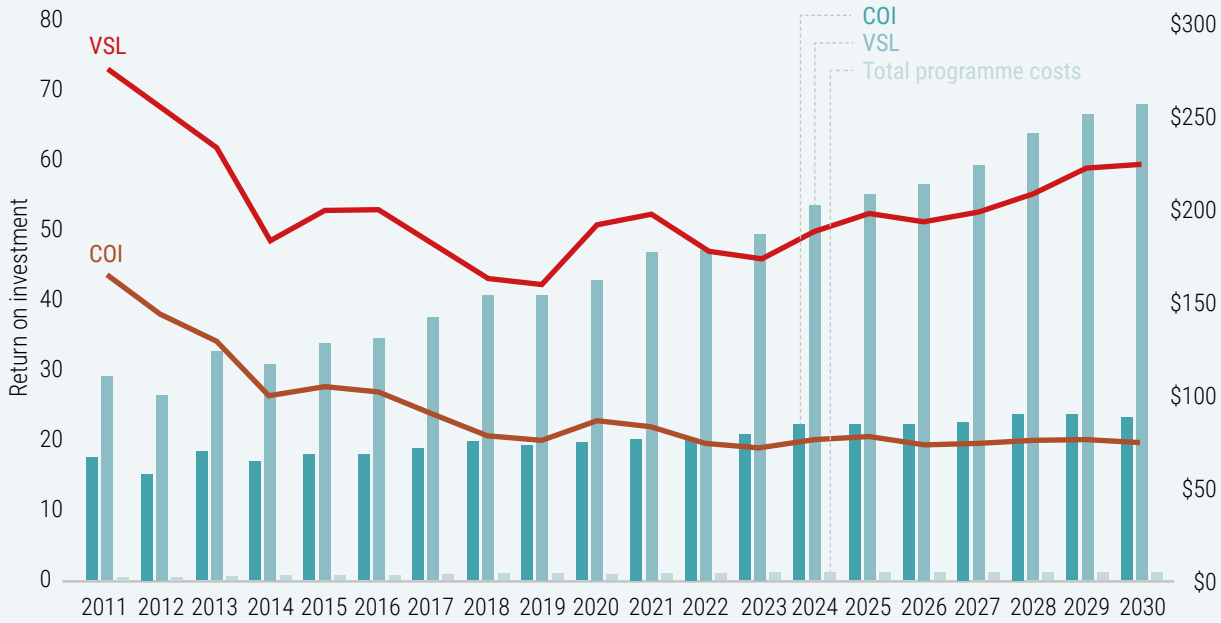
Regarding vaccination programmes in low- and middle-income countries:

- *The introduction of 6 vaccines (pneumococcal, Hib, rotavirus, pertussis, measles and malaria) in 72 of the world's poorest countries would save 6.4 million lives, prevent 426 million infections, and save US$6.2 billion in treatment costs and US$145 billion in costs related to lost productivity over the period 2011 to 2020[183].*
- *Similarly, vaccination against 10 diseases in 73 low- and middle-income countries, carried out in the period 2001 to 2020, is estimated to prevent 20 million deaths, and save 350 billion euros in disease costs,*

representing a social and economic value of 850 billion euros, as a result of increased life expectancy with improved quality of life184[184].

- *One study evaluated the return on investment of vaccination programmes against 10 pathogens. Using the cost-of-illness (COI) approach, for every $1 invested in vaccination, up to $26.1 in savings were generated. Using the Value of a Statistical Lifetime (VSL) approach, for every dollar invested in vaccination, up to $52.2 in savings were generated[135]. For the 94 low- and middle-income countries analysed between 2011 and 2030, the net benefit of vaccination programmes has been estimated at $1,445.3 billion and $3,371.5 billion, using the IOC and VSL approaches, respectively (Figure 73).*

FIGURE 73. RETURN ON INVESTMENT (RATIO OF NET BENEFITS TO COSTS) AND ECONOMIC BENEFITS TO COSTS OF IMMUNISATION PROGRAMMES (IN BILLIONS) FOR 94 COUNTRIES LOW- AND MIDDLE-INCOME COUNTRIES, 2011-30



Notes: Ten pathogens (Haemophilus influenzae type b, hepatitis B, human papillomavirus, Japanese encephalitis, measles, Neisseria meningitidis serotype A, Streptococcus pneumoniae, rotavirus, rubella and yellow fever) have been analysed. The economic costs and benefits of immunisation programmes are expressed in billions of 2018 US dollars.

Abbreviations: COI: cost of illness approach; **VSL:** value of a life approach.

Source: Sim (2020)[135]

Regarding COVID-19 vaccines:

- *Various literature reviews have shown that COVID-19 vaccination saves costs or is cost-effective compared to non-vaccination, leading to the conclusion that COVID-19 vaccination strategies are economically favorable across a wide range of countries and population groups[150,185].*
- *A study in Catalonia evaluated the cost-benefit ratio (CBR) of COVID-19 vaccination from January 2021 to September 2021. The vaccination costs were estimated at 137 million euros, which are offset by the positive impact of vaccination, with a total benefit of 470 million euros. The reported CBR is 3.4 from the social perspective and 1.4 from the healthcare system perspective. The social benefits of vaccination are estimated at 116.67 euros per vaccine dose, of which 19.93 euros correspond to benefits from the healthcare system perspective186[186].*
- *In a study conducted in the Basque Country, it was demonstrated that by preventing severe disease-related outcomes, COVID-19 vaccination resulted in monetary savings of 26.44 million euros*

in the first half of 2021, with an ICER of 707 €/QALY. Additionally, the analysis by comorbidities showed that vaccines were considerably more cost-effective in individuals with preexisting conditions[187].

- *Another study reported that vaccinating approximately 70% of the Spanish population, with a conservative efficacy estimate of 70% and two doses, would result in 5,132 euros (4,926-5,276) per QALY gained*[188].

Child and adult vaccination has been shown to cost-effectively reduce the burden of morbidity and mortality from various diseases in different countries. For every dollar invested in childhood vaccination, 7.5 dollars are generated in benefits from the healthcare payer's perspective and 2.8 dollars in additional social benefits. In Spain, for every euro invested in COVID-19 vaccination, benefits equivalent to 1.4 euros are generated from the healthcare system's perspective and 3.4 euros from the social perspective.

Carrico (2021)[136]; Carrico (2022)[151]; López (2021)[186]; Beck (2021)[164]

3

HEALTH OUTCOMES AND QUALITY OF LIFE

The evolution of innovative medicines has played a crucial role in the progress of human health. From the medicinal application of plants that accompanied our ancestors to today's advanced therapies of personalised genetic modification, continuous improvement in drug innovation has been intrinsically linked to the advancement of human well-being.

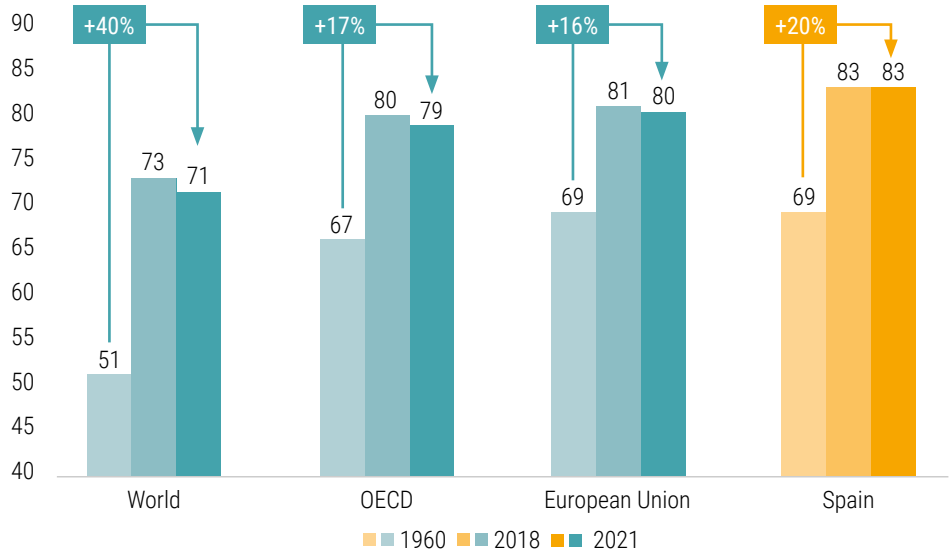
This chapter provides a multitude of illustrative examples of how the use of innovative medicines has contributed to improving the health and quality of life of people with different diseases, generating social value. In addition, an analysis is made of the evolution of life expectancy and mortality, focusing specifically on the case of Spain.

LIFE EXPECTANCY AND MORTALITY

Over the past 60 years, life expectancy at birth has grown steadily throughout the world[189]. Globally, life expectancy rose from 51 years in 1960 to 71 years in 2021, an increase of 40%. The countries of the European Union, which started from a better level (69 years in 1960), saw their life expectancy at birth increase by 16% to 80 years in 2021. It should be noted that the pandemic caused by COVID-19 has resulted in 14.9 million excess deaths worldwide in 2020 and 2021, leading to a drop in life expectancy at birth during those years.

In the case of Spain, this increase has been 20%, reaching a life expectancy at birth in 2021 of 83 years (Figure 74). However, Spain is no longer in the top 3 countries with the highest life expectancy, being overtaken by South Korea, Singapore and Australia[189].

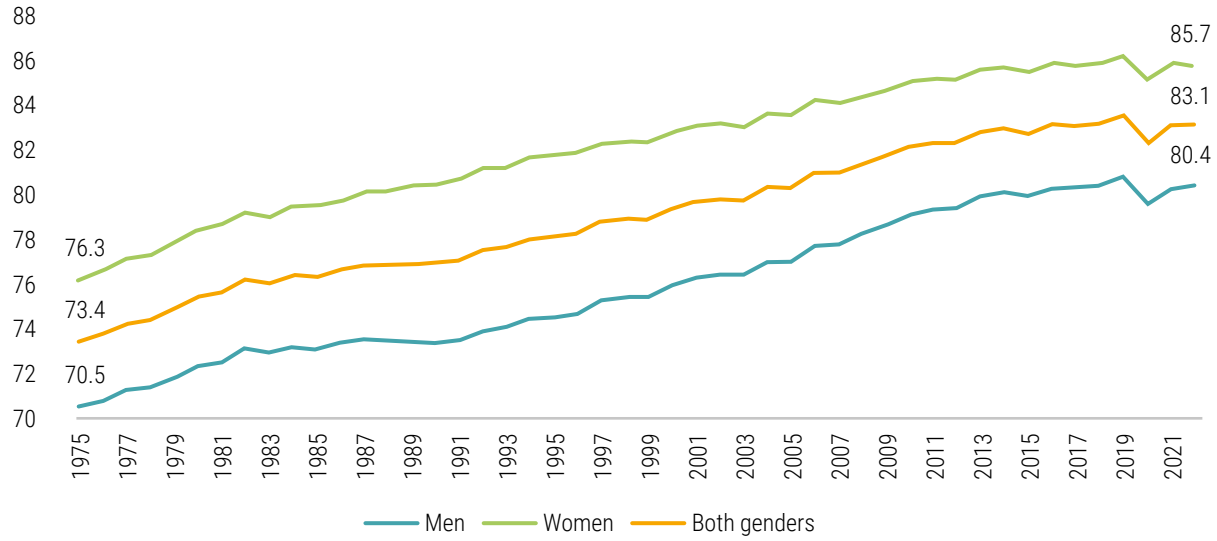
FIGURE 74. LIFE EXPECTANCY AT BIRTH IN THE WORLD, OECD, EUROPEAN UNION AND SPAIN, 1960-2021



Source: Own elaboration based on World Bank[189]

According to gender, life expectancy at birth for women continues to be higher than for men, although the trend is for the difference to become smaller each year. In Spain, this indicator currently stands at 85.7 years for women, which is 5.4 years higher than for men (Figure 75)[190].

FIGURE 75. EVOLUTION OF LIFE EXPECTANCY AT BIRTH IN SPAIN, BY GENDER, 1975-2022

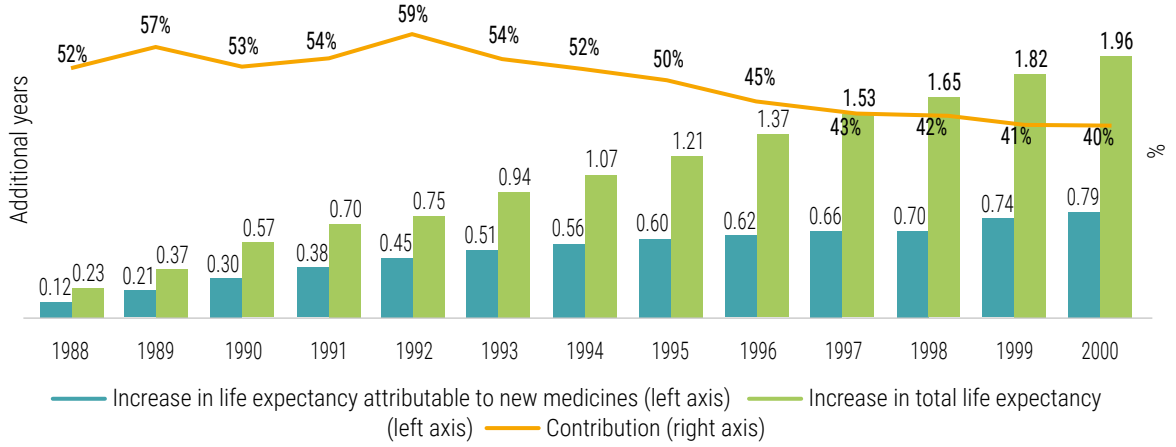


Source: Own elaboration based on INE[190]

In the first decades of the 20th century, the increase in life expectancy at birth was mainly explained by public health actions derived from knowledge about the specific cause of infectious diseases. This included measures such as improved water supply and proper sewage disposal. Later, gains in longevity were attributed to factors such as increased education, favourable socio-economic conditions and healthy lifestyles. In addition, advances in medical care, prevention and, notably, pharmaceutical innovation were recognised as key elements in the increase in life expectancy in recent decades[191–193].

Frank Lichtenberg is one of the authors who has most extensively studied the impact of pharmaceutical innovations on increasing life expectancy and decreasing mortality. One of his early works showed the impact of pharmaceutical innovation on the increase in life expectancy at birth in 52 countries. According to his study, the marketing of 864 new drugs between 1986 and 2000 was associated with an increase in life expectancy of 0.79 years, representing 40% of the total increase in life expectancy during that period, which was 1.96 years (Figure 76). This decrease in mortality was mainly caused by pathologies associated with the circulatory system, neoplasms and respiratory diseases[194].

FIGURE 76. CONTRIBUTION OF NEW MEDICINES TO THE AVERAGE INCREASE IN LIFE EXPECTANCY AT BIRTH IN 52 COUNTRIES, 1988-2000



Source: Lichtenberg (2003)[194]

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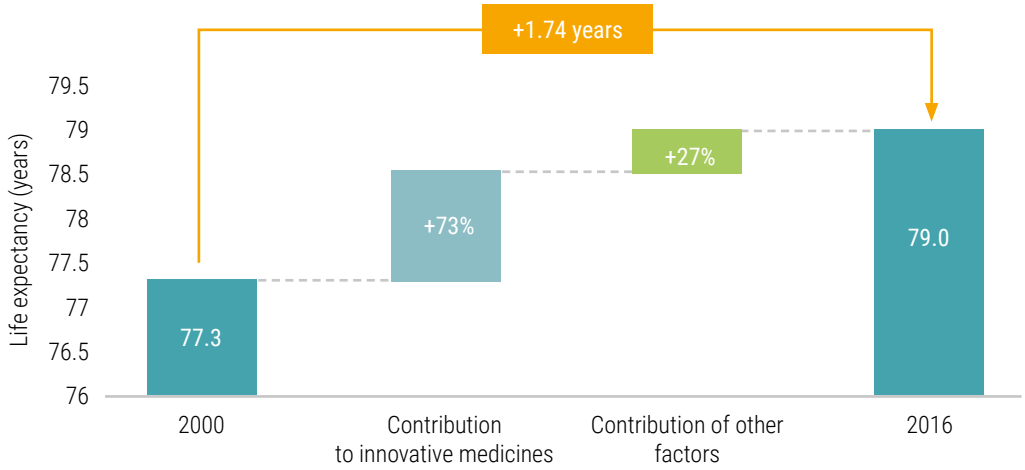
Another study by Lichtenberg, carried out in 30 developed countries, attributes an even greater contribution to population longevity to pharmaceutical innovation. The paper estimates that approximately 73% of the improvement in life expectancy at birth between 2000 and 2009 could be attributed to new medicines, i.e. 1.27 of the 1.74 years gained would be attributable to drugs marketed after 1990[195].

A recent study by the same author analysed the impact of pharmaceutical innovations on life expectancy at birth in 26 high-income countries, including Spain. The study estimates that more than 73% of the improvement in life expectancy at birth in the period 2006-2016 can be attributed to the arrival of new medicines, i.e. of the 1.7 years that life expectancy increased during that period, new medicines would have contributed 1.2 years (Figure 77)[57].

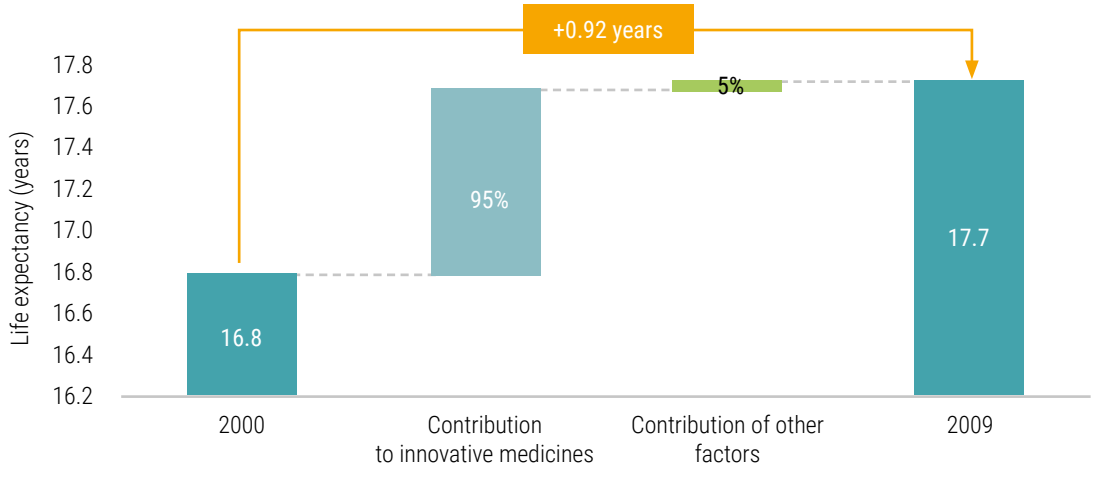
FIGURE 77. CONTRIBUTION OF INNOVATIVE MEDICINES AND OTHER FACTORS TO LIFE EXPECTANCY IMPROVEMENT AT BIRTH, 26 COUNTRIES 2006-2016



Source: Lichtenberg (2022)[57]

Lichtenberg also analysed how drugs impact life expectancy at age 65 in 30 developed countries. The paper estimates that approximately 95% of the improvement in life expectancy at age 65 between 200 and 2009 could be attributed specifically to new drugs, i.e. 0.87 of the 0.92 years gained were attributable to drugs marketed after 1990 (Figure 78)[195].

FIGURE 78. CONTRIBUTION OF NEW MEDICINES AND OTHER FACTORS TO LIFE EXPECTANCY IMPROVEMENT AT AGE 65, OECD 2000-2009



Source: Lichtenberg (2014)[195]

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Other studies by the author have replicated this methodology for different countries and periods, obtaining different magnitudes of the effect of pharmaceutical innovation. These new drugs may have contributed to an increase in life expectancy ranging from 20% to 83%, depending on the country and age range considered (Table 4).

TABLE 4. STUDIES ON THE IMPACT OF MEDICINES ON LIFE EXPECTANCY, LONGEVITY AND MORTALITY

REFERENCE	COUNTRY	PERIOD	VARIABLE	VARIATION ATTRIBUTABLE TO NEW MEDICINES
Lichtenberg (2003)[194]	52 countries	1986-2000	Life expectancy at birth	+0.79 years (40% of the total increase in the period)
Lichtenberg (2008)[196]	Australia	1995-2003	Longevity (average age at death)	+1.3 years (65% of the total increase in the period)
Lichtenberg (2010)[197]	Germany	2001-2007	Life expectancy at birthr	+0.43 years (31% of the total increase in the period)
Lichtenberg (2013)[53]	United States	1996-2003	Life expectancy in the elderly	0.28 years to 0.37 years (68% - 78% of the increase over the period)
Lichtenberg (2014)[195]	30 OECD countries	2000-2009	Life expectancy at birth	+1.27 years (73% of the total increase in the period)
Lichtenberg (2014)[48]	France	2000-2009	Life expectancy	+0.29 years (20% of the total increase over the period)
Lichtenberg (2014)[50]	Turkey	1999-2008	Life expectancy	+3 years (83% of the total increase in the period)
Lichtenberg (2015)[198]	United States	1991-2004	Life expectancy at birth	Between 0.48 and 0.54 years (20% - 23% of total increase over the
Lichtenberg (2020)[199]	South Korea	1995-2015	Longevity (average age at death)	+1.71 years (20.4% of the total increase in the period)
Lichtenberg (2022)[57]	26 high-income	2006-2016	Life expectancy at birth	+1.23 years (73% of the total increase in the period)

Source: Own elaboration based on different studies by Lichtenberg (see detailed references in the table)

A study published in 2019 analysed the impact of the introduction and use of pharmaceutical innovation on reducing the number of years of life lost before three different ages (85, 70 and 55 years) in 27 countries. The impact of the launch of 719 new medicines in 66 pathologies in the period between 2000 and 2013 was analysed. The results suggest that, in the absence of the new drugs marketed after 1981, the years of life lost would have been 2.16, 2.45 and 2.83 times higher than those actually lost for the under-85, 70 and 55 age groups, respectively. These results mean that, in 2013 alone, the introduction of the new medicines prevented the loss of about 148 million years of life up to the age of 85 in the countries analysed (Table 5)[51].

TABLE 5. IMPACT OF THE INTRODUCTION OF NEW MEDICINES ON LIFE YEARS SAVED, BY AGE GROUP, IN 27 DEVELOPED COUNTRIES, 2000-2013

AGE	ESTIMATED YLL RATIO IN ABSENCE NEW MEDICINES	TOTAL NUMBER OF YLL IN 2013 (A)	NUMBER OF YLL IN 2013 IN THE ABSENCE OF NEW MEDICINES LAUNCHED AFTER 1981 (B)	NUMBER OF YLG IN 2013 ATTRIBUTABLE TO LAUNCH OF NEW MEDICINES LATER A 1981 (B - A)
85 years	2.16	128,128,140	276,784,982	148,656,842
70 years	2.45	56,931,332	139,553,867	82,622,535
55 years	2.83	24,494,810	69,429,796	44,934,986

Abbreviations: YLG: years of life gained; **YLL:** years of life lost

Source: Adapted from Lichtenberg (2019)[51]

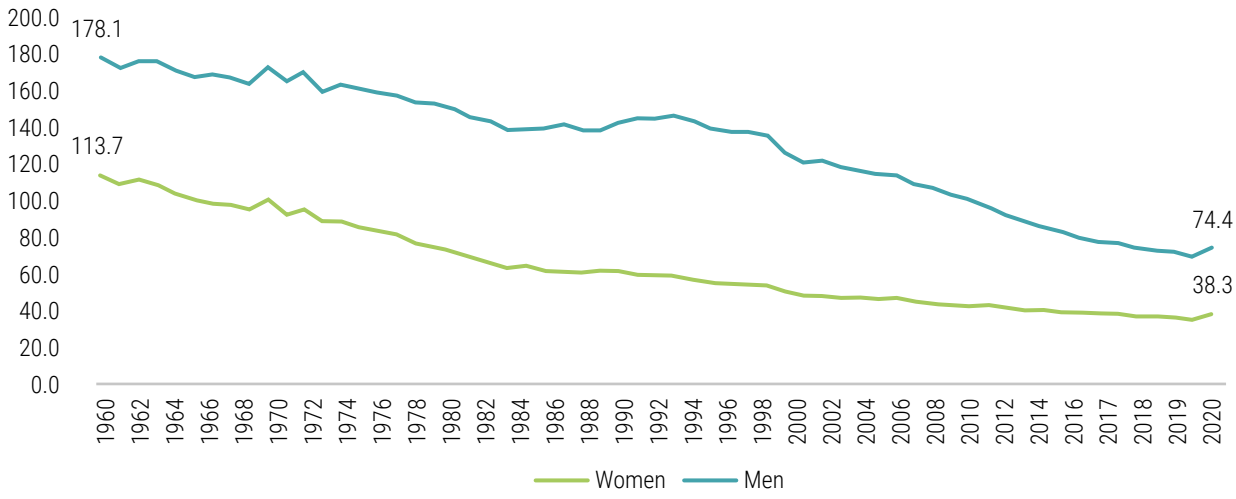
The impact attributable to new medicines on improving life expectancy in developed countries increased from 40% in 1986-2000 to 73% in 2000-2009, and remained at 73% during the period 2006-2016, reflecting the significant contribution of pharmaceutical innovation.

Lichtenberg (2003)[194], Lichtenberg (2014)[195] and Lichtenberg (2022)[57]

Globally, the mortality rate in the population aged 15-60 years has fallen substantially over the last century, from 394 deaths per 1,000 population in 1950 to the current figure of 138 in 2019[200]. Progress has been particularly significant in child mortality, which fell by 80 per cent between 1950 and 2019, to 28 deaths per 1,000 children under five years of age.

In Spain, mortality has also followed a downward trend, with a small spike in 2020 due to the COVID-19 pandemic. Among adult women, the mortality rate fell by 66% between 1960 and 2020, to 38 cases per 1,000 women. Among men, the mortality rate is higher than that of women over the entire period, although it has also maintained a steady decline, in this case by 58%. Mortality in men is double that of women, at 74 cases per 1,000 population (Figure 79)[201,202].

FIGURE 79. TREND IN ADULT MORTALITY RATE PER 1,000 INHABITANTS, BY GENDER, SPAIN, 1960-2020

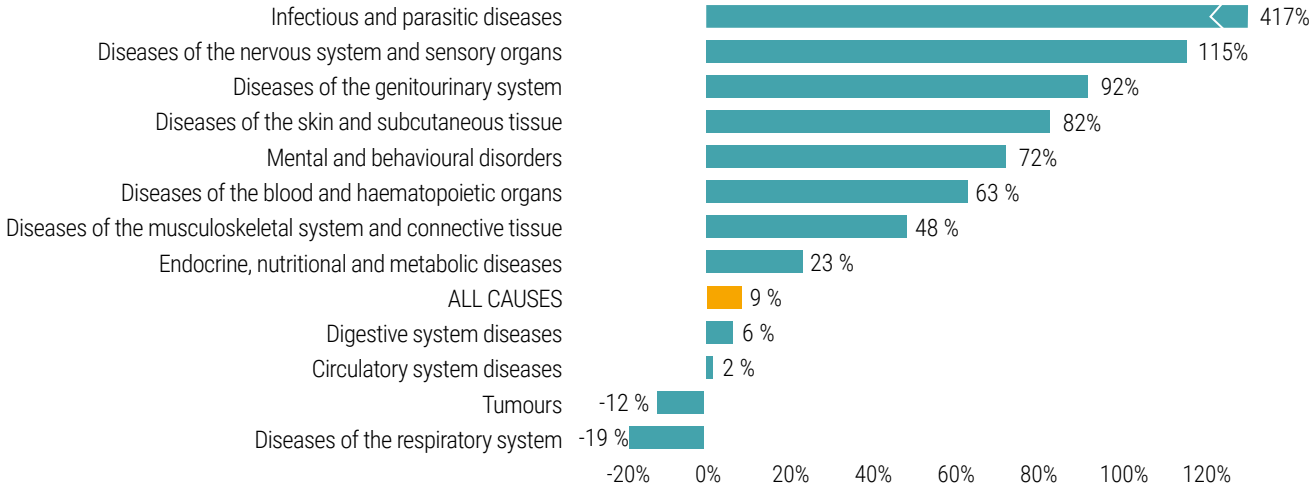


Source: Own elaboration based on World Bank data[201,202]

In terms of the number of deaths, data from the National Statistics Institute (INE) show that in 2022 there were 464,417 deaths in Spain, which is 13,500 more than the previous year and around 104,000 more deaths than in 2000 (28.9% variation)[203].

With regard to the variation in the mortality rate by cause of death, infectious and parasitic diseases have been the group with the highest growth in mortality rate (417% since 2000), mainly due to deaths related to COVID-19 (more than 31,000 deaths in 2022). This group would be followed by diseases of the nervous system and diseases of the sensory organs and genitourinary system (growth of 115% and 92% since 2000, respectively) (Figure 80). On the opposite side, diseases of the respiratory system and those caused by tumours have decreased their mortality rate since 2000 (Figure 80)[203].

FIGURE 80. EVOLUTION OF THE MORTALITY RATE (PER 100,000 INHABITANTS) BY CAUSE OF DEATH GROUPS, SPAIN, 2000-2022

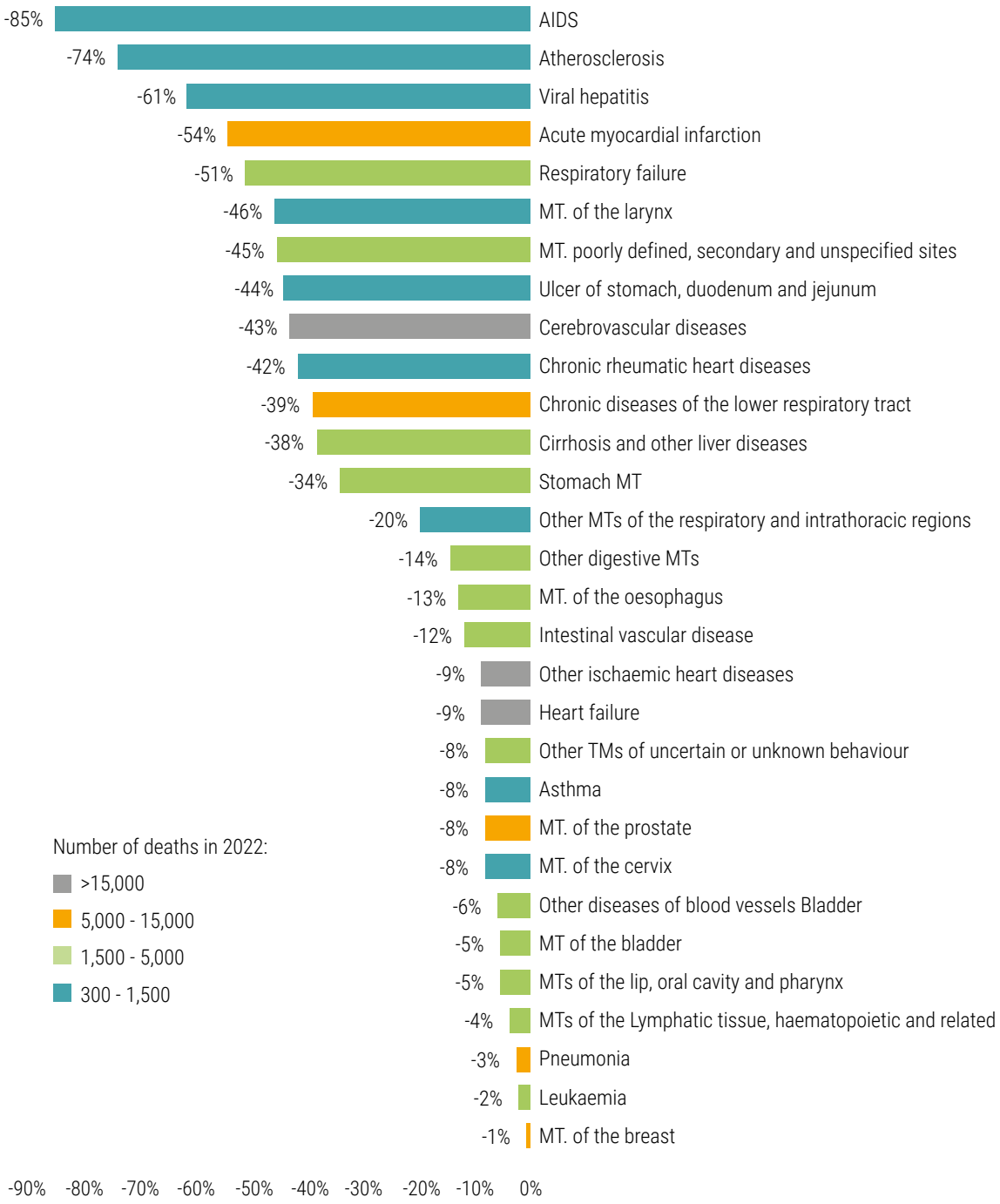


Note: Non-external causes of death included in ICD-10 are represented. Causes of death due to pregnancy/childbirth have not been considered, fetal, perinatal, congenital and unclassified malformations.

Source: Own elaboration based on INE data[203]

A more detailed analysis of the different pathologies shows that AIDS, atherosclerosis and hepatitis are the pathologies whose mortality rate has fallen most sharply during the period 2000-2022, with a decrease of 85%, 74% and 61%, respectively (Figure 81)[203]. Also noteworthy is the decrease in mortality in diseases that account for more than 15,000 deaths per year, such as cerebrovascular diseases, other ischaemic heart diseases and heart failure, with a decrease of 43%, 9% and 9%, respectively[203].

FIGURE 81. NON-EXTERNAL CAUSES OF DEATH WITH DECREASED MORTALITY RATES (PER 100,000 POPULATION) IN SPAIN, 2000-2022



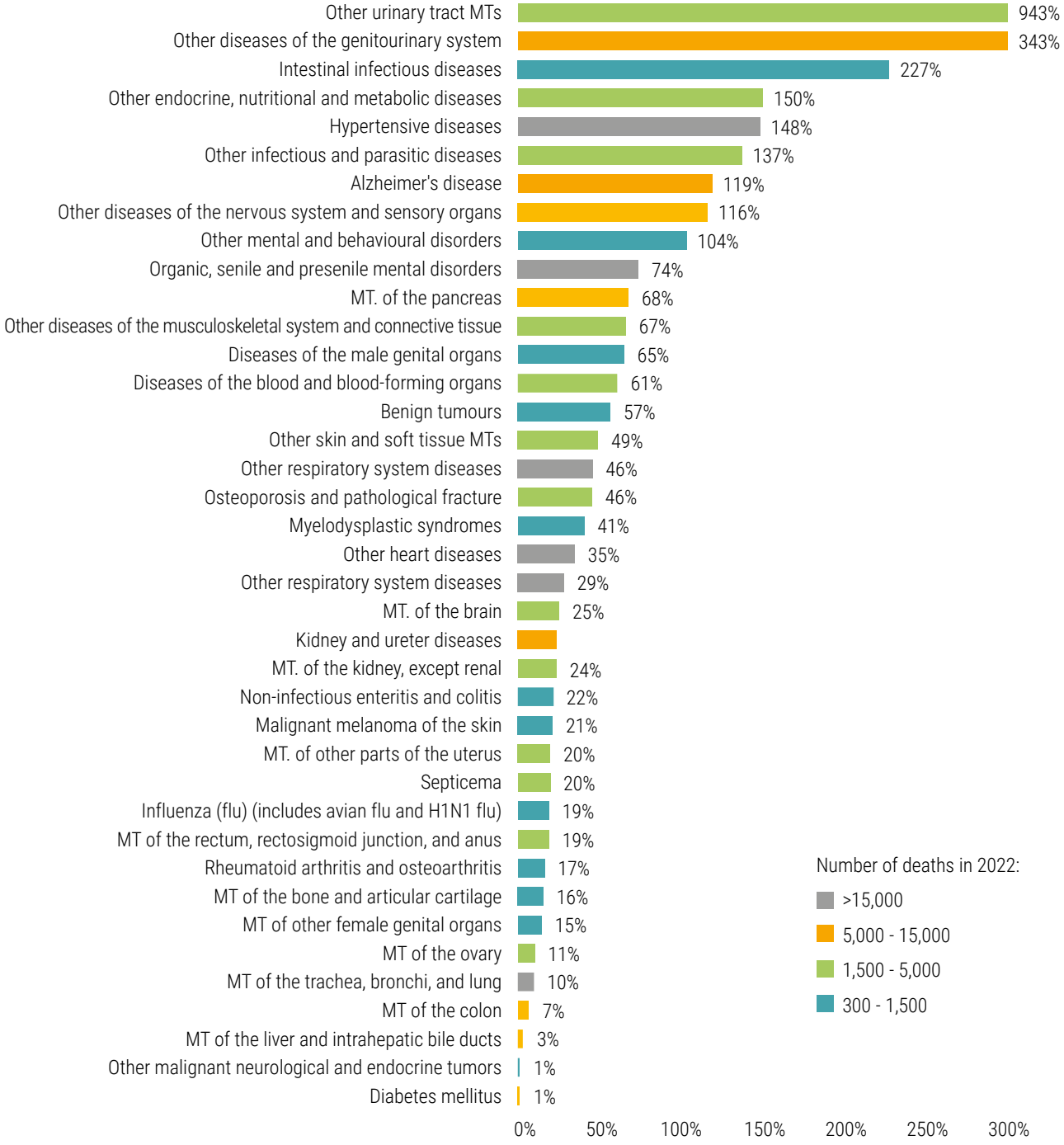
Note: Non-external causes of death included in ICD-10 are represented. Causes of death that accounted for less than 300 deaths in the year 2022 and the following causes of death have not been considered: COVID-19, pregnancy/partum, foetal, perinatal, congenital malformations and unclassified.

Abbreviations: MT: Malignant tumour

Source: Own elaboration based on INE data[203]

In contrast, the pathologies whose mortality rate has increased the most in the period 2000-2022 are tumours related to the urinary tract, with an increase of more than 940%, followed by other diseases of the genitourinary system (343%) and other infectious intestinal diseases (227%) (Figure 82)[203].

FIGURE 82. NON-EXTERNAL CAUSES OF DEATH WITH INCREASED MORTALITY RATES (PER 100,000 POPULATION), IN SPAIN, 2000-2022



Note: Non-external causes of death listed in ICD-10 are represented. Causes of death that accounted for less than 300 deaths have not been considered. deaths in 2022 nor the following causes of death: COVID-19, pregnancy/partum, foetal, perinatal, congenital malformations and unclassified.

Abbreviations: MT: Malignant tumour

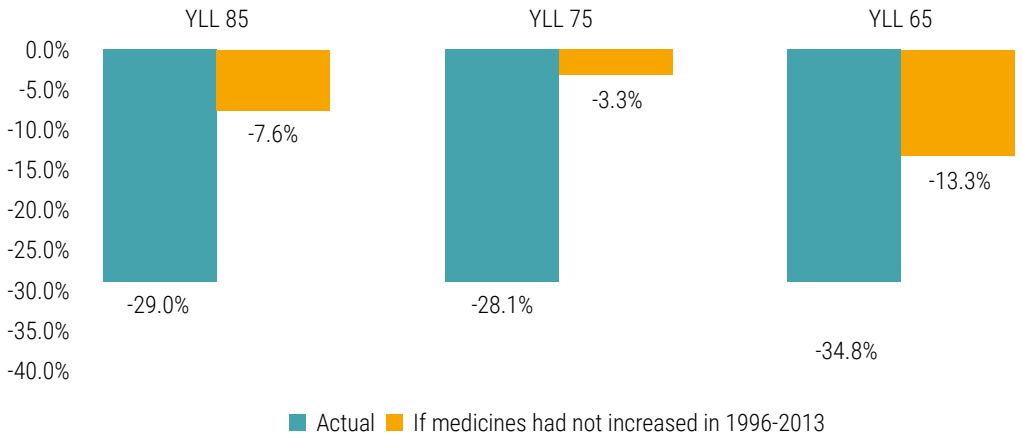
Source: Own elaboration based on INE data[203]

Another example can be found in a study published in 2018, carried out for 9 countries in Africa and the Middle East[49]. According to Lichtenberg's calculations, and analysing the premature mortality generated by 17 pathologies, the greater the number of drugs marketed in these regions, the greater the reduction in premature mortality for each disease. Furthermore, it is estimated that, in the absence of the drugs marketed since 1992, 2.8 million years of potential life would have been lost before the age of 75, which is

equivalent to about half of the reduction experienced in the period 1992-2015 in the region. New medicines are also responsible for about one-third of the reduction in the premature mortality rate in the region over the period.

More recent studies (published in 2022) in Australia and Switzerland have also demonstrated the impact of medicines on mortality and years of life lost. In Australia, the decrease in years of life lost (YLL) before the age of 85 was 29.0%, compared to 7.6% if no medicines had been marketed in the country during the period 1996-2013. These figures are similar for YLL75 (28.1% versus 3.3%) and for YLL65 (34.8% versus 13.3%) (Figure 83). In the case of DALYs75 and YLL65, this decline associated with medicines would be 88% and 62%, respectively[56].

FIGURE 83. CHANGE IN YEARS OF LIFE LOST BEFORE AGES 85, 75, AND 65: ACTUAL VS. ESTIMATED IF THE NUMBER OF MEDICINES HAD NOT INCREASED IN THE COUNTRY, AUSTRALIA, 2002-2019



Abbreviations: YLL: years of life lost

Source: Lichtenberg (2022)[56]

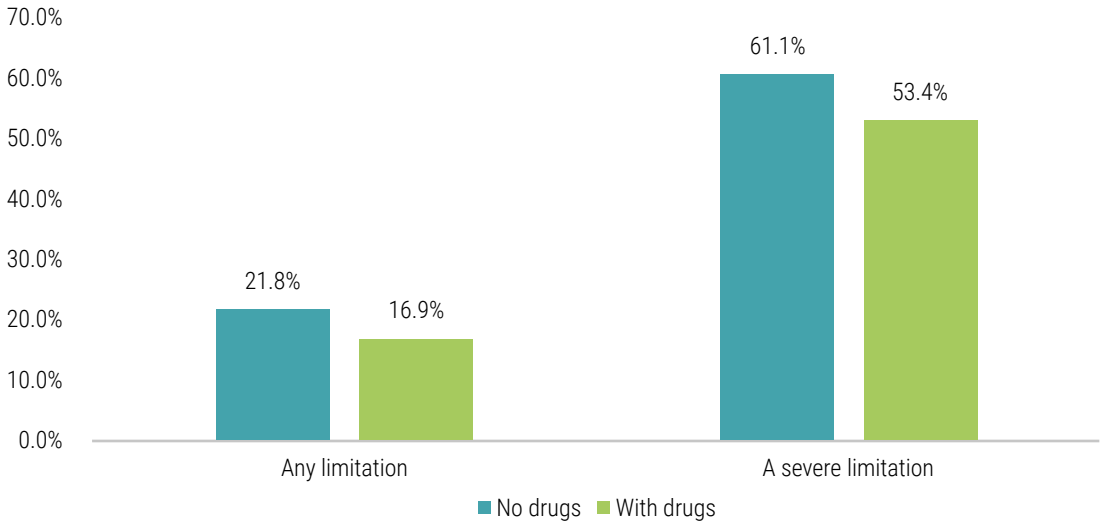
In the case of Switzerland, Lichtenberg's estimates show that the number of years of potential life lost (YPLL) before the age of 85, 75 and 65 is inversely related to the number of medicines registered 6-9, 3-9 and 0-9 years earlier, respectively. That is, the higher the number of drugs launched 6-9 years earlier, the lower the number of YPLL before the age of 85. Likewise, the new therapies registered during the period 1990-2011 are associated with a reduction of 257,000 years of YPLL before the age of 85. This reduction would be 163,000 years and 102 for YPLL before the age of 75 and 65, respectively[204].

One of the latest studies published by Lichtenberg focused on measuring the effect of both new (marketed after 2002) and old (marketed before 2003) drugs in Thailand. The study estimates that the introduction of a new drug for a given disease in Thailand reduced the number of deaths from that disease by 25% two years later. Similarly, the introduction of a drug before 2003 would have reduced the number of deaths two years later by 5%[205].

Moreover, the impact of new medicines is not only important as a determining factor in reducing mortality and increasing life expectancy, but it is also important to consider their beneficial impact on patients' quality of life. Some studies have exemplified this contribution by analysing the effect of certain marketed drugs on disability-adjusted life years. Thus, according to a study carried out in 11 European countries, the launch of different drugs in 31 pathologies during the period 1982-2015 reduced the probability of suffering a severe limitation by 4.9 percentage points, from 21.8% to 16.9% (Figure 84).

On the other hand, the launch of medication reduced the average number of limitations in daily activities by 29%, with a positive effect on the quality of life and well-being index[206].

FIGURE 84. PROBABILITY OF EXPERIENCING ANY TYPE OF LIMITATION OR A SEVERE LIMITATION BASED ON MEDICINES MARKETED BETWEEN 1982-2015, 11 EUROPEAN COUNTRIES



Source: Own elaboration based on Lichtenberg (2019)[206]

Similar studies have been carried out in different countries with similar results. For example, other recent studies on this topic, in this case for Canada and Ireland, respectively, are worth noting. The Canadian study estimates that the drugs launched between 1986 and 2001 reduced disability-adjusted life years (DALYs) by 2.3 million (21% of the total)[i] in 2016, reducing years of life lost YLL by 28% and the average length of hospital stay by 16%[55]. The Irish study quantified 234,600 disability-adjusted life years averted annually due to drugs marketed between 1983 and 1997 in Ireland, a reduction of 22.1%[208].

ANALYSIS BY PATHOLOGY

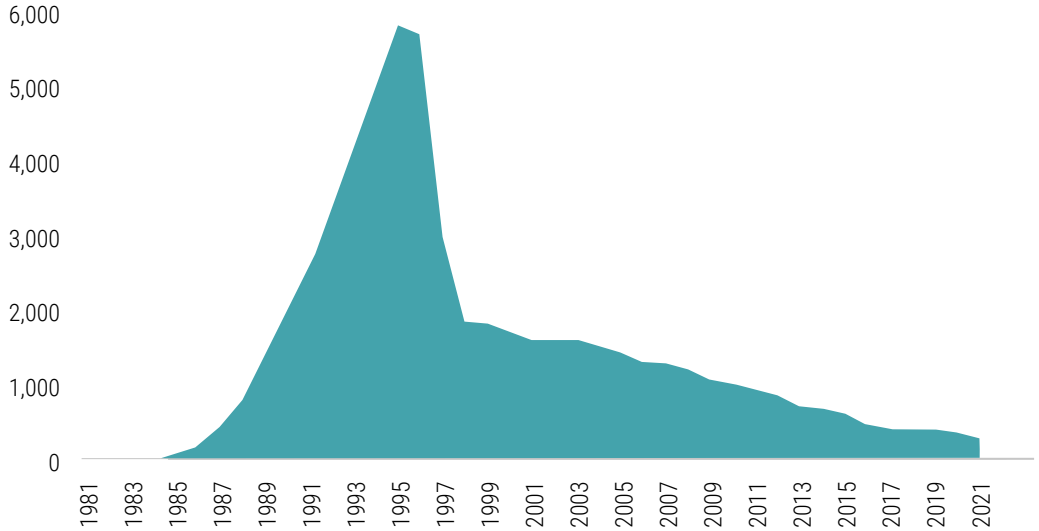
HIV / AIDS

HIV infection has been one of the most significant health problems of the 20th century, claiming more than 40 million lives from 1981 to date. In 2022, an estimated 630,000 people worldwide died of AIDS-related causes. By the end of that year there were approximately 39 million people globally infected with HIV, and there were 1.3 million new infections[209]. In Spain, the number of people currently living with HIV is 162,000, with 2,786 new cases diagnosed annually and a total of 306 deaths per year (16% less than the previous year)[210–212].

In Spain, the AIDS epidemic reached its peak in the mid-1990s, with almost 6,000 deaths per year and an incidence of almost 7,500 new cases per year. From 1996 onwards, the trend reversed drastically and there was a rapid decline in both the number of new cases reported and the number of deaths per year (Figure 85)[211].

i **DALY:** *Expresses years of life lost due to premature death, and years lived with a disability of specified severity and duration. A DALY is therefore one year of healthy life lost*[207].

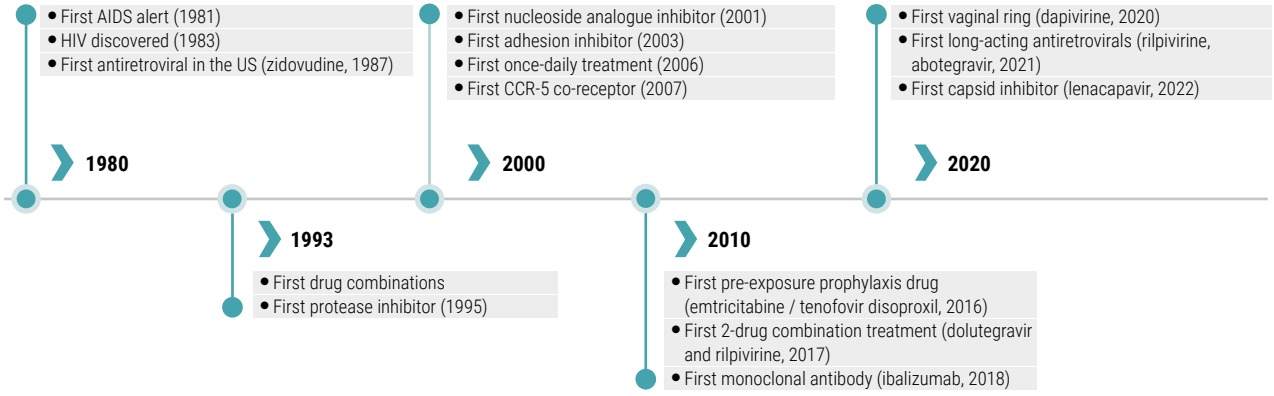
FIGURE 85. EVOLUTION OF AIDS DEATHS IN SPAIN, 1981-2021



Source: Prepared by the authors based on ISCIII (2023)[211]

Although there is still no cure for HIV infection today, AIDS is one of the diseases for which there has been the greatest progress in treatment over the past 25 years. The major therapeutic innovations in the field of HIV occurred from 1995 onwards (Figure 86)[213], known as the "HAART era" (**High Active Anti-Retroviral Therapy**). These include the approval of the first protease inhibitor (in 1995), the first nucleoside analogue inhibitor (2001), the first adhesion inhibitor (2003), the first once-daily treatment (2006), the first CCR-5 co-receptor (2007) and the first **pre-exposure prophylaxis medicines** (PrEP) (2012)[214].

FIGURE 86. EVOLUTION OF AVAILABLE HIV/AIDS TREATMENT, 1980-2023



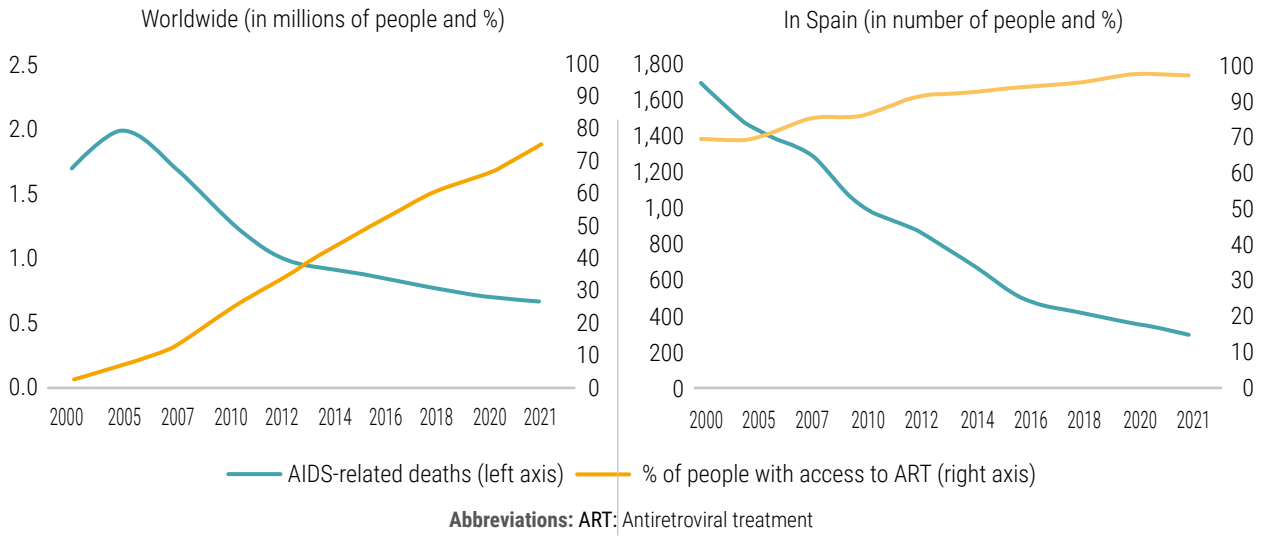
Source: Own elaboration based on UNAIDS (2023)[213], FDA and EMA

Early detection of HIV and slowing its spread was established as one of the United Nations Millennium Development Goals[215]. By 2030, the goal is to reach 95% of people diagnosed; 95% of people diagnosed on treatment; and 95% of treated cases with an undetectable viral load. Spain currently exceeds the second of these goals, with 97% compliance, and is closer to the first (an estimated 7.5% of people living with HIV are undiagnosed) than the third (almost 10% of treated patients do not achieve viral suppression)[216].

Advances in antiretroviral treatment have enhanced prevention of transmission, slowed progression and increased survival and quality of life, transforming HIV/AIDS from an acute and fatal short-term disease into a

chronic condition in which those affected can live a near-normal life. Access to these treatments correlates strongly with the reduction in deaths caused by the disease (Figure 87).

FIGURE 87. RELATIONSHIP BETWEEN ACCESS TO ANTIRETROVIRAL TREATMENT AND THE NUMBER OF AIDS-RELATED DEATHS. GLOBAL AND SPAIN, 2000-2021

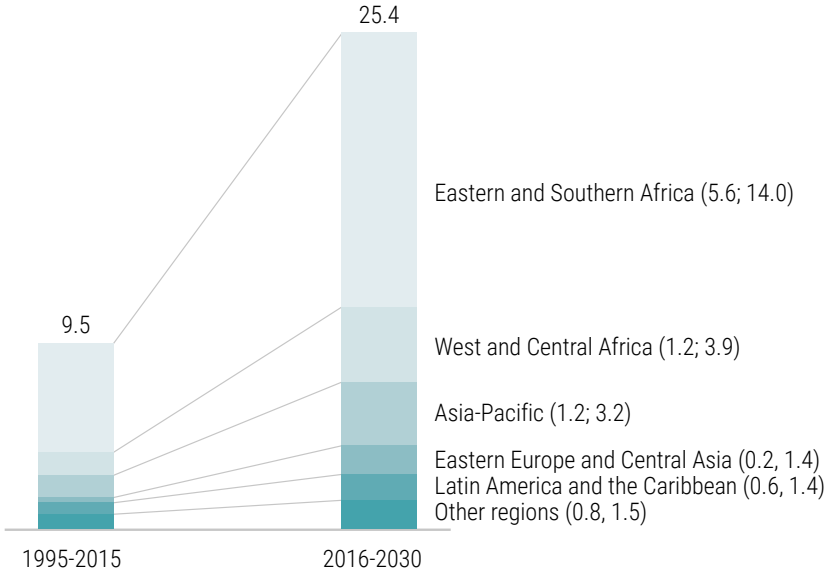


Abbreviations: ART: Antiretroviral treatment

Source: Own elaboration based on UNAIDS (2023)[217] and Instituto de Salud Carlos III [(2022)[218] and (2023)][219]

Several studies have analysed the aggregate impact of antiretroviral treatment (ART) use on the number of deaths averted. It is estimated that the number of deaths averted globally by ART between 1995 and 2015 was 9.5 million, and it is expected that, by 2030, the use of ART will avert an additional 25.4 million deaths, most of them in Africa (Figure 88)[220].

FIGURE 88. ESTIMATES OF THE NUMBER OF AIDS DEATHS AVERTED BY ANTIRETROVIRAL TREATMENT, GLOBAL, 1995-2030 (MILLIONS)



Source: Own elaboration based on Forsythe (2019)[220]

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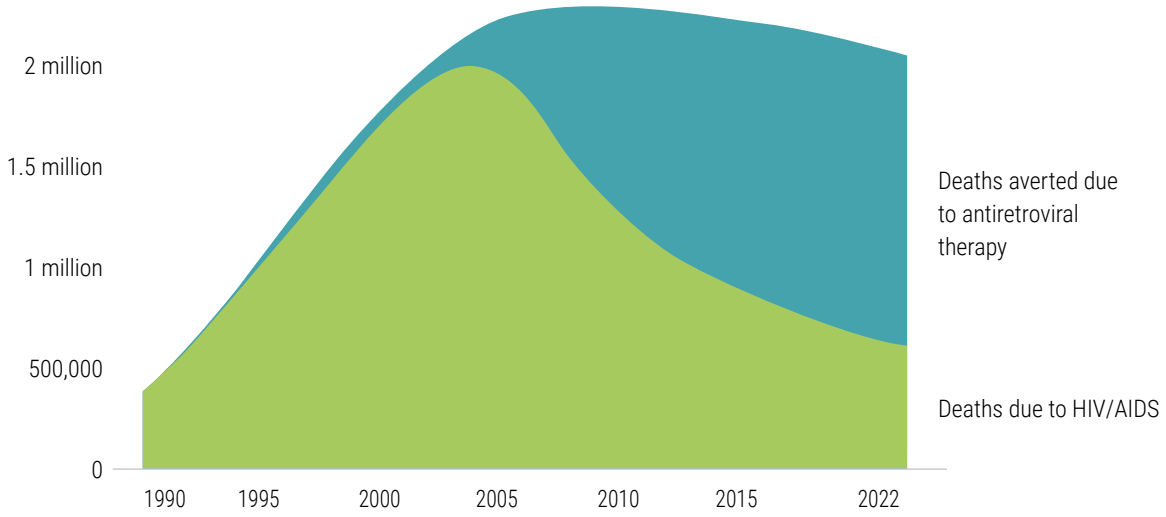
More recent estimates indicate that HIV treatment has averted nearly 21 million AIDS-related deaths worldwide between 1996 and 2022 (Figure 89). Without antiretroviral therapy, more than twice as many people would have died of HIV/AIDS[214,221].

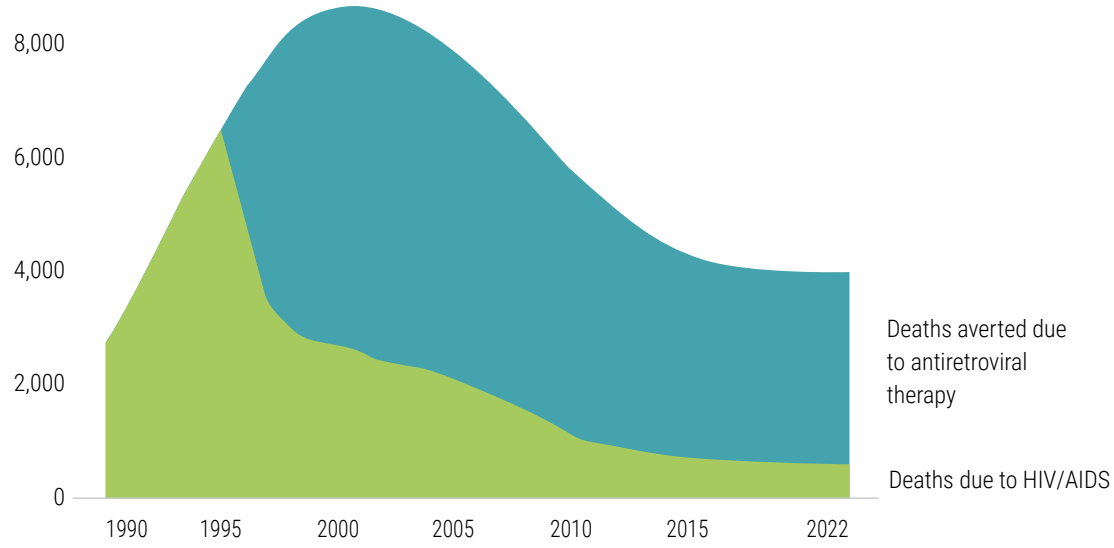
FIGURE 89. NUMBER OF AIDS-RELATED DEATHS IN THE CURRENT SCENARIO VERSUS THE SCENARIO WITHOUT ANTIRETROVIRAL THERAPY IN THE WORLD, 1990-2022



Source: UNAIDS (2023)[214] and Our World in Data (2023)[221]

According to UNAIDS estimates, the use of antiretrovirals would have prevented an estimated 122,000 deaths in Spain between 1995 and 2022 (Figure 90)[221].

FIGURE 90. NUMBER OF AIDS-RELATED DEATHS IN THE CURRENT SCENARIO VERSUS THE NO ANTIRETROVIRAL THERAPY SCENARIO IN SPAIN, 1990-2022



Fuente: Our World in Data (2023)[221]

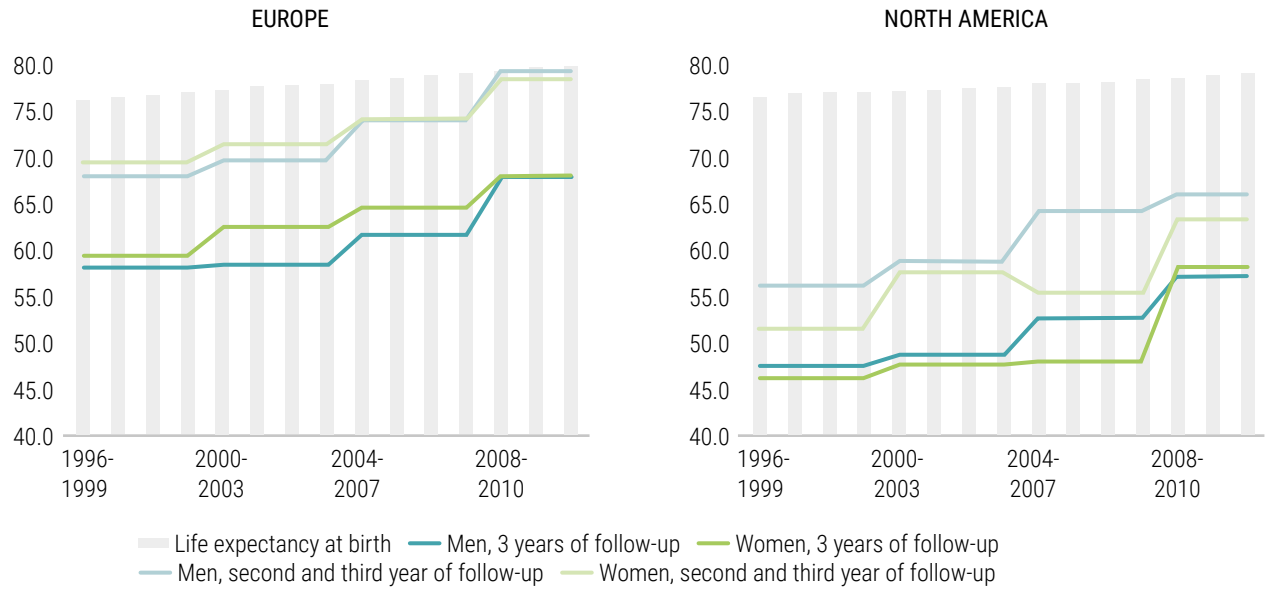
Similarly, several studies have analysed the effects of ART implementation on the 10-year survival of HIV-infected patients. For example, Pierre et al. (2016) estimated, in one of the largest long-term studies, with 910 patients (half of whom lived in extreme poverty), that the 10-year survival rate of people treated with ART

ranged from 63% to 71%[222]. A meta-analysis of data from 57 studies and 294,662 participants reached similar conclusions. It found that the majority of patients (61%) who develop AIDS will survive for more than 10 years because of ART use. In contrast, more than half of patients who do not receive ART will die within 2 years of AIDS infection[223].

Despite treatment, however, mortality in HIV-infected patients remains higher than in uninfected patients. In particular, two observational studies analysing data from a total of 102,723 patients in the UK and Canada over a 15-year period found that the mortality rate in HIV-infected patients was 3-6 times higher than in the general population[224,225].

Early diagnosis of the disease is key to increasing the life expectancy of patients with HIV. This is evidenced by work such as that of Trickey et al. (2017) who estimated life expectancy in patients in 18 cohorts from Europe and North America[226]. They found that early diagnosis (represented by patients studied in the last period of analysis, 2008-2010) was correlated with increased life expectancy, and based on estimates from data from the second and third year of treatment, the life expectancy of patients in Europe reached the same levels as the general population (Figure 91)[226,227].

FIGURE 91. COMPARISON OF THE EVOLUTION OF LIFE EXPECTANCY OF HIV-INFECTED PATIENTS WITH THAT OF THE GENERAL POPULATION, BY GENDER AND PERIOD OF ONSET, EUROPE AND NORTH AMERICA, 1996-2010



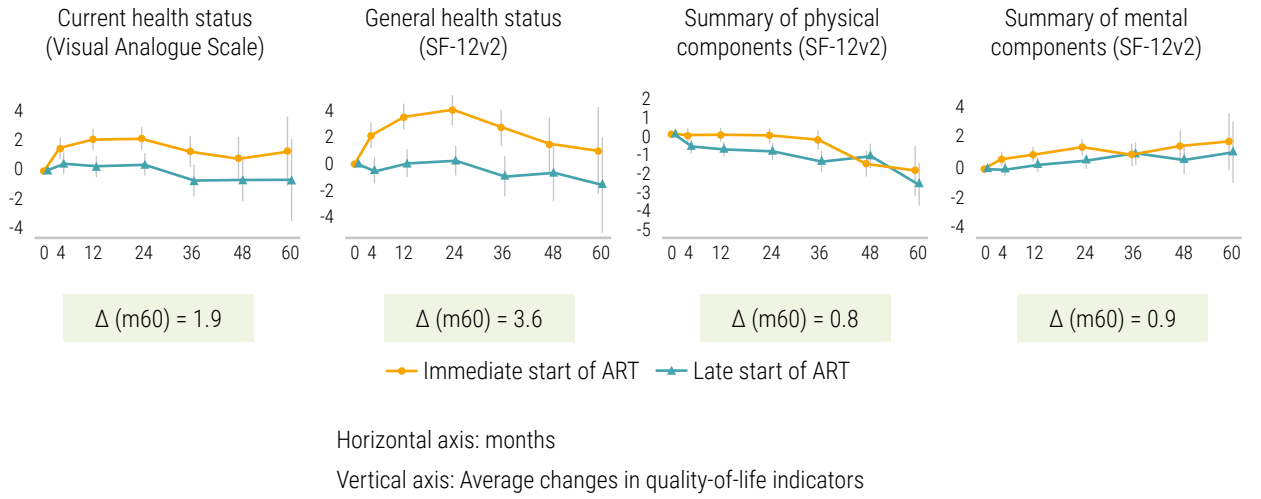
Source: Own elaboration based on Trickey (2017)[226] and World Bank (2018)[227]

New therapies have not only improved mortality and life expectancy, but also the morbidity and quality of life of patients. The immunodeficiency caused by HIV leads to infections and other illnesses, also known as non-AIDS-associated events (NAEs), which reduce the quality of life of HIV-positive patients. NAEs are the most frequent cause of morbidity and mortality in HIV/AIDS patients, especially those related to psychiatric, liver, tumour, cardiovascular and renal events[228,229]. A Spanish study of HIV-positive patients treated with ART for the first time suggests that ART has a beneficial effect on the incidence of NAEs, especially on psychiatric and renal events[229].

On the other hand, the earlier treatment is given, the greater the effect on quality of life. A randomised study of 4,684 participants in 35 countries over a 5-year follow-up period found that immediate ART initiation in HIV-in-

fected patients has a positive effect on quality of life compared to delayed initiation. The mean differences observed between the two groups were larger (1.9-3.6 points) for health status-related indicators, and more modest (0.8-0.9 points), but significant, for physical and mental components (Figure 92)[230].

FIGURE 92. IMPROVEMENTS IN QUALITY OF LIFE IN HIV PATIENTS BY HIV TREATMENT INITIATION. OVERALL, 5-YEAR FOLLOW-UP

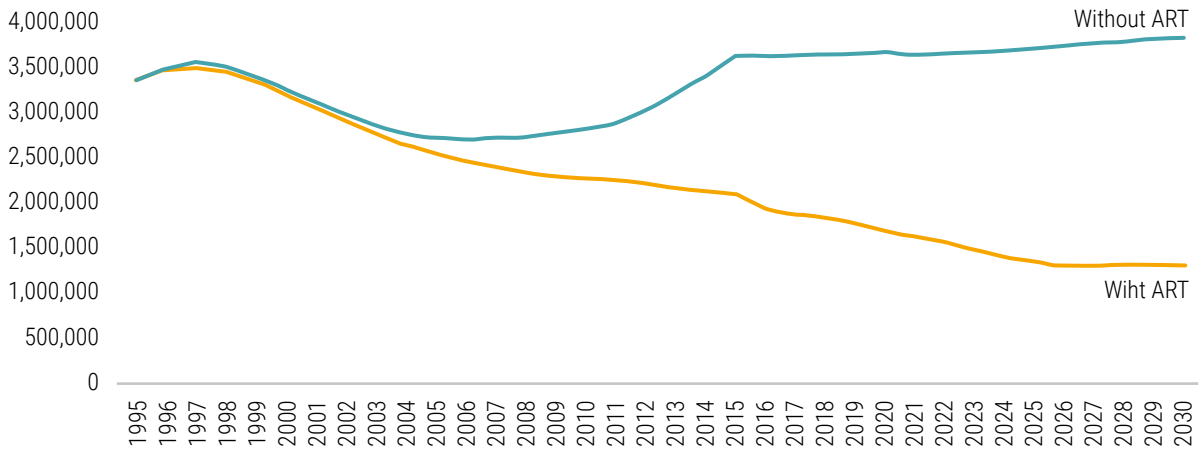


Notes: SF-12v2: SF-12 health questionnaire version 2. **ART:** antiretroviral treatment.

Source: Lifson (2017)[230]

In addition to the above-mentioned benefits related to mortality, life expectancy and quality of life, the advent of ART has also benefited HIV prevention by averting new cases. Thus, ART is estimated to have averted a total of 7.9 million HIV infections globally between 1995 and 2015, and between 2016 and 2030, ART will have averted 32.3 million new infections, if the Millennium Development Goals are met (Figure 93)[220].

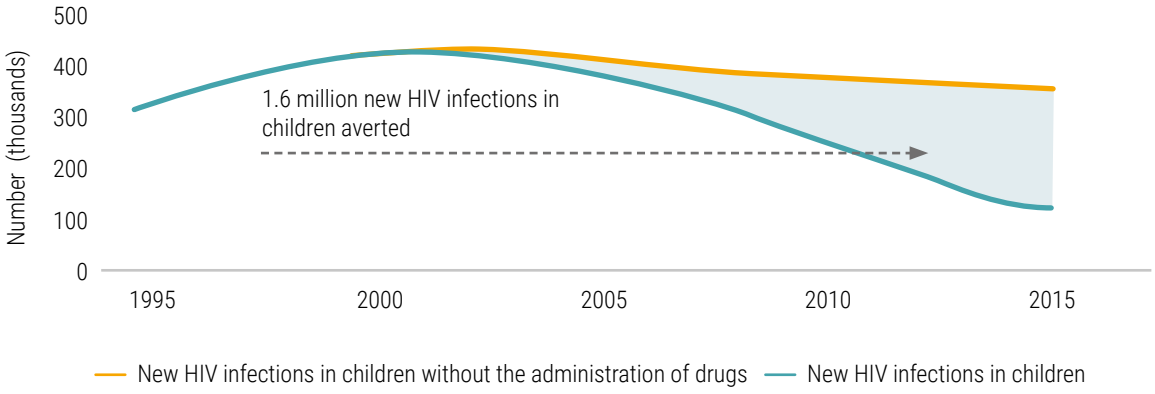
FIGURE 93. EVOLUTION OF NEW HIV INFECTIONS WITH AND WITHOUT ANTIRETROVIRAL THERAPY. GLOBAL, 1995-2030



Note: ART: antiretroviral treatment. **Source:** Forsythe (2019)[220]

On the other hand, in the period 2000-2015, ART also prevented 1.6 million children from being born with the disease, as viral load control associated with maternal treatment during pregnancy prevents vertical transmission of the disease (Figure 94)[231].

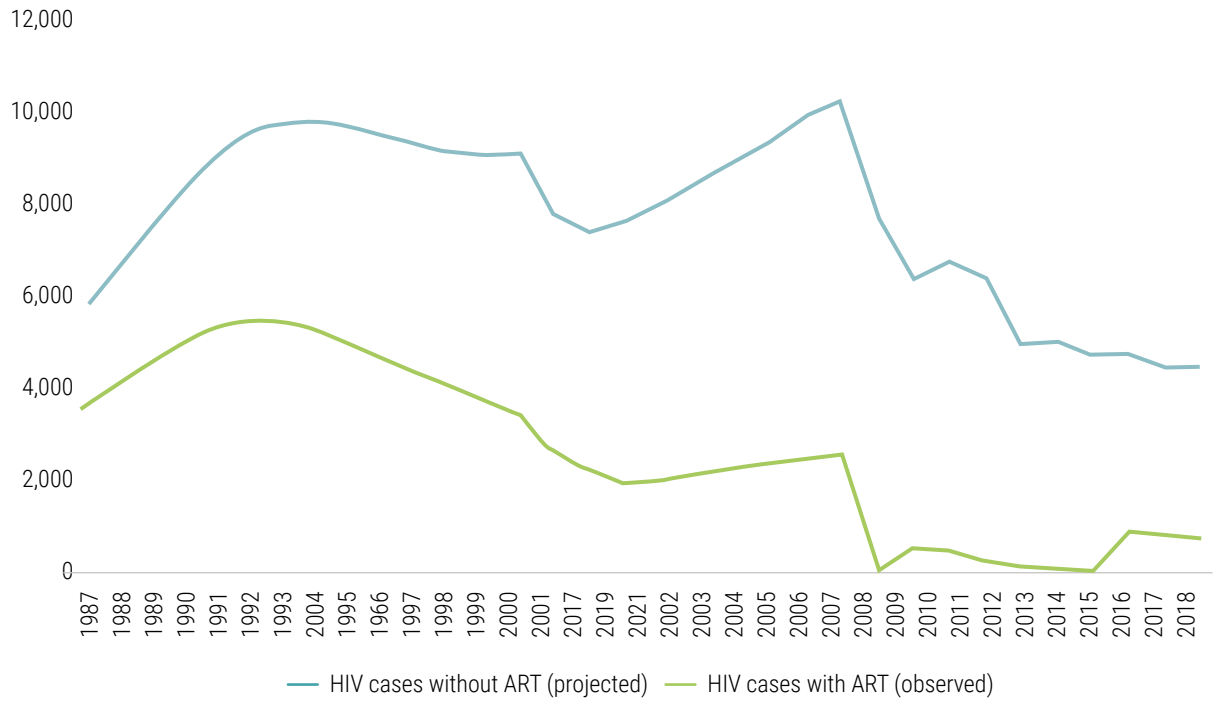
FIGURE 94. COMPARISON OF NEW HIV INFECTIONS IN CHILDREN AGED 0-14 YEARS WITH AND WITHOUT ART. OVERALL, 1995-2015



Note: ART: antiretroviral treatment. **Source:** IQVIA (2018)[231]

In Spain, it is estimated that, during the period 1987-2018, antiretroviral treatment has prevented 323,651 AIDS deaths, 500,129 AIDS cases and 161,417 HIV cases (Figure 95)[232].

FIGURE 95. HIV CASES WITH ART (OBSERVED) AND WITHOUT ART (ESTIMATED) IN SPAIN, 1987-2018



Abbreviations: HIV: human immunodeficiency virus; **ART:** antiretroviral treatment

Source: Pérez-Elías (2022)[232]

In the most recent period, advances in new drug development have resulted in the approval of five drugs by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In 2017, the first two-drug combination HIV treatment (dolutegravir and rilpivirine) was introduced instead of the usual three-drug treatment. This has minimised cumulative exposure to drugs that cause increased long-term risk of fractures, osteoporosis, kidney and metabolic disorders, central nervous system disorders, cardiovascular disease and liver disease[233,234].

In 2018, three new drugs were approved. One of them, ibalizumab, is indicated for patients with resistance to multiple treatments. Its efficacy has been demonstrated in a clinical trial of 40 HIV patients who had previously been treated with multiple ART without improvement. After 25 weeks of treatment, viral load reduction was observed in 83% of treated patients, and undetectable HIV levels (<50 copies/ml) were found in 43-44% of patients[235].

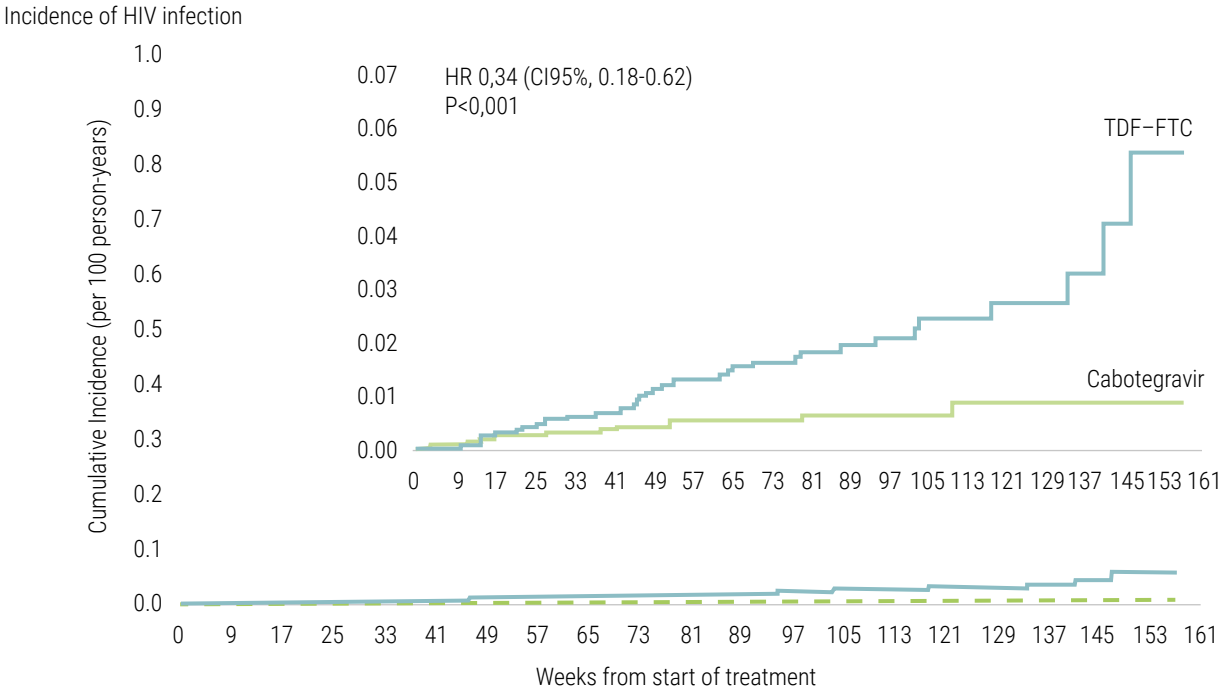
A three-compound combination (bictegravir sodium, emtricitabine and tenofovir alafenamide fumarate) was also approved in 2018 and is indicated for treatment of HIV-infected adults who are treatment-naïve or virologically suppressed. In clinical trials involving nearly 2,500 patients in more than 10 countries (including Spain), with follow-up periods of between 1 and 3 years, the combination has demonstrated non-inferiority to standard treatment in efficacy, as measured by viral load suppression, a high barrier to the development of resistance and a favourable drug-drug interaction profile[236–238].

In 2019, a new two-drug combination (dolutegravir sodium and lamivudine) was introduced as a single fixed-dose tablet for people without prior ART treatment. This simplified regimen provides patients with non-inferior efficacy to standard treatment, as well as reduced cumulative drug exposure and toxicities, and the convenience of single-tablet treatment[239].

Pre-exposure prophylaxis (PrEP) is a biomedical intervention aimed at preventing HIV transmission in HIV-negative people at high risk of HIV infection. WHO guidelines recommend daily use of PrEP for both men and women at substantial risk of HIV infection[240]. At the end of 2019, PrEP with emtricitabine and tenofovir disoproxil fumarate was authorised for funding in Spain as a strategy to prevent HIV infection in high-risk populations. According to a real-life study in France, the effectiveness of this treatment increased with the level of use, ranging from 18% (95% CI: -18 to 43) for low use, 69% (95% CI: 41 to 84) for intermediate use and 93% (95% CI: 84 to 97) for high use. PrEP efficacy reached 86% (95% CI 78-92) if periods after PrEP discontinuation were excluded[241].

In 2023, the EMA approved cabotegravir in combination with rilpivirine, the first long-acting injectable pre-exposure prophylaxis treatment for HIV prevention[242]. According to a clinical trial comparing its efficacy with a daily oral alternative in cisgender men and transgender women who have sex with men at risk in the US, followed for 153 weeks, the incidence rate of HIV infections in the treatment group was 0.41 per 100 person-years versus 1.22 per 100 person-years in the control group (HR of 0.34; 95% CI 0.18 to 0.62), with a consistent effect in all pre-specified subgroups (Figure 96)[243].

FIGURE 96. CUMULATIVE INCIDENCE OF HIV INFECTIONS (PER 100 PERSON-YEARS) AMONG THE LONG-ACTING VERSUS ORAL PREP GROUP



Abbreviations: TDF-FTC: tenofovir/emtricitabine

Source: Landovitz (2021)[243]

Currently, the HIV/AIDS therapeutic arsenal contains 65 innovative drugs approved by the EMA for the treatment of HIV infections. There are also a number of topical microbicides that reduce the likelihood of contracting HIV. For example, dapivirine (vaginal ring) probably reduces the risk of acquiring HIV infection: risk ratio (RR) 0.71 (95% confidence interval [CI95%]: 0.57 to 0.89)[244].

Thus, while there is still no curative treatment for HIV, there is a wide arsenal of highly effective oral and injectable antiretroviral combinations that achieve viral suppression, thereby preventing transmission and significantly reducing HIV-related morbidity and mortality. Recent advances have been directed towards the development of simplified regimens with more favourable safety profiles, targeted therapies for patients with multidrug-resistant infections and depot formulations that promote adherence to treatment, as well as treatments that reduce the risk of infection in non-HIV-at-risk populations. In addition, there are currently around 100 ongoing clinical trials involving new drugs for HIV treatment and prevention (vaccines).

Advances in antiretroviral treatment have made it possible to prevent the transmission of HIV. The new technologies have slowed the progression of the HIV virus and increased the survival and quality of life of patients, transforming HIV/AIDS from an acute and fatal disease in the short term into a chronic disease with a good quality of.

Trickey (2017)[226], Lifson (2017)[230], Forsythe (2019)[220], Llibre (2018)[233], Emu (2018)[235] and Cahn (2019)[239]

In recent years, advances have been directed towards simplification of treatment regimens, new depot formulations and HIV prevention strategies, which provide a more favourable safety profile and improved adherence to treatment, with not only individual benefit but also public health implications.

Obiero (2021)[244] and Pérez-Elías (2022)[232]

CANCER

In recent decades, research has gained a deeper understanding of the mechanisms that trigger and progress cancer diseases. These findings have led to the development of specific molecules for different forms of cancer, as well as improved methods to prevent, detect, treat and cure the disease, leading to better health outcomes.

Recently, the most significant progress in the fight against cancer has been linked to the discovery of various cellular mutations that promote cancer development[245]. Thanks to the identification of cellular mutations and the emergence of precision medicine, treatments are being personalised to the genetic characteristics of each patient and their tumour, significantly improving success rates and reducing the side effects associated with treatment[246]. In addition, new therapeutic avenues have been discovered and innovative approaches are being explored, such as the use of specific biomarkers, advanced therapies or targeted therapies, which are paving the way for a new era of disease.

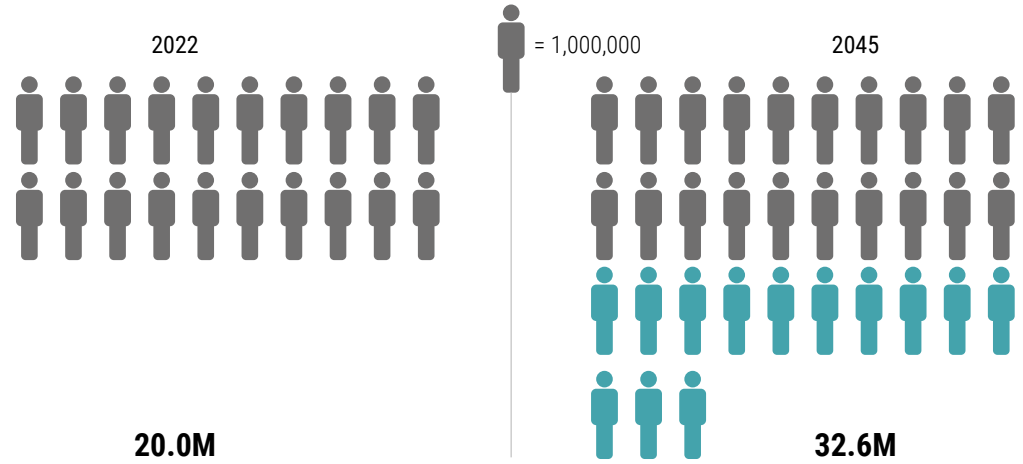
In this section we will examine the most significant therapeutic advances in the field of oncology, focusing on the latest innovations. We will begin by reviewing the main cancer indicators in terms of incidence, mortality and five-year survival rate. We will then analyse some of the most recent and revolutionary drugs in the treatment of this disease, which have represented significant progress in both morbidity and mortality associated with the disease and in patients' quality of life.

Cancer in figures

Incidence

An estimated 20 million new cancer cases were diagnosed worldwide in 2022 (incidence of 2,532 per million population) and the number of cases is expected to increase over the next two decades to 32.6 million new cases per year in 2045 (incidence of 3,835 per million population), mainly due to demographic changes (Figure 97)[247].

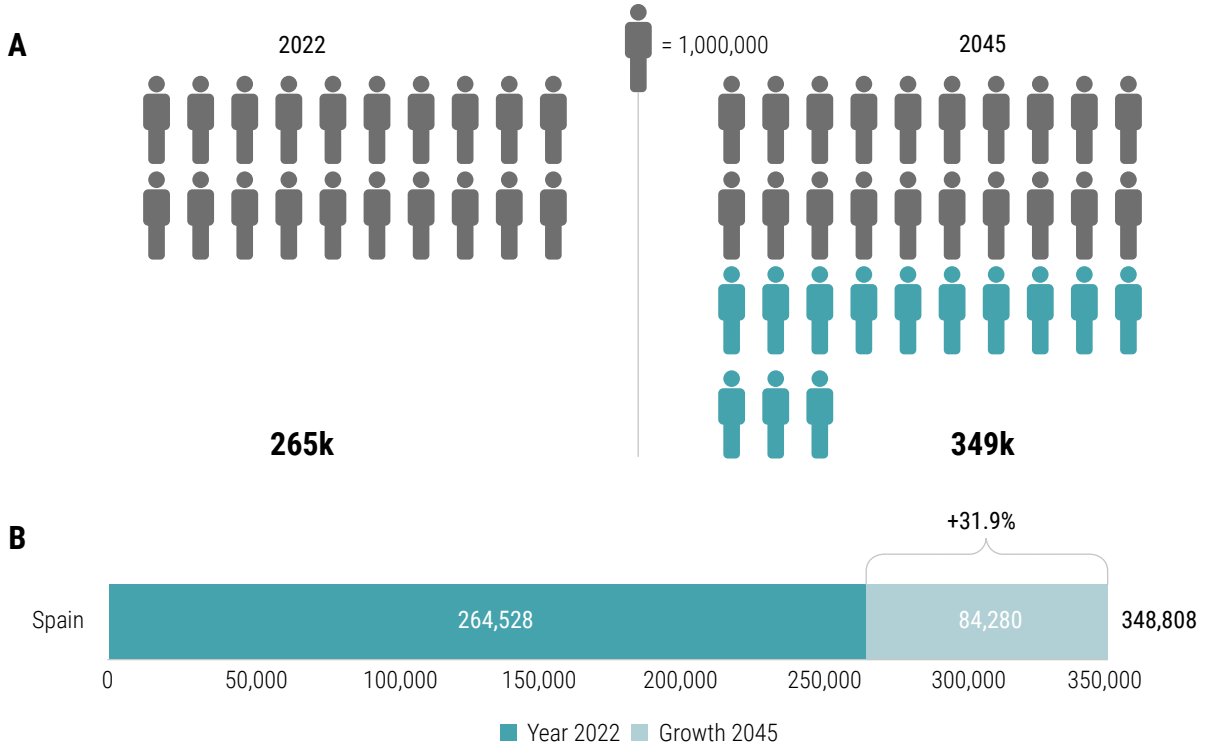
FIGURE 97. ESTIMATED CANCER INCIDENCE (PER MILLION POPULATION) FOR 2022 AND 2045, BOTH GENDERS, WORLD



Source: IQVIA (2018)[213]

In Spain, the incidence of cancer has also been increasing over the last decades and this increase is expected to continue to reach 349,000 new cases per year in 2045 (incidence of 7,756 per million inhabitants), compared to 265,000 new cases in 2022 (incidence of 5,638 patients per million inhabitants). This increase would be explained by improved diagnostic techniques and, above all, by the demographic changes expected to occur in Spain in the coming years (Figure 98A). In more detail, the increase in cancer incidence is estimated to reach 31.9%, which would mean that 84,000 more cases of cancer would be diagnosed in Spain in 2045 than in 2022 (Figure 98B)[247].

FIGURE 98. ESTIMATED CANCER INCIDENCE (PER 10,000 INH.) FOR THE YEARS 2022 AND 2045, BOTH GENDERS (EXCLUDING NON-MELANOMA SKIN CANCERS), SPAIN



Source: IARC/WHO (2024)[247]

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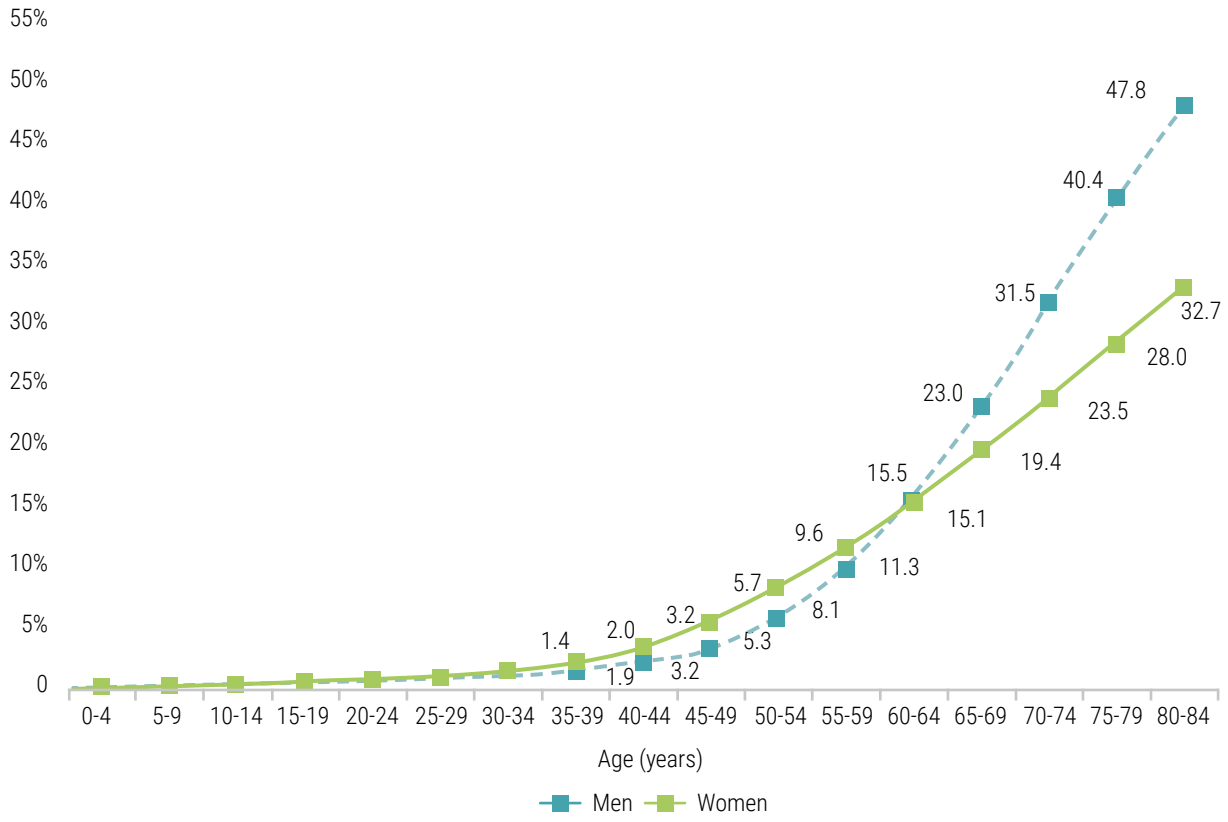
In fact, the risk of developing tumours increases with age, especially among males (Figure 99)[248].

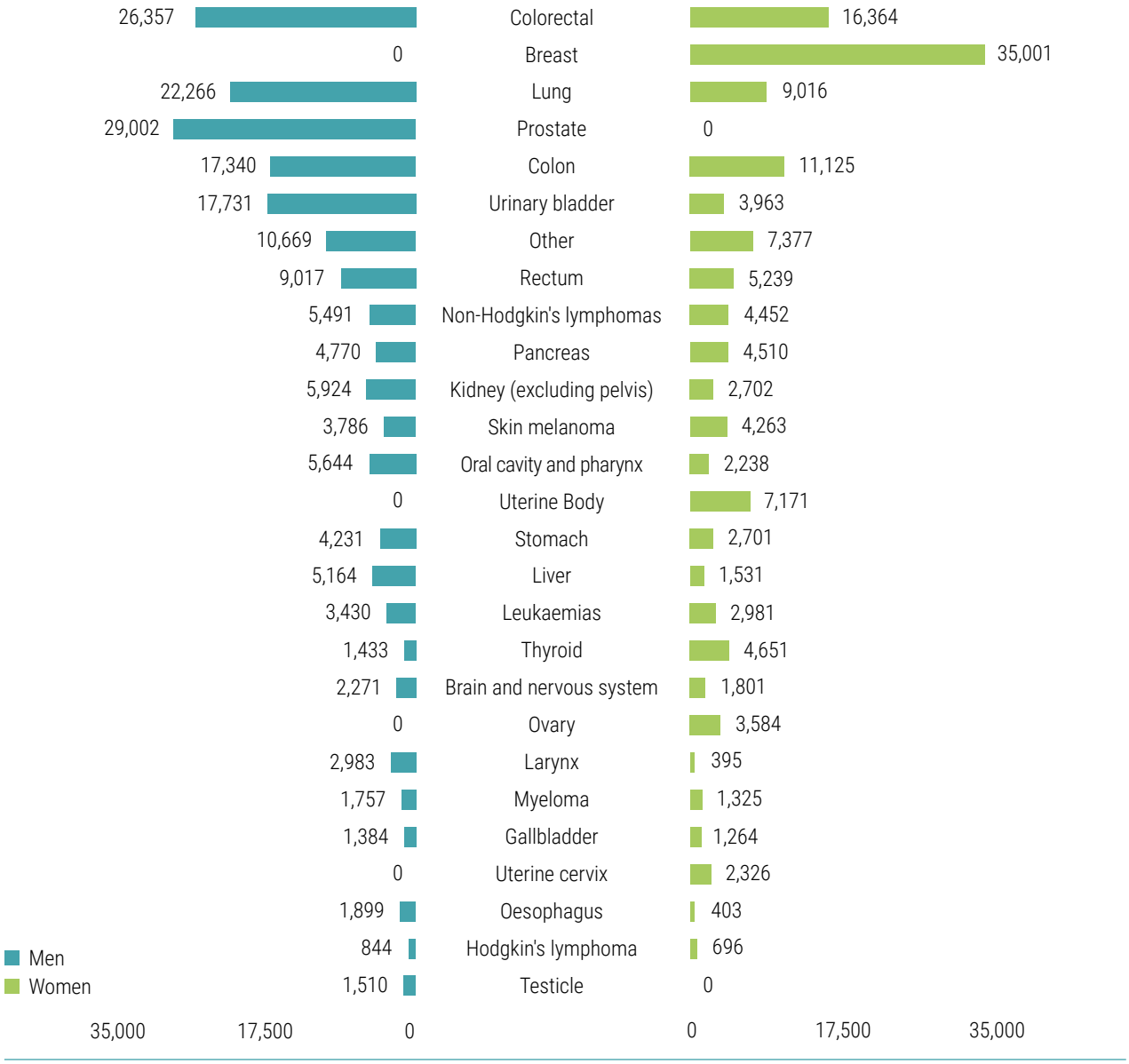
FIGURE 99. PROBABILITY (%) OF DEVELOPING CANCER (EXCLUDING NON-MELANOMA SKIN CANCER) IN SPAIN BY GENDER AND AGE GROUP, ESTIMATES 2024



Source: SEOM (2024)[248]

According to data from the Spanish Network of Cancer Registries (REDECAN), the type of tumour with the highest incidence in Spain is colorectal cancer, with 42,721 new cases, followed by breast (35,001 cases), lung (31,282 cases) and prostate (29,002 cases). In an analysis by gender, the most frequently diagnosed cancer in men is prostate cancer (29,002 cases), colorectal cancer (26,357 cases), lung cancer (22,266 cases) and urinary bladder cancer (17,731 cases). The tumours with the highest incidence in women are breast (35,001 cases), colorectal (16,364 cases), colon (11,125 cases) and lung (9,016 cases) (Figure 100)[249].

FIGURE 100. ESTIMATED INCIDENCE OF CANCER BY TYPE OF CANCER BY GENDER 2023, SPAIN



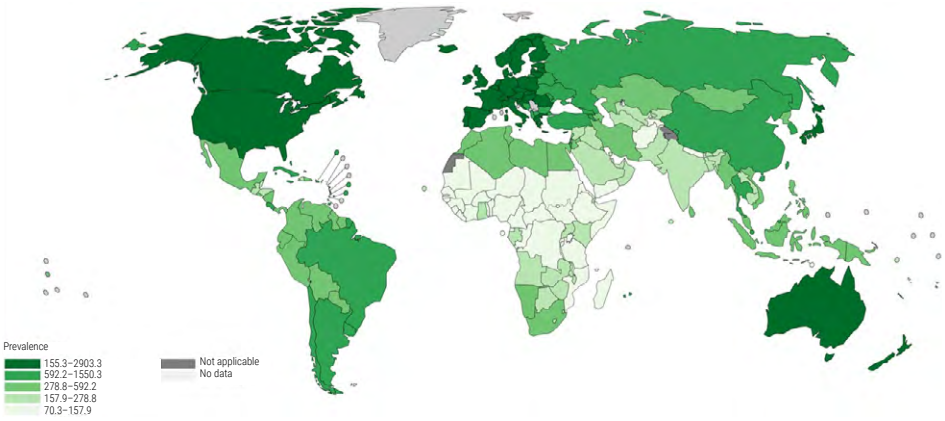
Source: Own elaboration based on REDECAN (2023)[249]

Prevalence

One aspect to take into account is that prevalence is determined by survival, i.e. prevalence is higher in cancers with longer survival, while cancers with lower survival rates may have a lower prevalence, although they are more frequently diagnosed[250].

According to the rate per 100,000 inhabitants, European countries, together with the USA, Canada, Japan, Australia and New Zealand are the areas with the highest cancer prevalence in the world. By country, Australia (2,903 per 100,000 population), Denmark (2,723) and the Netherlands (2,532) are the countries with the highest 5-year cancer prevalence (Figure 101). Differentiating between gender and type of cancer, in men the most prevalent types of cancer at 5 years are prostate cancer (5,033,178 cases), colorectal cancer (3,183,756) and tracheal, bronchial and lung cancer (1,898,235). In the case of women, the most prevalent type of tumour is breast cancer, with 8,178,393 cases at 5 years, followed by colorectal cancer with 5,767,781 cases and thyroid cancer with 2,911,382 cases[251].

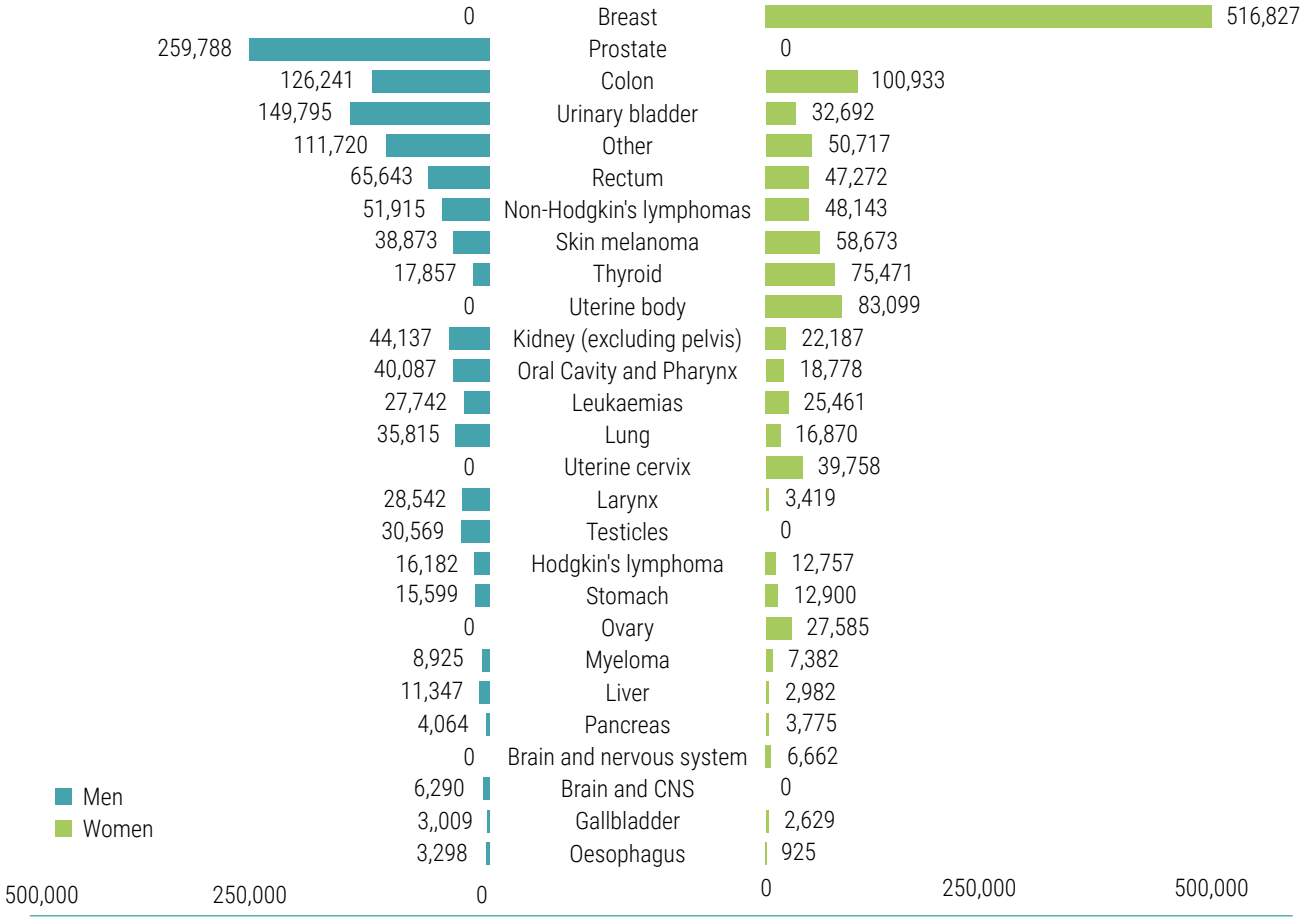
FIGURE 101. ESTIMATED NUMBER OF PREVALENT CANCER CASES AT 5 YEARS (PER 100,000 POPULATION), BOTH GENDERS, 2022



Source: IARC/WHO (2024)[251]

In Spain, the estimated number of total prevalent cases in 2020 is 2,265,152 (1,066,959 in men and 1,198,193 in women). This represents a total of 4,611 cases per 100,000 men and 4,961 cases per 100,000 women. As the main factors influencing cancer prevalence are incidence and survival, the most frequent tumours with a good prognosis are particularly well represented in the prevalence. The most prevalent cancers are breast (516,827 cases), prostate (259,788), colon (227,174), urinary bladder (182,487), rectum (112,915) and non-Hodgkin's lymphomas (100,058) (Figure 102)[250].

FIGURE 102. ESTIMATED PREVALENCE OF CANCER BY TYPE OF CANCER BY GENDER IN SPAIN



Note: CNS: Central Nervous System. **Source:** Own elaboration based on REDECAN (2021)[250]

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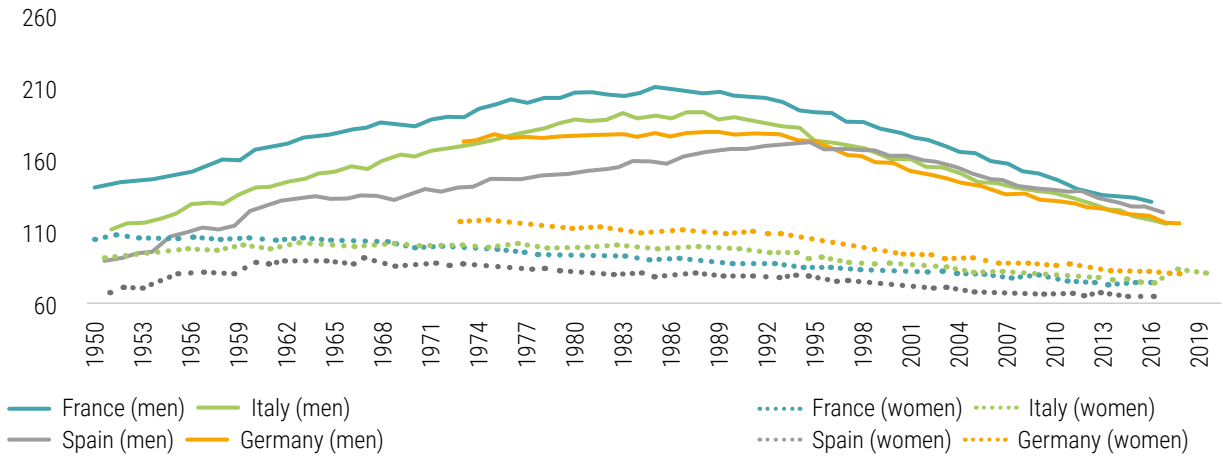
Mortality

Globally, cancer continues to be one of the main causes of mortality in the world, being responsible for almost 10 million deaths in 2020, which represents 1 out of every 6 deaths worldwide. Despite the increase in incidence, mortality rates have followed a downward trend, both in Spain and in neighbouring countries, especially since the 1970s in women and the mid-1980s in men (Figure 103)[253].

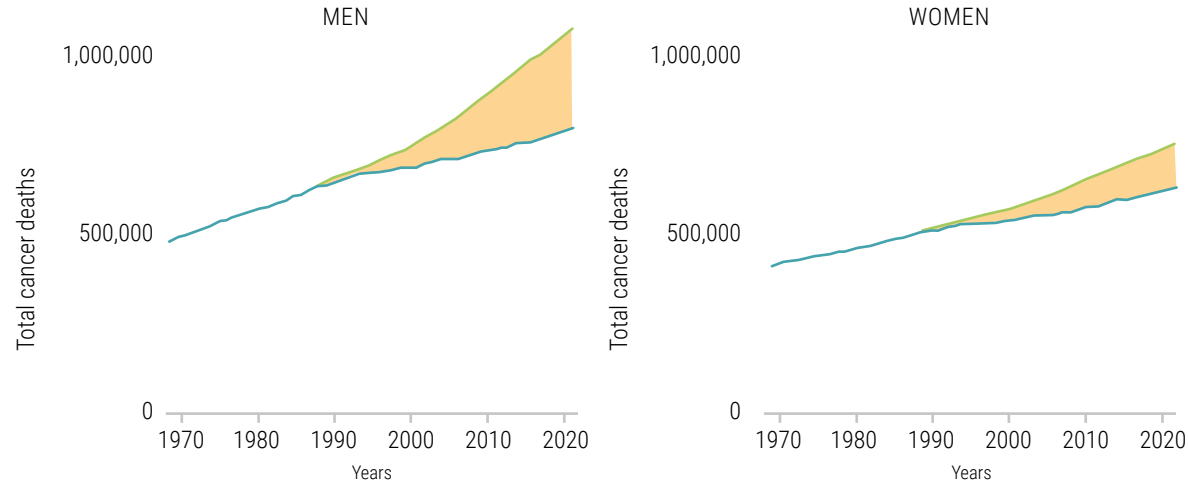
FIGURE 103. TREND IN AGE-STANDARDISED CANCER MORTALITY RATE IN SELECTED EUROPEAN COUNTRIES, BY GENDER, 1950 AND 2019



Source: IARC/WHO (2024)[253]

In Europe, the decline in cancer mortality has resulted in 5.8 million fewer cancer deaths over the past 35 years (3.9 million in men and 1.9 million in women) and 400,800 fewer cancer deaths by 2023 alone (286,800 in men and 114,000 in women) (Figure 104)[254]. This decline in mortality has been driven by, among other factors, improvements in cancer therapies, advances in diagnostic techniques and better early detection of cancer. However, although the mortality rate has decreased, in absolute terms total deaths have increased, mainly due to the increase and ageing of the European population.

FIGURE 104. TOTAL NUMBER OF CANCER DEATHS AVERTED, BY GENDER, EUROPE, 1988-2023



Source: Malvezzi (2023)[254]

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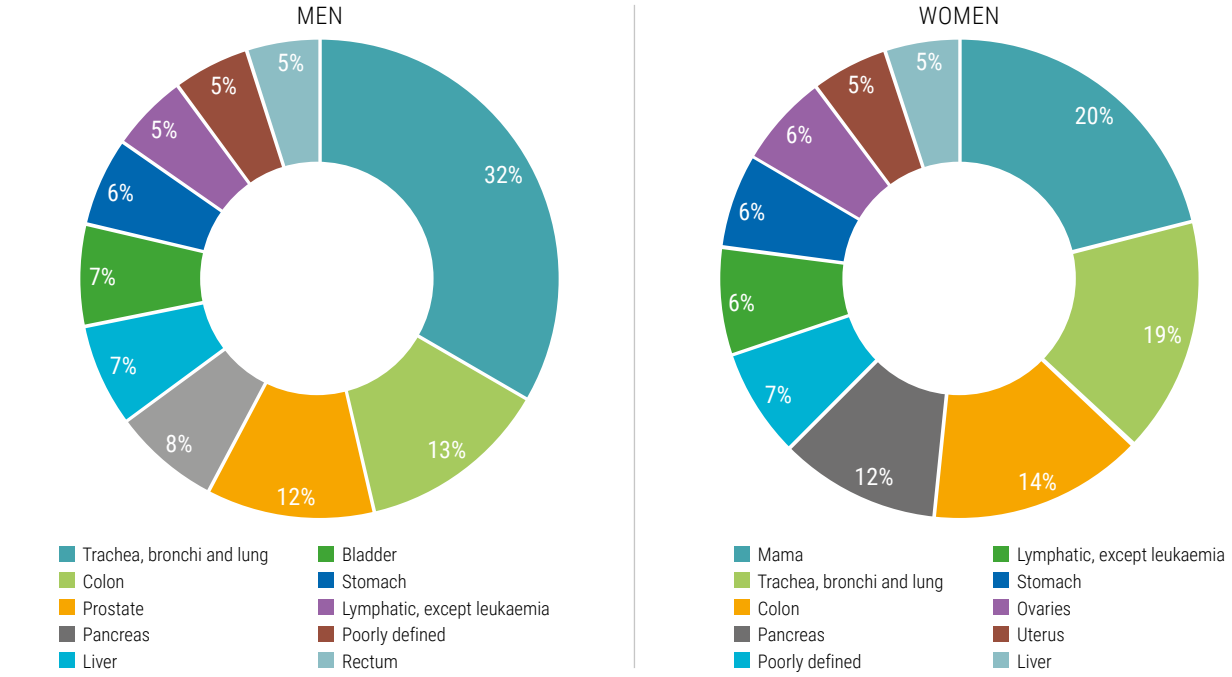
In Spain, according to data collected by the INE, in 2022 tumours caused 114,828 deaths, which represents 24.7% of the total deaths registered that year. By type, the tumour with the highest mortality is lung cancer, with a rate of 47.3 deaths per 100,000 inhabitants, followed by colon cancer. According to the mortality of the top 10 tumours by sex, lung, trachea and bronchus cancer accounts for the highest mortality in men, corresponding to 32%, followed by colon cancer, with 13%. In women, the tumour types with the highest mortality are breast (20%) and trachea, bronchi and lung (19%) (Figure 105)[203].

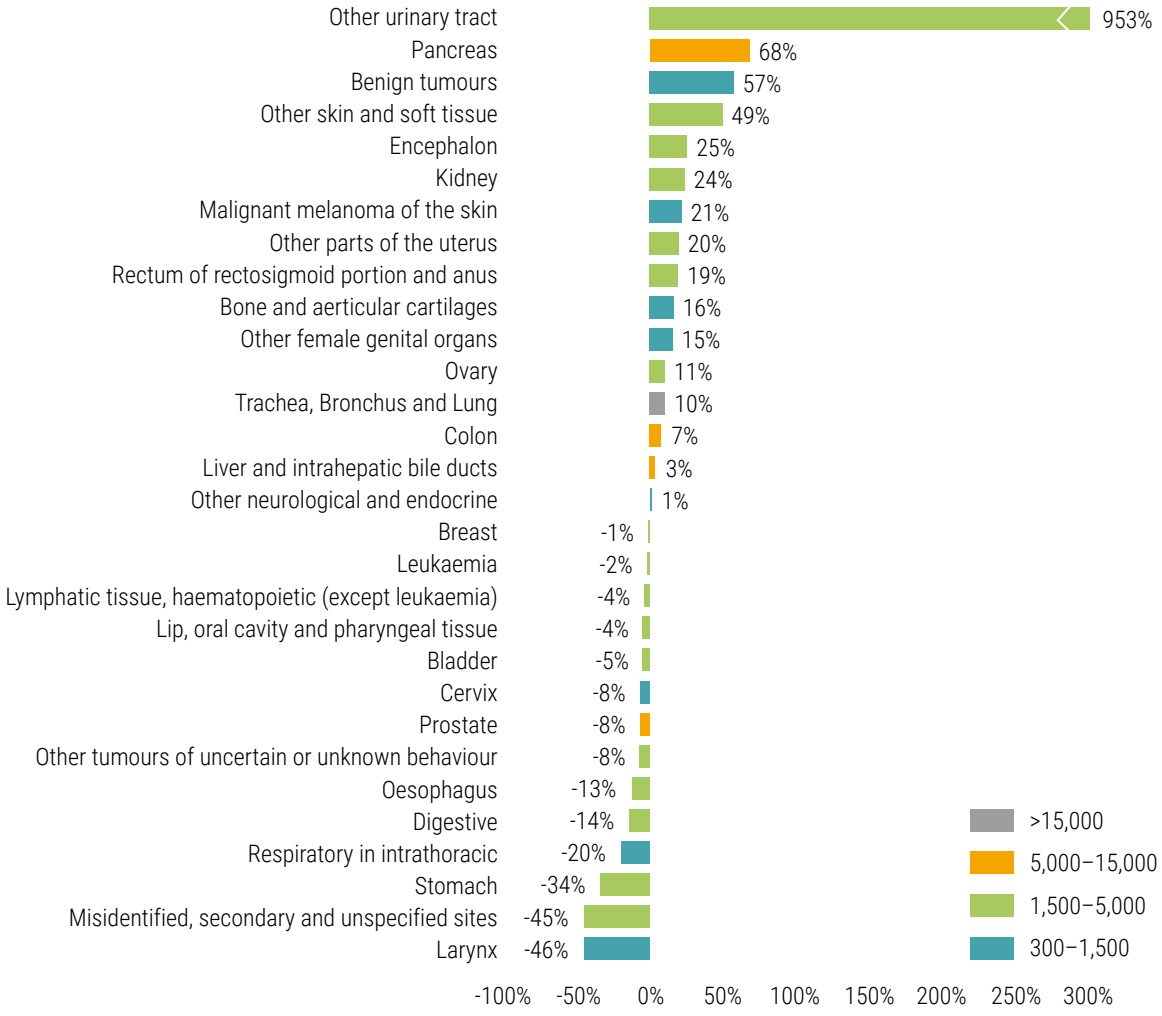
FIGURE 105. DISTRIBUTION OF MORTALITY OF THE FIRST 10 TYPES OF CANCER, BY GENDER, SPAIN, 2022



Source: Own elaboration based on INE data (2024)[203]

In terms of evolution over time, the type of cancer whose mortality rate has decreased most markedly in Spain during the period 2000-2022 has been the larynx tumour (46%) and the group of poorly defined and unspecified tumours (45%), with a mortality rate per 100,000 inhabitants of 2.4 and 9.47 by 2022, respectively (Figure 106)[203]. In contrast, the largest increase in the relative mortality rate has occurred in other tumours of the urinary tract (including tumours of the ureter, urethra and others), from 148 deaths in 2000 to 1,833 in 2022.

FIGURE 106. EVOLUTION OF THE MORTALITY RATE (PER 100,000 INHABITANTS) OF THE DIFFERENT TYPES OF TUMOURS, SPAIN, 2000-2022



Source: Own elaboration based on INE data (2024)[203]

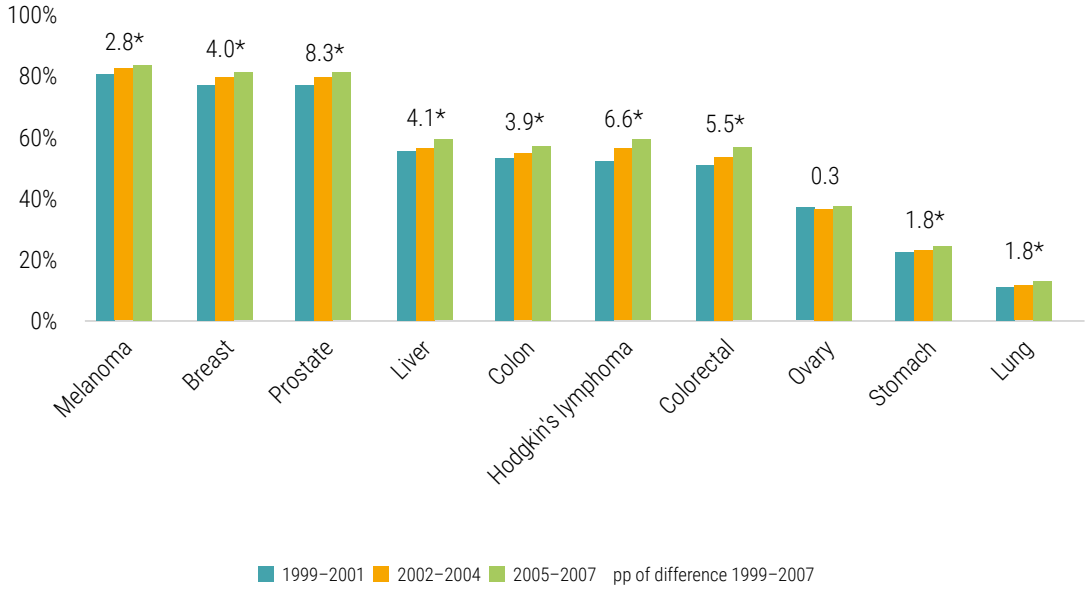
Survival

Survival is one of the most widely used indicators of the status of different types of cancer, beyond incidence, prevalence and mortality. The use of this indicator is made possible by the decline in mortality, making the measure of long-term survival (5 years) meaningful.

According to data from the CONCORD-3 study, an analysis of more than 37.5 million patients diagnosed with cancer in over 71 countries, 5-year survival has increased in recent decades for most tumours, including those with the highest mortality rates. These improvements in survival (between 2000 and 2014) have been especially important in breast, prostate and childhood lymphoid cancer, with 78%, 85% and 88% improvement respectively255. In this respect, the USA, Canada, Australia, New Zealand and the Nordic countries are the countries with the highest cancer survival rates.

The tumour types with the highest 5-year survival rates in Europe were testicular cancer (88.6%) and lip cancer (88.1%), followed by thyroid cancer (86.5%), prostate (83.4%), squamous cell melanoma (83.2%), breast (women only; 81.8%) and Hodgkin's lymphoma (80.8%). About one-third of all cancer cases maintained a survival of more than 80%, while it was less than 30% in about one-quarter of cases (Figure 107)[256].

FIGURE 107. EVOLUTION OF 5-YEAR RELATIVE SURVIVAL RATES IN ADULT CANCER PATIENTS, EUROPE, 1999-2007

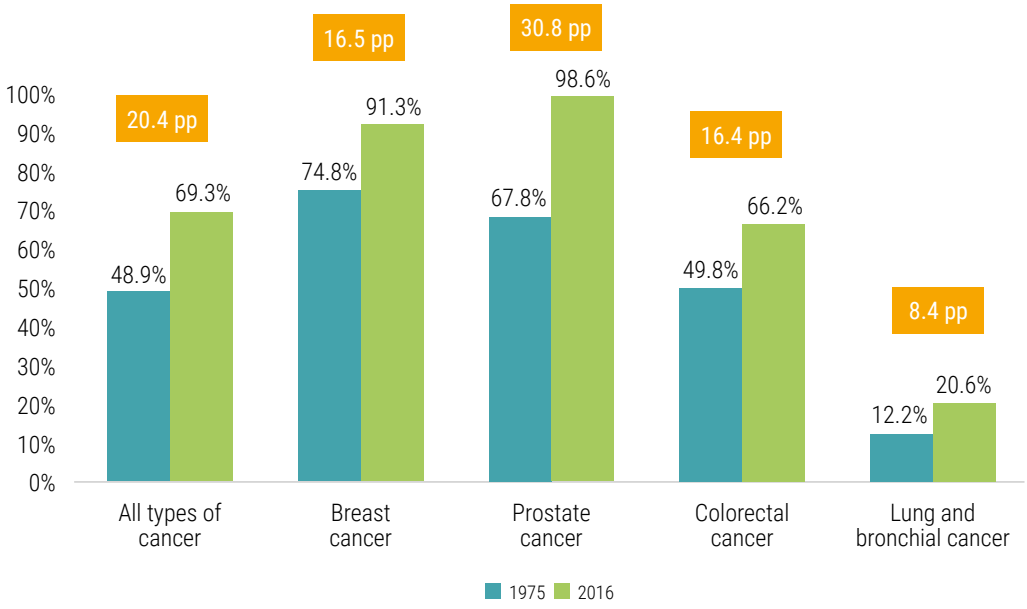


Note: Age-standardised 5-year survival rates. Differences between the first and last follow-up period are presented in percentage points. *: p<0,001.

Source: Own elaboration based on EUROCARE-5 data[256].

In the US, 5-year survival has also followed a positive trend, increasing by more than 20 percentage points in the period 1975-2016 (Figure 108)[257,258].

FIGURE 108. AGE-STANDARDISED 5-YEAR SURVIVAL RATES FOR THE MOST COMMON TUMOURS, USA, 1975-2016

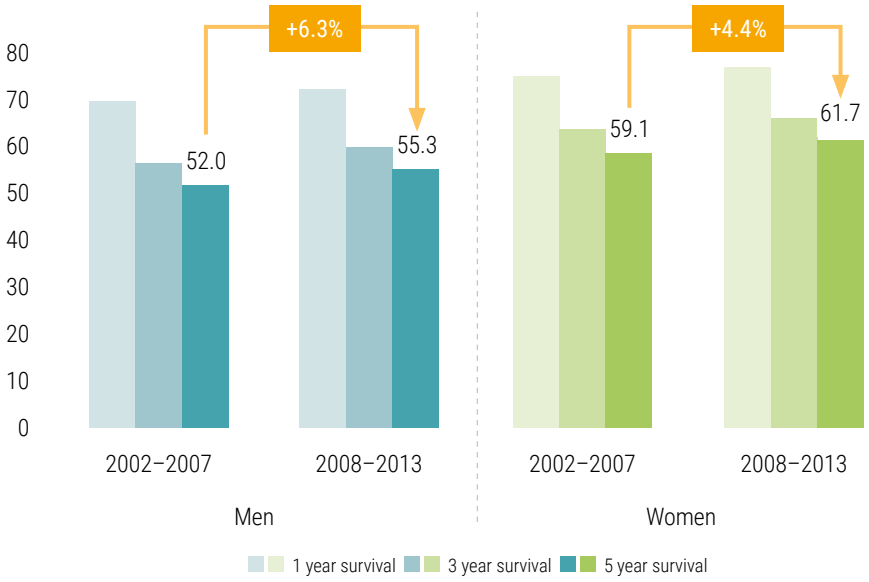


Abbreviation: pp: percentage points.

Source: Own elaboration based on data from the US National Cancer Institute (2020)[258] and Howlader (2019)[257]

In Spain, the survival of cancer patients has continued to increase in recent years, whether at 1, 3 or 5 years. Between the periods 2002-2007 and 2008-2013, 1-year survival has increased from 70% to 72.7% among men and from 75.3% to 77.4% among women. The measure that has increased the most in both sexes is 5-year survival (an increase of 3.3 percentage points in men and 2.6 percentage points in women), although there are differences between tumour types (Figure 109)[259]. Thus, among men, 5-year survival has increased to 90% for prostate cancer and 86% for thyroid cancer, while among women, breast cancer and cutaneous melanoma reached 86% and 89% survival, respectively[260].

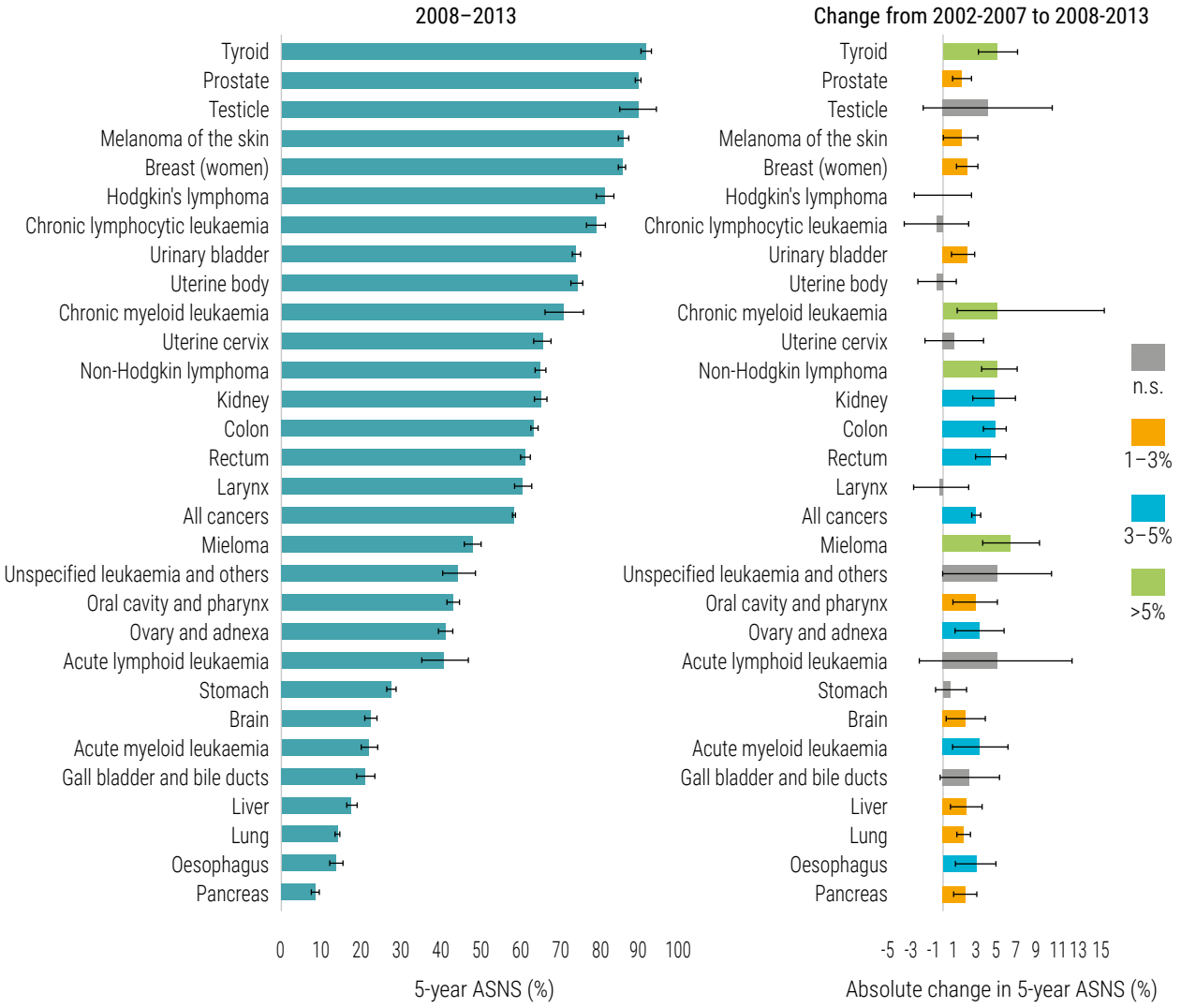
FIGURE 109. SURVIVAL RATE (%) AT 1,3 AND 5 YEARS FOR CANCER (EXCEPT NON-MELANOMA SKIN CANCER) BY SEX, SPAIN, 2002-2007 AND 2008-2013



Source: Own elaboration based on REDECAN (2020)[259]

In both sexes combined, there were significant increases in overall survival and for most cancer groups between 2002-2007 and 2008-2013 as seen in Figure 110. 5-year age-standardised net survival increased by more than 5% in patients with thyroid cancer, chronic myeloid leukaemia, non-Hodgkin's lymphoma and myeloma. Absolute increases of 3-5% were observed in kidney, colon, rectum, ovary and adnexa, acute myeloid leukaemia and esophageal cancer. In addition, 1-3% increases in 5-year age-standardised net survival (ASNS) were found in patients with prostate, melanoma skin, female breast, urinary bladder, oral cavity and pharynx, brain, liver, lung and pancreatic cancers[261].

FIGURE 110. FIVE-YEAR AGE-STANDARDISED NET SURVIVAL BY CANCER GROUP IN PATIENTS DIAGNOSED WITH CANCER IN SPAIN IN 2008-2013 (LEFT PANEL) AND ABSOLUTE CHANGE FROM 2002-2007 TO 2008-2013 (RIGHT PANEL)



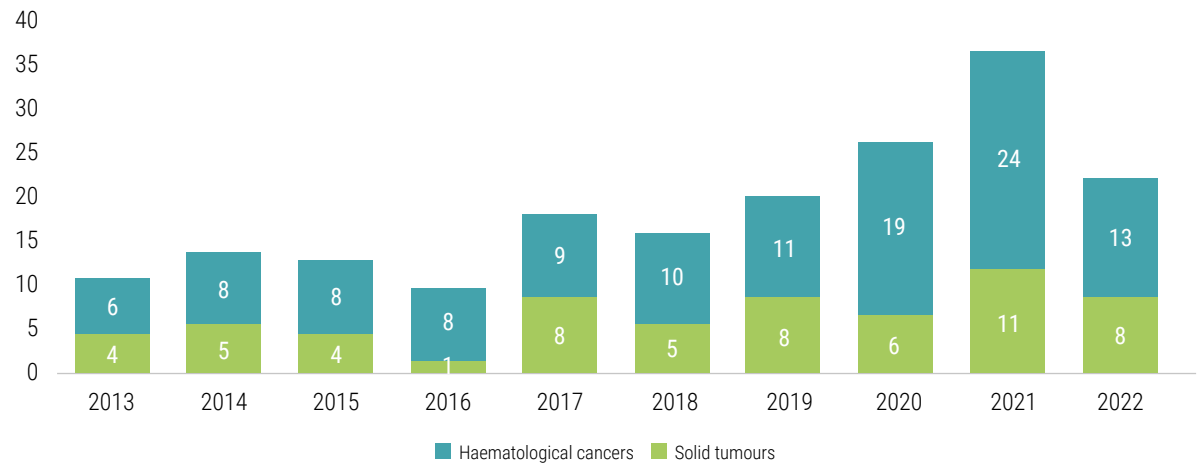
Abbreviation: ASNS: age-standardised net survival

Source: Guevara (2022)[262]

Advances in treatment options

Advances in cancer prevention and early diagnosis, as well as improvements in the quality of care, have contributed significantly to improving cancer prognosis. In this regard, it is worth highlighting the role of pharmacological treatment both in prevention, with the implementation of vaccination strategies against viruses responsible for the development of tumours such as HPV and hepatitis B virus (HBV), and in the therapeutic approach to cancer[248,263]. Thus, science has made substantial progress in cancer treatment, improving the therapeutic arsenal for different types of tumours. This progress is evidenced by the worldwide launch of a total of 237 new active substances against cancer in the last 20 years, 115 of which were authorised in the last five years (Figure 111)[264]. In addition, more than 100 new cancer medicines are expected to be launched in the next 5 years, including innovative treatments using cell therapy, RNA therapy and immuno-oncology treatments[265].

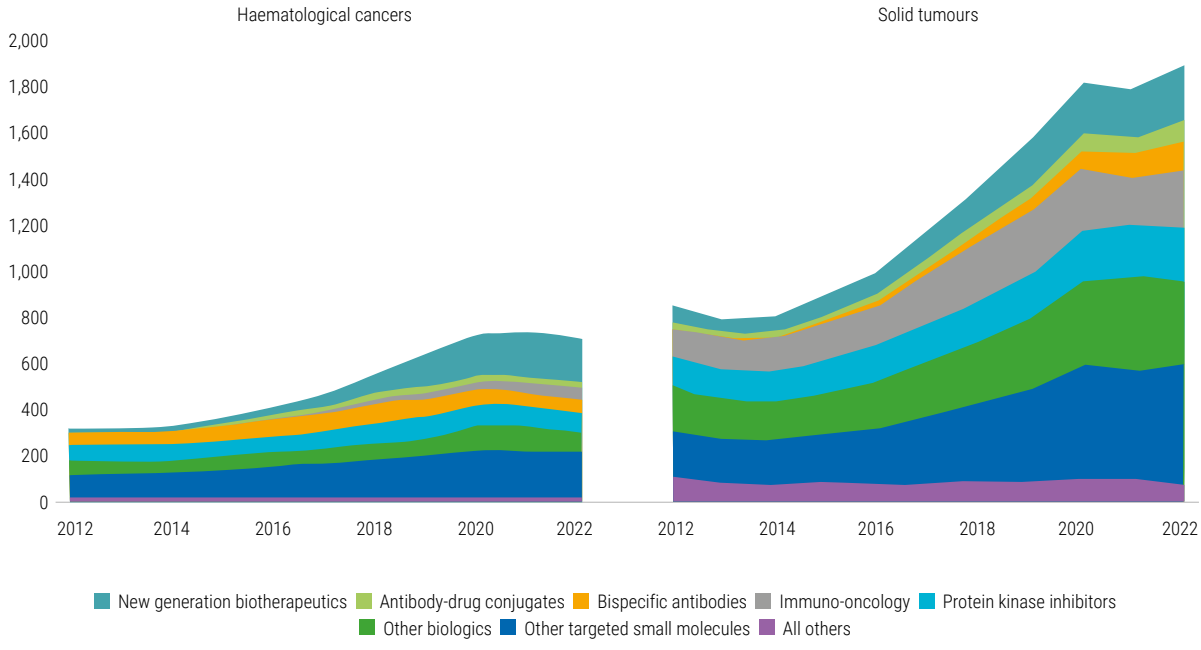
FIGURE 111. EVOLUTION IN THE NUMBER OF GLOBAL LAUNCHES OF NEW CANCER THERAPIES, 2013-2022



Source: IQVIA (2023)[264]

While drug development for haematological cancers declined by 4% in 2022, clinical development of drugs for solid tumours grew by 5%. The development of bispecific antibodies for cancer treatment has grown significantly, and now accounts for 7% of drugs in development for both haematological cancers and solid tumours, while conjugated antibodies have grown by 65% in the last five years. On the other hand, new generation biologic therapies (based on nucleotides, mRNA, etc.) are a novel group of drugs that are increasingly being investigated in both haematological cancer and solid tumours, and in the case of haematological tumours represent 28% of the drugs in development in 2022 (Figure 112)[264].

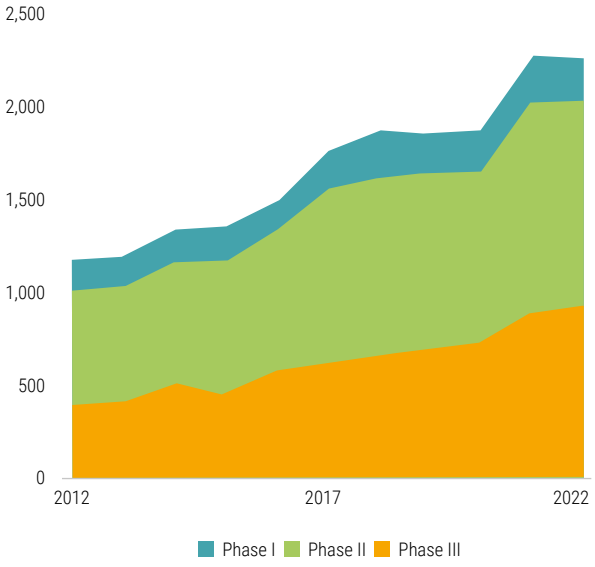
FIGURE 112. EVOLUTION IN THE NUMBER OF FIRST-STAGE MOLECULES IN CANCER TREATMENT, 2012-2022



Source: IQVIA (2023)[264]

In addition to approvals in recent years, the future of cancer treatment is promising, with more than 2,000 active clinical trials in different phases in 2022, with new trials starting in 2023 (Figure 113)[264].

FIGURE 113. NUMBER OF CLINICAL TRIALS IN ONCOLOGY BY PHASE, 2012-2022



Source: IQVIA (2023)[264]

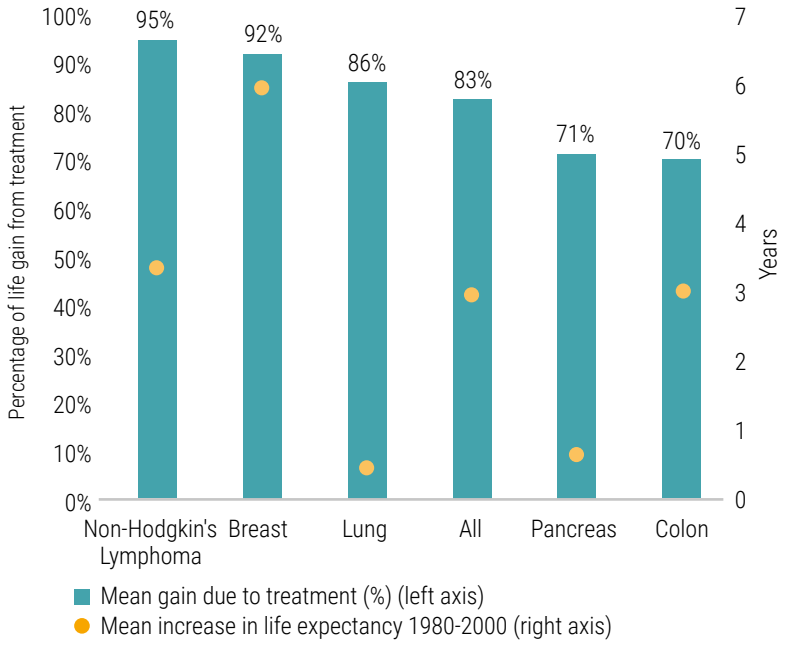
Traditionally, in oncology, tumours have been identified by their origin, classifying patients by histological type and tumour stage. Nowadays, thanks to the implementation of new sequencing techniques, it is possible to rapidly identify genomic alterations in tumours, helping to understand the evolution and function of the human genome and providing valuable information for the treatment of diseases[266–268]. The applicability of mass sequencing in clinical practice is a medical and scientific revolution worldwide that has given rise to a new, more effective model of personalised medicine[269]. Thus, knowledge of the biology of cancer allows for a deeper understanding of the biological tumour profile of each patient, as well as how these alterations condition the behaviour of the disease[270]. Immunotherapy and, more recently, advanced and targeted therapies with radioligands are clear examples of the development of pharmacological innovation in oncology.

As mentioned above, pharmacological advances have considerably improved the health of patients. Thus, according to a study by Lichtenberg (2004), new cancer drugs are directly responsible for a large part (between 50 and 60%) of the increase in survival of cancer patients. The paper specifies that those types of cancer for which the therapeutic arsenal of drugs grew most rapidly sustained the greatest increases in survival rates. Specifically, it estimates that the therapeutic arsenal of new drugs launched in the United States between 1975 and 1995 generated an increase of 6.7 percentage points (pp) in 1-year survival, 5.8 pp in 5-year survival and 3.9 pp in 10-year survival[271].

Continuing the impact of new treatments and pharmacological approaches on the survival of cancer patients, a study analysed the relationship between improved treatments over the period 1980-2000 and increases in life expectancy. The study examined the gains for all types of cancer, and specifically for breast, lung, colon, non-Hodgkin's lymphoma and pancreatic cancer. The results of the study indicated that during this period there was an average increase of 3 years in life expectancy for all tumours studied, and that 83% of this increase came from the effect of drug treatments. Broken down by type, the treatments with the greatest impact on life expectancy were those indicated for non-Hodgkin's lymphoma and breast cancer, with an impact of 95% and 92%, respectively, followed by lung (86%), pancreatic (71%) and colon cancer (70%) (Figure 114)[272].

Another study goes further and concludes that 73% of the reduction in cancer mortality (3-year) for the period 1997-2007 in the US is attributable to new treatments, while the remainder is due to advances in early detection (Figure 115)[273].

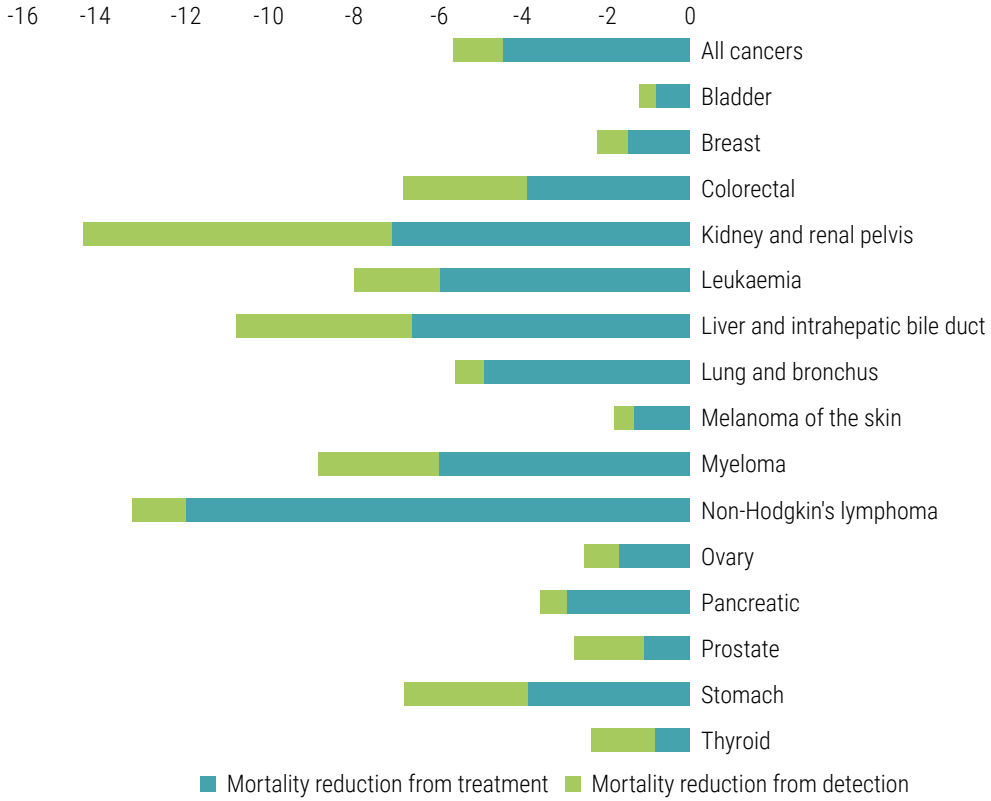
FIGURE 114. AVERAGE GAIN IN LIFE EXPECTANCY DUE TO DRUG TREATMENT (%) AND INCREASE IN AVERAGE LIFE EXPECTANCY IN CERTAIN TYPES OF TUMOUR 1980-2000



Source: Own elaboration based on Sun (2008)[272]

In recent years, Lichtenberg has completed his line of research with similar studies for countries such as South Korea, New Zealand and Spain (Table 6). For South Korea, he estimates that new cancer drugs increased the five-year relative survival rate for all cancers combined by 23.2 percentage points (78.5% of the total increase) between 1993-1995 and 2011-2015[199]. In the case of New Zealand, new cancer drugs approved during 1985-2001 reduced the number of years of potential life lost before the age of 85 in 2017 by 67%. In addition, the odds of surviving at least 5 years after diagnosis are significantly related to the number of previously approved therapies[72].

FIGURE 115. REDUCTIONS IN CANCER-RELATED MORTALITY DUE TO TREATMENT AND DETECTION BY TUMOR TYPE, USA, 1997–2007



Source: Seabury (2015)[273]

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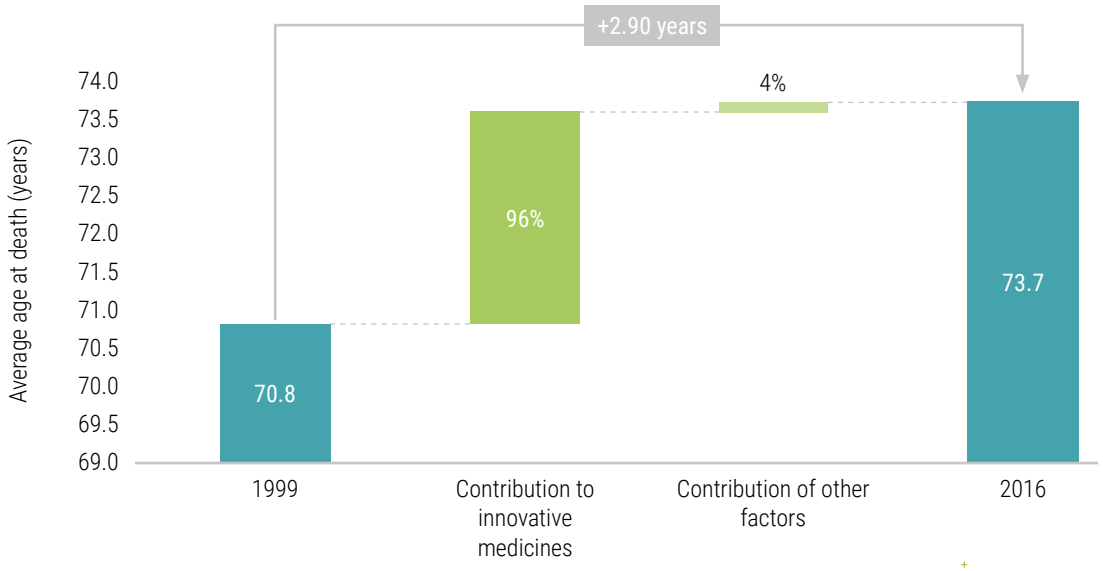
COUNTRY	YEAR OF PUBLICATION	STUDY CONCLUSION
United States[271]	2004	The introduction of cancer drugs in 1975-1995 led to a 6.7, 5.8 and 3.9 pp increase in 1-, 5- and 10-year survival, respectively. This means that between 50% and 60% of the increase in survival in that period is directly associated with the new cancer drugs.
France[274]	2012	The introduction of new cancer treatments is associated with a reduction in mortality in the period 2002-2006 of between 1% and 3% (between 16% and 50% of the total reduction in mortality for that period in France).
United States[275]	2015	The introduction of chemotherapy in 1997 to treat myeloma patients resulted in an increase in life expectancy of 0.99 years (65% of the total increase) in the period 1997-2005.
Canada[276]	2015	The launch of new cancer drugs between 1985-1996 generated a cumulative gain of 105,366 years of life before age 75 in 2011.
Slovenia[277]	2015	Approximately two-thirds of the decline in premature cancer mortality between 2000 and 2010 was due to pharmaceutical innovation. In the absence of such innovation, the number of deaths would have been 12.2% higher.
Switzerland[60]	2016	17,000 years of life were gained before the age of 75 in 2012 as a result of the launch of new cancer drugs between 1990-2007.
Belgium[278]	2016	Cancer mortality was reduced by 20% in 2012 (life expectancy increased by 1.52 years), thanks to cancer drugs launched in 1987-1995.
Australia[279]	2017	Sixty percent of the reduction in premature mortality in the period 1998-2007 was due to prior pharmaceutical innovation. Such innovation was responsible for 40% of the increase in 5-year survival during that period.
Colombia[280]	2017	Cancer-specific results estimate that the number of years potentially lost by patients is inversely proportional to the number of cancer drugs launched 3-4 years earlier.
Mexico[281]	2017	The launch of new cancer drugs between 1991-2001 generated a gain of 105,661 years of life before the age of 70 in 2013.
Russia[71]	2018	The reduction of 243,774 years of life potentially lost before the age of 75 in 2011 stems from the launch of oncology drugs, which are responsible for 94% of the reduction in the mortality rate between 2001 and 2011..
36 countries[282]	2018	The launch of new cancer drugs between 1982 and 2010 averted 23% of the years of life lost in patients with 19 types of cancer in 2015 (equivalent to 6,049,000 years of life gained).
United States[283]	2018	Seventy per cent of the gain in 5-year survival for all cancer types during the period 1994-2008 comes from the increase in medical innovations 12-24 years earlier.
United States[70]	2020	Oncological drugs approved between 2000 and 2014 reduced potential years of life lost before the age of 75 by 719,133 in 2014.
South Korea[199]	2020	New drugs increased the five-year relative survival rate for all cancers combined by 23.2 percentage points (78.5% of the total increase) between 1993-1995 and 2011-2015.
New Zealand[72]	2021	New cancer drugs approved during 1985-2001 reduced the number of years of potential life lost before age 85 in 2017 by 67%.
Spain[73]	2023	Pharmaceutical innovation in oncology was associated with a 2.77-year increase (96% of the observed increase) in the median age of death from cancer between 1999 and 2016.

Source: Own elaboration based on Lichtenberg (references detailed in the table).

In Lichtenberg's study on the impact of cancer drugs in Spain, the author concludes that innovative cancer drugs approved in the period 1999-2016 for 58 types of cancer were associated with an average increase of 2.77 years in the average age of death from cancer in 2016, accounting for 96% of the observed increase (Figure 116). Thus, new cancer medicines approved in that period were associated with a reduction of 42,138 cancer deaths in 2016. The author estimates that new drug approvals between 1997 and 2014 were associated with a 29.2% reduction in the number of cancer deaths in 2016. This implies that, if there had been no new drug additions in that period, the number of deaths in 2016 would have been 41.2% higher than today (i.e. 42,138 more deaths). Similarly, new drug approvals were associated with a 29.7%, 35.1% and 35.2% reduction, respectively, in the number of years of life potentially lost before the age of 65, 75 and 85 years in 2016[73].

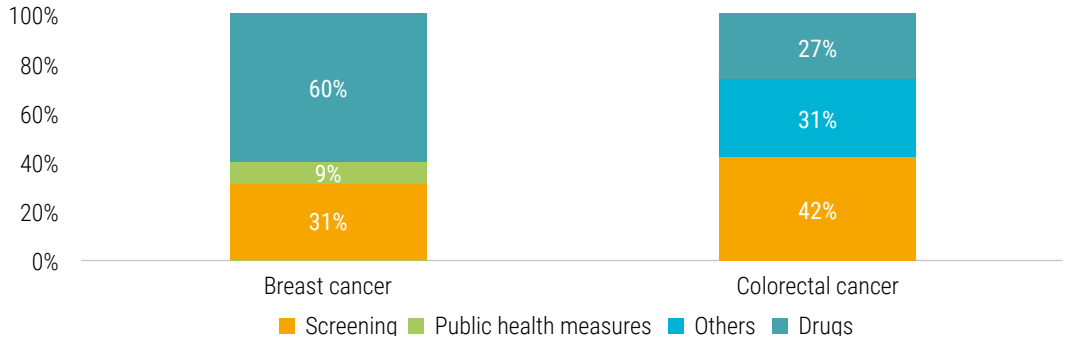
FIGURE 116. CONTRIBUTION OF NEW DRUGS TO THE AVERAGE AGE OF DEATH FROM CANCER, SPAIN 1999-2016



Source: Lichtenberg (2023)[73]

Another example along the same lines can be found in the results of Buxbaum, who showed that 60% of life extension in breast cancer and 30% in colorectal cancer can be attributed to drugs (Figure 117)[284]. In addition, other authors have also indicated that an important part of these mortality gains is due to new drugs[285–287].

FIGURE 117. ESTIMATED IMPACT OF DRUGS, OTHER MEDICAL CARE AND PUBLIC HEALTH MEASURES ON CHANGES IN BREAST AND COLORECTAL CANCER MORTALITY, USA.



Source: Own elaboration based onBuxbaum (2020)[284]

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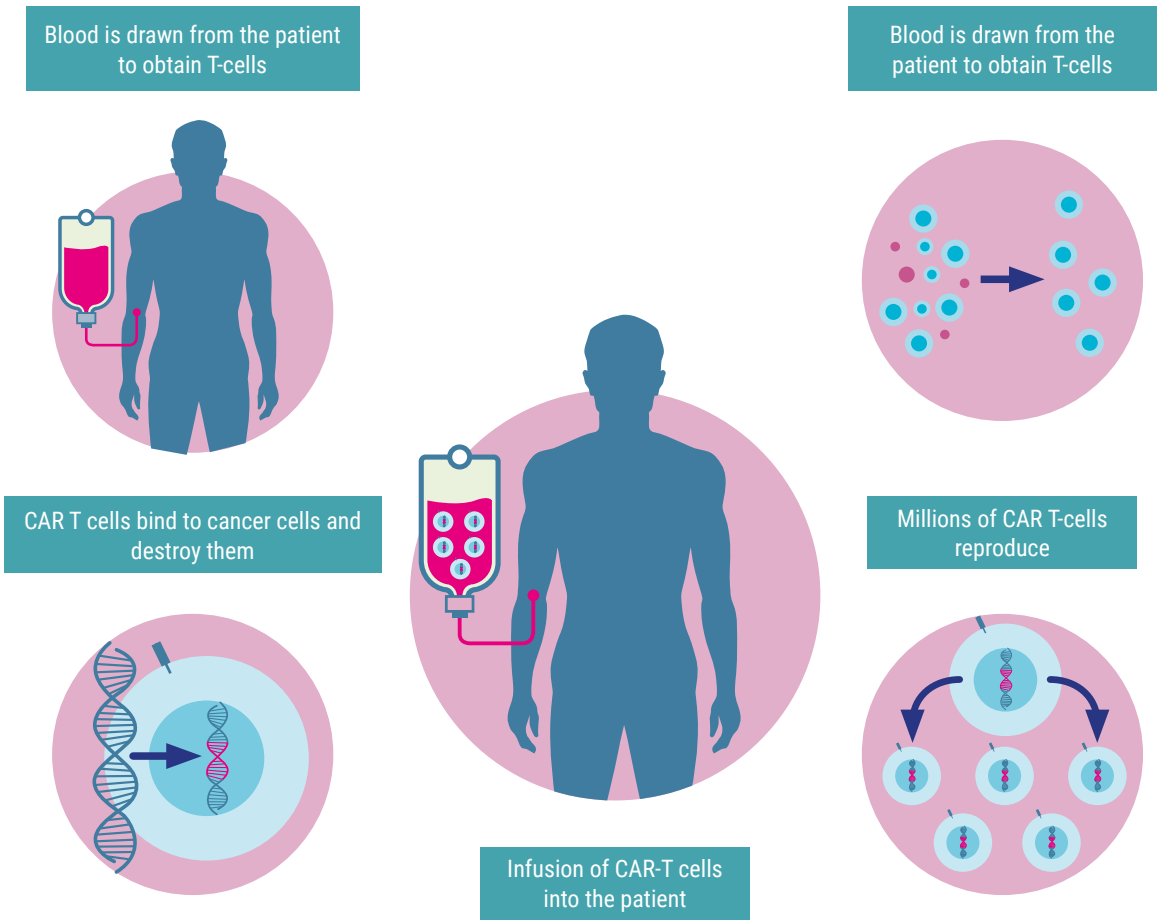
On the other hand, it is important to understand the impact that the entry of new oncology drugs has had on patients' quality of life. According to a study by Lichtenberg (2018), the commercialisation of cancer drugs between 1982 and 2010 averted 23% of disability-adjusted life years lost in cancer patients in 2015 in 36 countries. Likewise, the launch of a cancer drug for a given tumour type during the period 2006-2010 reduced the number of years of life lost due to disability for that tumour by 5.8%. This implies that if no cancer drug had been launched during that period, a total of 8.04 million years of life would have been lost in patients affected by that disease[282].

Examples of concrete breakthroughs in some cancers

In recent decades, a deeper understanding of the nature of cancer cells has facilitated the development of more effective therapies[270]. The emergence first of immunotherapy and targeted therapies, and then of advanced therapies (CAR-T) and targeted therapies with radioligands, have opened a new framework for action in the era of personalised precision medicine, resulting in better health outcomes for patients.

FIGURE 118. OPERATION OF CAR T-CELL THERAPY (CAR-T)



Source: Own elaboration based on CADIME (2020)[288]

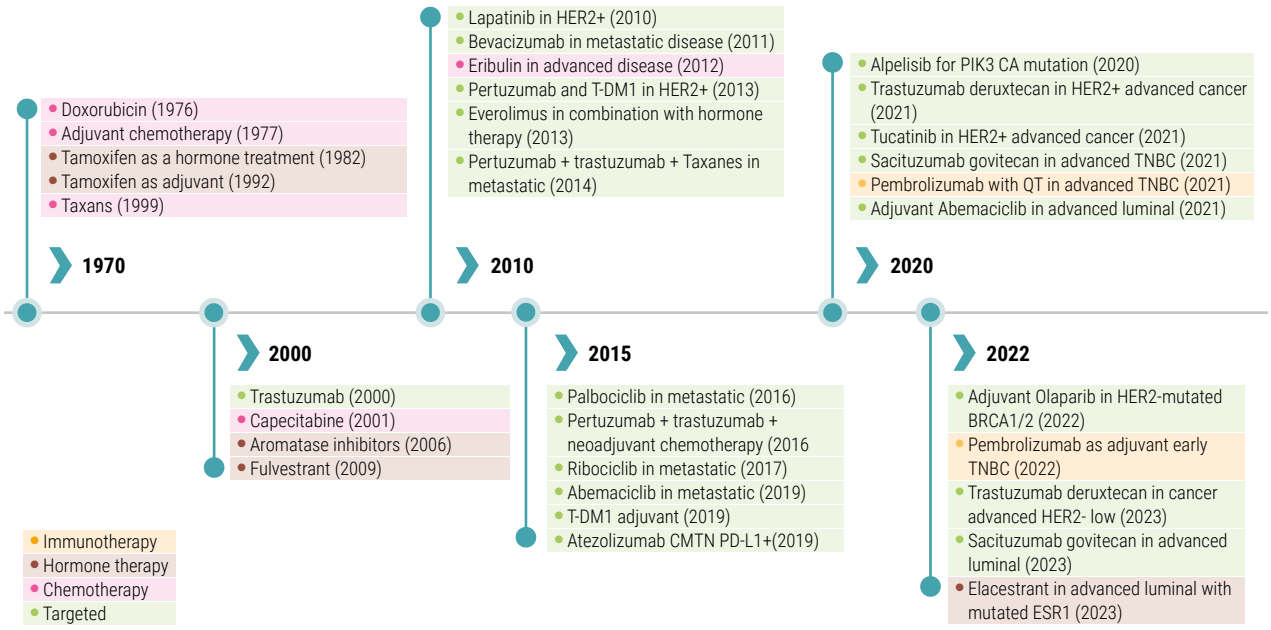
In the following, we will exemplify different cases of progression, by tumour type.

Advances in solid tumours have gone hand in hand with research in precision medicine, creating new substances that target specific mutations in each cancer, leaving behind therapies based on systemic chemotherapy in certain conditions.

In breast cancer, the 5-year survival rate has reached 90%, which has improved significantly in the last 20 years due to molecular classification diagnosis and personalised breast cancer treatment, as well as the

advancement of antineoplastic drugs[289]. In more detail, the incorporation of new drugs into breast cancer treatment has improved survival for patients with the 3 main breast cancer subtypes[290]. Since 2020, the advent of new biologic therapies such as abemaciclib, olaparib or sacituzumab, as well as new forms of chemotherapy and immunotherapy, have provided new avenues of treatment that offer improvements in health for women with breast cancer (Figure 119).

FIGURE 119. ADVANCES IN BREAST CANCER TREATMENT, 1970-2023



Abbreviations: TNBC: triple-negative breast cancer; QT: chemotherapy

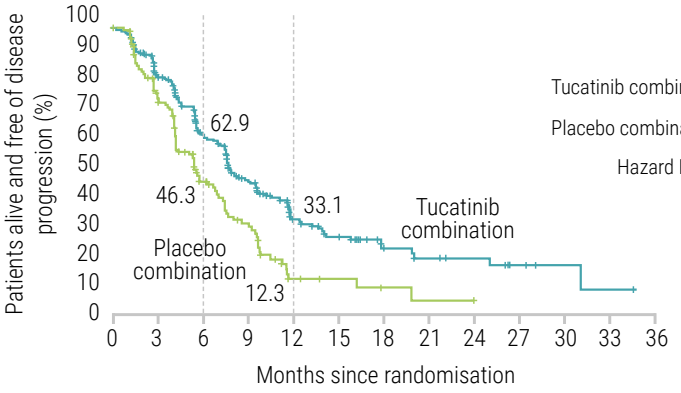
Source: Own elaboration based on SEOM (2023)[290] and the National Cancer Institute (2024)[291]

The discovery of tumours expressing the HER2 gene has led to the development of monoclonal antibodies, such as trastuzumab and pertuzumab. The combination of these two monoclonal antibodies has shown improvements in efficacy, reducing the risk of relapse by 19% vs. trastuzumab and chemotherapy treatment[292]. In recent years, the combination of different drugs has shown health improvements over monotherapy regimens. For example, patients treated with the combination of pembrolizumab plus chemotherapy had improved PFS compared to chemotherapy alone (9.7 vs. 5.6 months)[293].

On the other hand, another trastuzumab/pertuzumab combination, this time with chemotherapy and the molecule tucatinib, has shown an improvement in the percentage of patients surviving at 2 years (45% vs 27% of the control group) and free of progression (33% vs 12%) (Figure 120)[294].

FIGURE 120. PROGRESSION-FREE SURVIVAL IN BREAST CANCER PATIENTS TREATED WITH TUCATINIB IN COMBINATION WITH TRASTUZUMAB AND CAPECITABINE

Kaplan-Meier estimates of progression free survival



	Nº. of episodes/ Nº. of patients	Median of duration (95%CI)
Tucatinib combination	178/320	7.8 (7.5-9.6)
Placebo combination	97/160	5.6 (4.2-7.1)

Hazard Ratio (HR) for disease progression or death: 0.54 (95%CI: 0.42-0.71), p<0.001

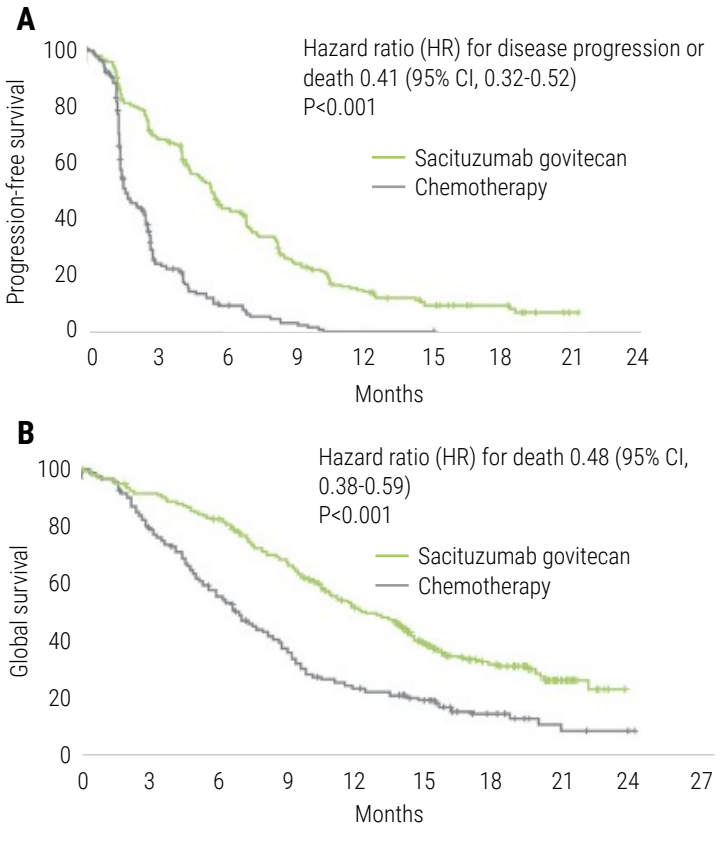
Source: Murthy (2019)[294]

There have also been significant advances in hormone-sensitive patients, with the arrival of biologic drugs which, together with conventional treatments such as hormone therapy, have achieved significant advances in the disease. For example, the arrival of everolimus, followed by CDK4/CDK6 inhibitors such as palbociclib, ribociclib or abemaciclib have further improved survival in this subgroup of patients[295].

One of the latest innovations in breast cancer treatment is the approval of the monoclonal antibody sacituzumab govitecan by the EMA in 2021 for the treatment of breast cancer. The study was conducted in adult patients with unresectable or metastatic triple-negative breast cancer who had received two or more prior treatments[296]. In a study of 468 patients, the median progression-free survival among patients treated with sacituzumab govitecan was 5.6 months (95% CI 4.3-6.3) vs. 5.6 months among patients treated with sacituzumab govitecan (95% CI 4.3-6.3). The median OS was 1.7 months (95% CI 1.5 to 2.6) for the control group treated with chemotherapy. In addition, median OS was 12.1 months (95% CI, 10.7 to 14.0) with sacituzumab govitecan and 6.7 months (95% CI, 5.8 to 7.7) with chemotherapy (Hazard Ratio [HR] of death, 0.48; 95% CI, 0.38 to 0.59;P <0.001) (Figure 121)[297].

In the field of lung cancer, research has enhanced understanding of the disease, leading to the introduction of new drugs and drug combinations that have marked

FIGURE 121. PROGRESSION-FREE SURVIVAL (A) AND OVERALL SURVIVAL (B) IN PATIENTS WITH BREAST CANCER. BREAST TREATED WITH SACITUZUMAB GOVITECAN



Fuente: Bardia (2021)[297]

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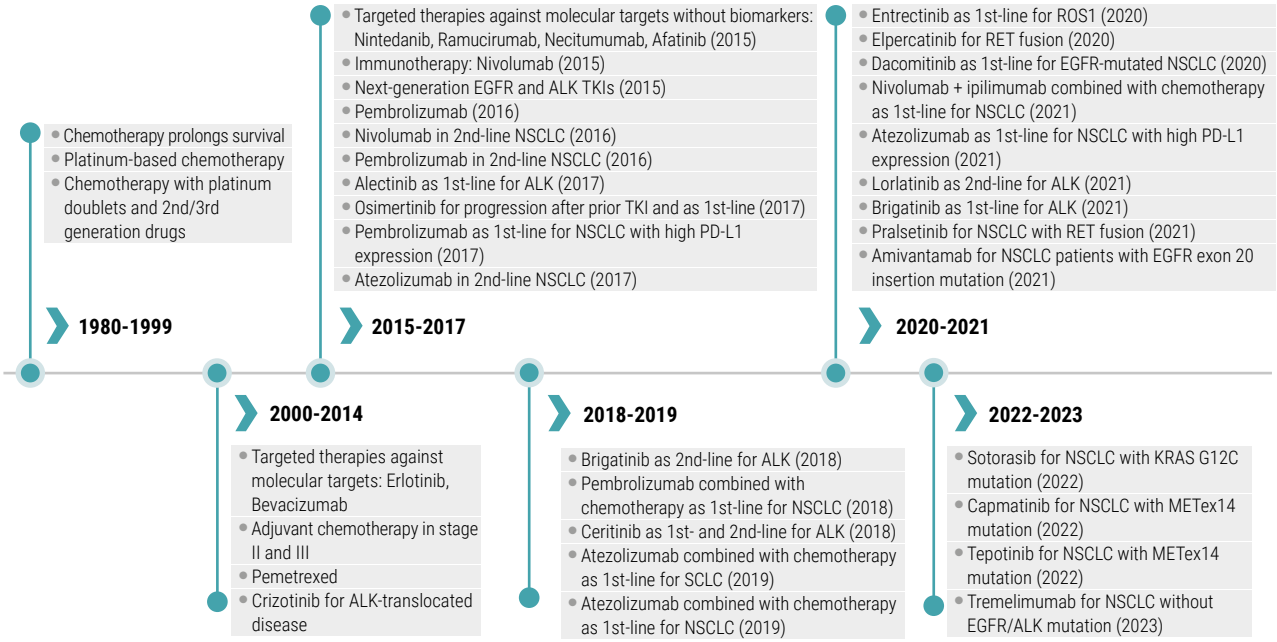
significant progress in combating this highly prevalent type of tumour. In this regard, immunotherapy—particularly PD-1/PD-L1 inhibitors (pembrolizumab, nivolumab, atezolizumab), either alone or in combination with CTLA-4 inhibitors (ipilimumab)—has revolutionized the treatment of lung cancer in both localized and advanced stages, demonstrating significant improvements in patient survival. Currently, immunotherapy has been established as a first-line option in combination with chemotherapy or as a second-line monotherapy treatment for patients with metastatic disease[298].

On the other hand, advances in the identification of molecular targets in lung cancer have driven the development of precision medicine, with numerous targeted drugs transforming the prognosis of many patients. Since the approval of the first drugs for EGFR mutations, such as erlotinib and gefitinib, significant progress has been made in the targeted treatment of these tumours. New drugs such as afatinib and more recently osimertinib, dacomitinib, mobocertinib and amivantamab have proven to be highly effective for patients with specific EGFR mutations[298].

For patients with ALK rearrangements, numerous drugs have been developed such as crizotinib, followed by alectinib, brigatinib, ceritinib, ensartinib and lorlatinib. In the treatment of tumours with ROS1 rearrangements, crizotinib and entrectinib have been approved, while for RET gene fusions, the drugs selpercatinib and pralsetinib have been approved. In addition, entrectinib and larotrectinib are used for NTRK-fusion tumours (Figure 12)[298].

FIGURE 122. ADVANCES IN LUNG CANCER TREATMENT, 1980-2023

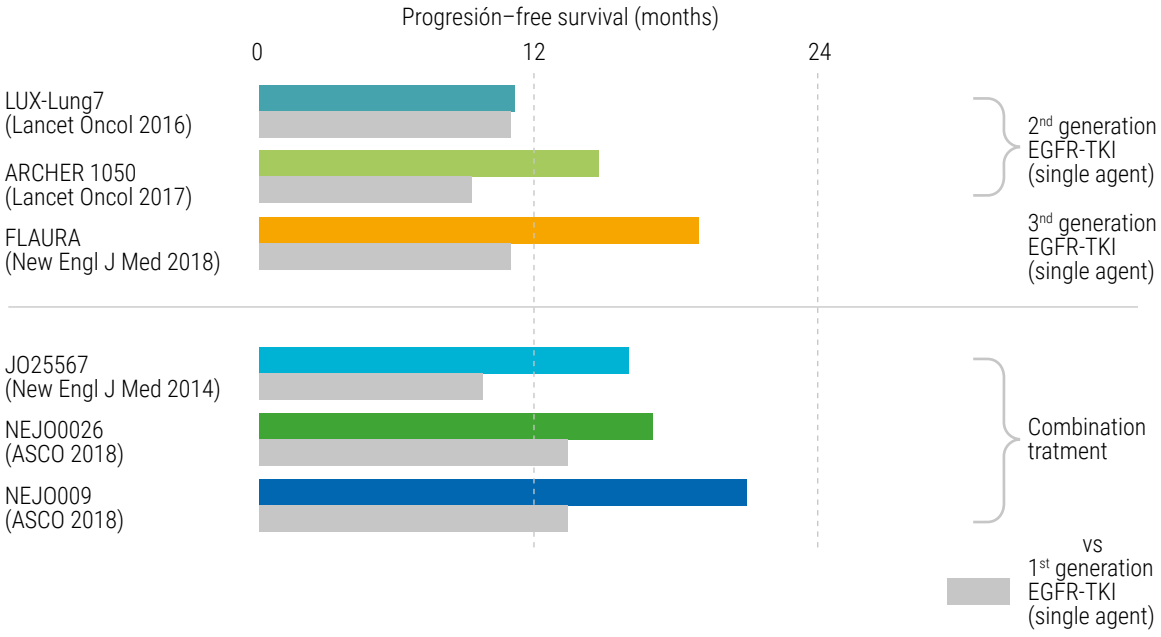


Abbreviations: **NSCLC:** non-small cell lung carcinoma; **SCLC:** small cell lung carcinoma

Source: Own elaboration based on SEOM (2021)[298] and EMA (2024)[299]

The study of the patient's genomic profile has been at the centre of advances, investigating which molecules are most effective for certain gene mutations expressed in patients' tumour cells. In this area, the recent emergence of new generation tyrosine kinase inhibitors has led to very significant advances in ALK and ROS1 translocations, as well as in the EGFR mutation[300–302]. Other molecular targets such as BRAF, HER2, HER3, KRAS, MET, PD-L1 and RET, among others, are also being investigated[301,303].

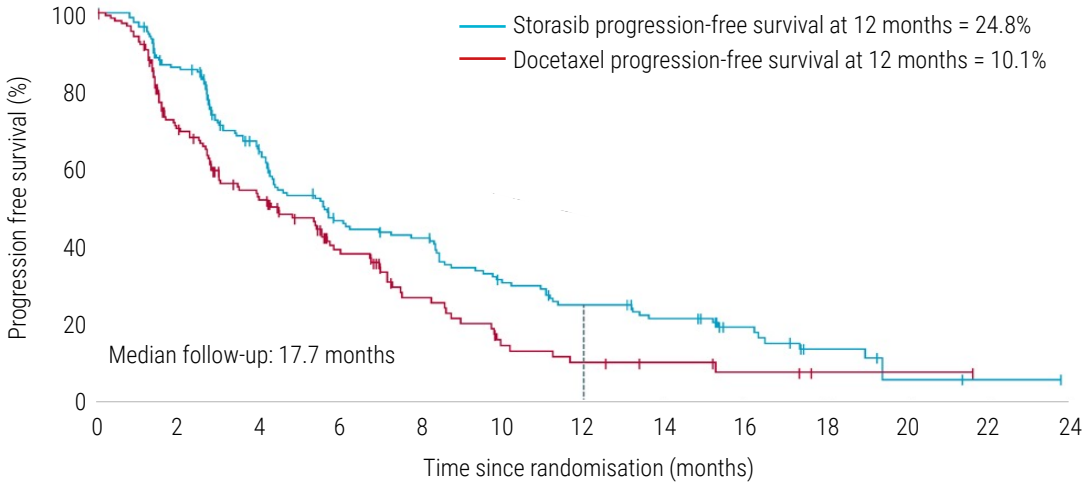
FIGURE 123. PROGRESSION-FREE SURVIVAL IN RANDOMISED CLINICAL TRIALS OF TYROSINE KINASE INHIBITORS WITH EGFR-TKI MUTATION



Fuente: Yoneda (2019)[302]

The latest treatments approved for this type of cancer also bring benefits, even for patients with advanced or metastatic disease. This is the case with sotorasib, which was approved by the EMA in 2022 for the treatment of patients with advanced non-small-cell lung cancer (NSCLC) with KRAS G12C mutation[304]. Treatment with sotorasib resulted in a median duration of response of 12.3 months, a progression-free survival of 6.3 months, an OS of 12.5 months and a 2-year OS rate of 33%[305]. Sotorasib has also demonstrated better health outcomes than treatment with chemotherapy (docetaxel). Sotorasib achieved a longer PFS than docetaxel (5.6 months vs 4.5), as well as fewer grade 3 or worse (33% vs 40%) and serious treatment-related adverse events compared to docetaxel (11% vs 23%) (Figure 124)[306].

FIGURE 124. PROGRESSION-FREE SURVIVAL IN LUNG CANCER PATIENTS TREATED WITH SOTORASIB VERSUS DOCETAXEL



Source: Of Langen (2023)[306]

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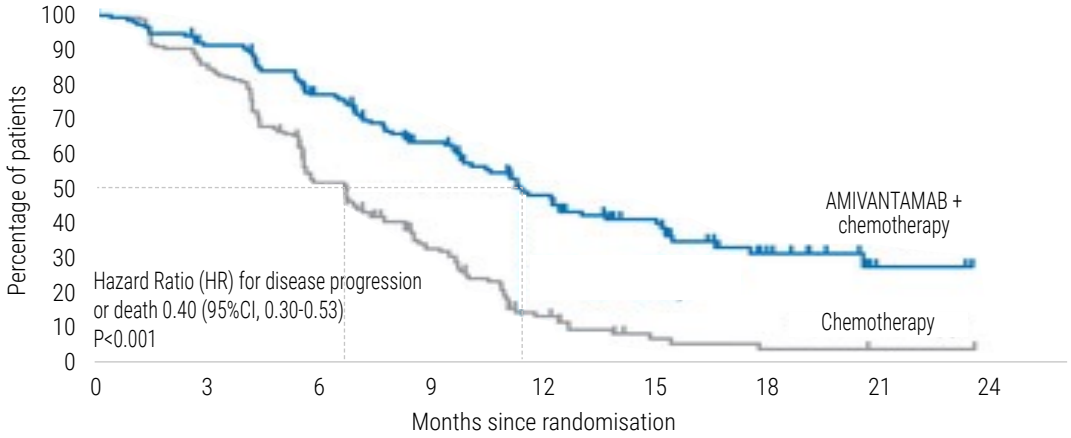
Another of the latest treatments approved by the EMA for lung cancer is the monoclonal antibody amivantamab, which targets activating insertional mutations in exon 20 of the EGFR[307]. In a study of 308 patients, co-therapy of amivantamab with chemotherapy showed better results than chemotherapy alone. Specifically, a median progression-free survival of 11.4 months versus 6.7 months, respectively, was achieved, and at 18 months follow-up, progression-free survival was reported in 31% of patients in the amivantamab chemotherapy group and 3% in the chemotherapy group (Figure 125)[308].

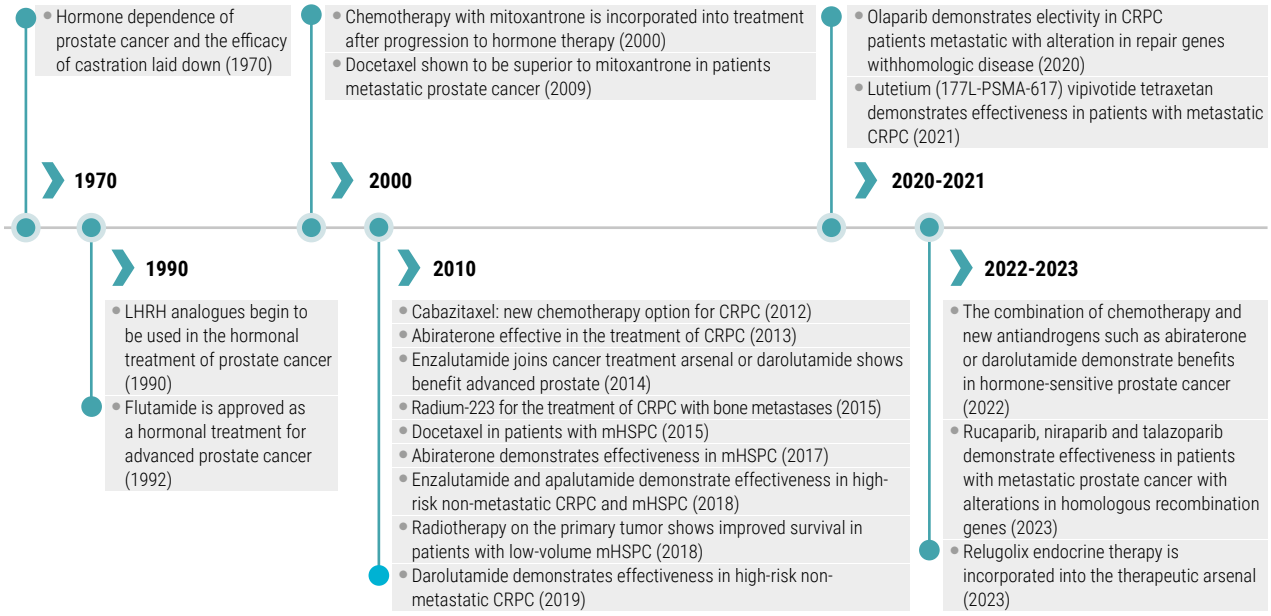
FIGURE 125. PROGRESSION-FREE SURVIVAL IN LUNG CANCER PATIENTS TREATED WITH AMIVANTAMAB IN COMBINATION WITH CHEMOTHERAPY VERSUS CHEMOTHERAPY



Source: Zhou (2023)[308]

Significant therapeutic advances have also been made in **prostate cancer**, aimed at treating tumours resistant to conventional hormone therapies and/or castration or hormone-sensitive metastatic disease. An example of progress in the treatment of prostate cancer can be seen in (Figure 126)[309].

FIGURE 126. PROGRESS IN PROSTATE CANCER TREATMENT, 1970-2023



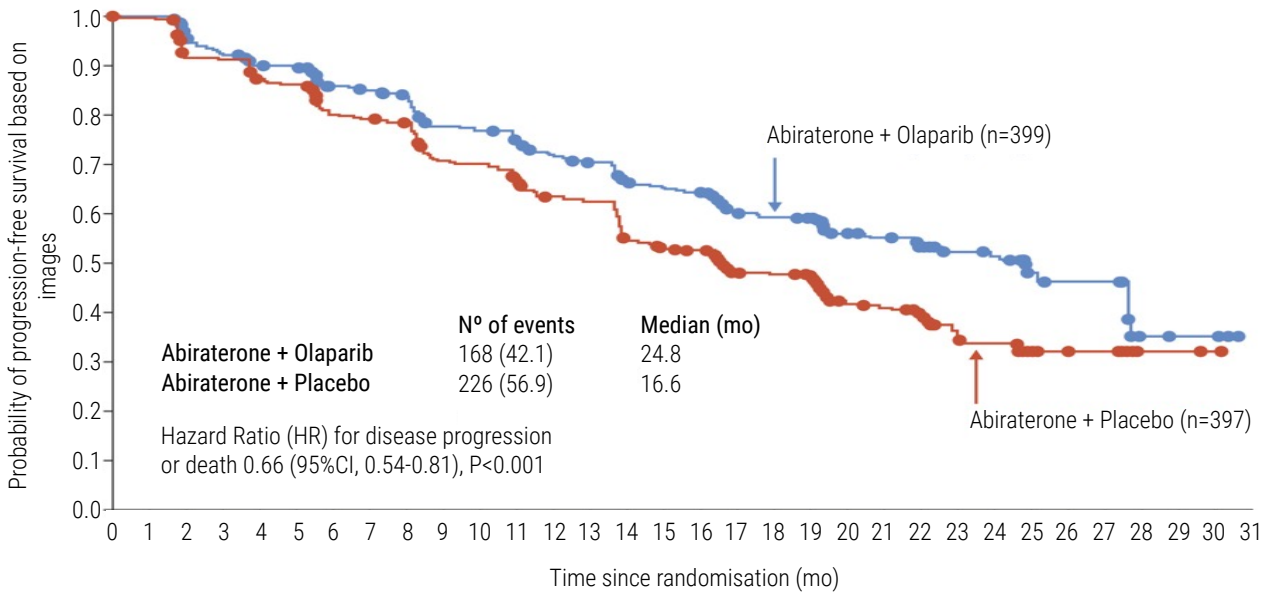
Abbreviations: **CRPC:** hormone-sensitive metastatic prostate cancer; **CRPC:** castration-resistant prostate cancer

Source: Own elaboration based on SEOM (2023)[309] and EMA (2024)[299]

In addition, the value of treatment with both chemotherapy and these new hormonal agents, such as abiraterone, apalutamide or enzalutamide, in combination with androgen deprivation therapy (hormone therapy), has been demonstrated in new studies in patients with metastatic disease at diagnosis. Across different clinical trials, these agents have demonstrated a reduction in the risk of death of up to 38%, even in high-risk patients, and an increase in median survival from 32 to 50 months[310]. The improvement in disease management came primarily from the discovery and further development of testosterone-modifying therapies, such as agonists and antagonists of the disease-related hormone LHRH. In this context, abiraterone and enzalutamide treatments achieved very positive results in castration-resistant cancer, delaying the development of metastases by up to two years, as well as reducing the risk of developing symptoms by more than 50%[310].

On the other hand, multi-drug combination therapies have also shown better results in prostate cancer than monotherapies. An example of this is the comparative study of abiraterone + olaparib versus abiraterone + placebo for patients with metastatic castration-resistant prostate cancer. Median PFS was significantly longer for the abiraterone and olaparib group than for the abiraterone and placebo group (24.8 versus 16.6 months) (Figure 127)[311].

FIGURE 127. PROGRESSION-FREE SURVIVAL IN PROSTATE CANCER TREATMENT WITH ABIRATERONE + OLAPARIB VERSUS ABIRATERONE + PLACEBO



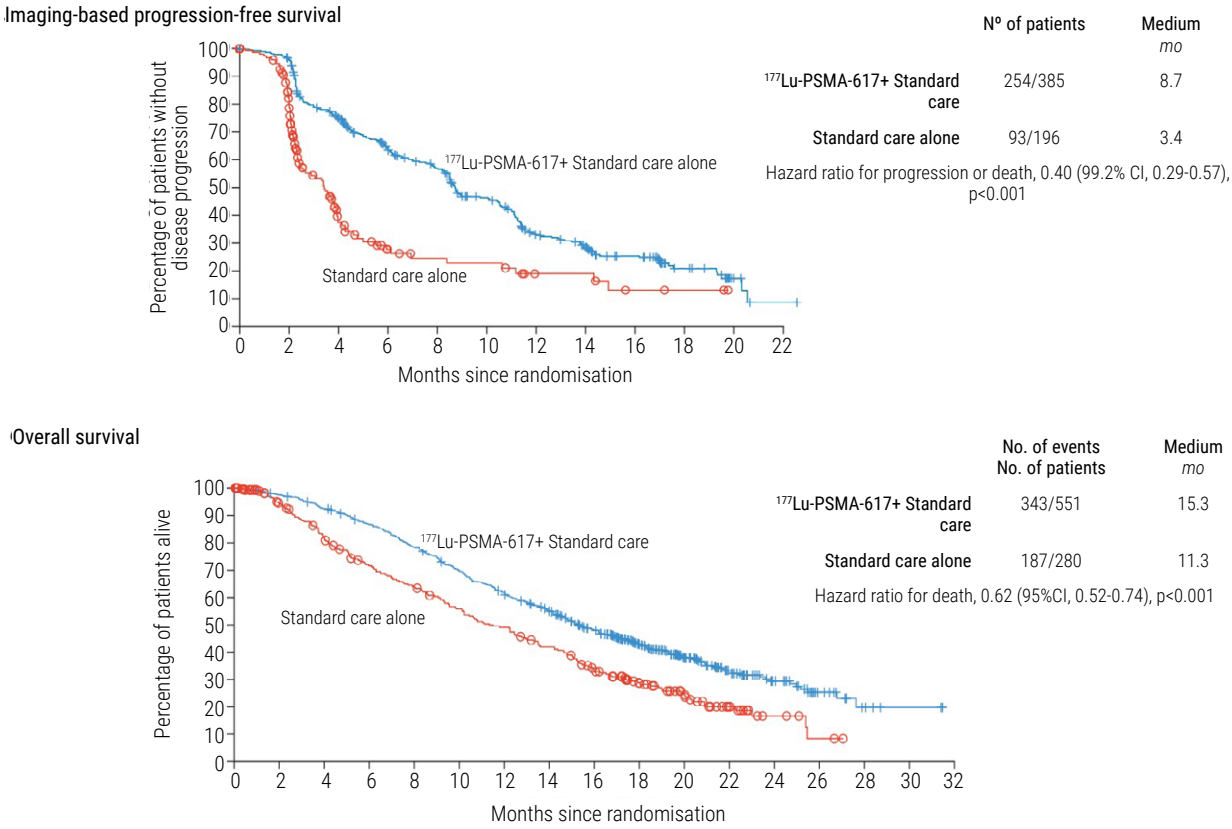
Source: Clarke (2022)[311]

One of the latest treatments approved for the treatment of prostate cancer is relugolix, an oral drug belonging to the LHRH hormone antagonists. In a 48-week study randomising 934 patients with advanced androgen-sensitive prostate cancer, 96.7% (95% CI 94.9%, 97.9%) of men receiving relugolix achieved and maintained castration for 48 weeks compared to 88.8% of the group receiving an injectable LHRH antagonist[312].

Another milestone was the approval, in 2022, of the first targeted therapy with radioligands for metastatic castration-resistant prostate cancer (lutetium-177 vipivotide tetraxetan)313. The pivotal trial of the therapy was conducted on 831 patients from 84 centres in North America and Europe, comparing 177Lu-PSMA-617 treatment every 6 weeks along with standard treatment versus standard treatment alone. In the experimental treatment group, an increase in PFS of 5.3 months (median 8.7 vs. 3.4 months in the experimental and control groups, respectively) was observed, a reduction of risk of progression of 60% (HR of 0.40; 95%CI: 0.29-0.57; p < 0.001), and an improvement in 4-month OS (target of 15.3 vs. 11.3 months in experimental

and control groups, respectively), with a reduction in risk of death of 38% (HR of 0.62; 95%CI: 0.52-0.74; p < 0.001)) (Figure 128)[314].

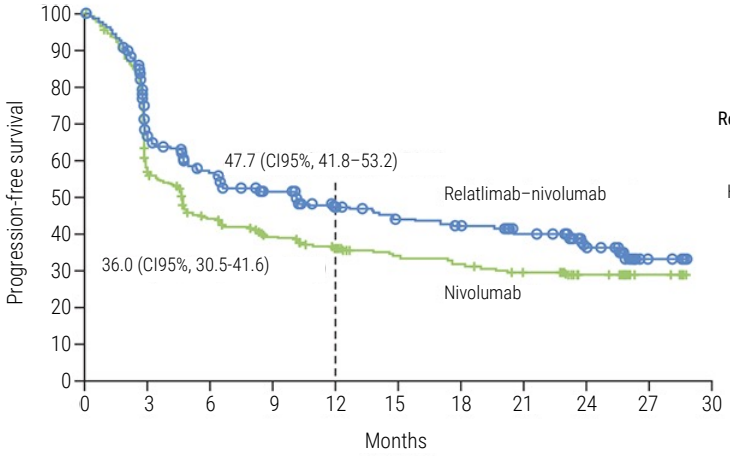
FIGURE 128. PROGRESSION-FREE SURVIVAL (A) AND OVERALL SURVIVAL (B) OF LUTETIUM (177LU) VIPIVOTIDE TETRAXETAN IN THE TREATMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER



Source: Sartor (2021)[314]

With regard to cutaneous melanoma, the first treatments based on high doses of interferon alpha and prolonged periods of time in the 1990s had obtained some improvements, but with very high toxicity. The emergence of immunotherapy years later favoured the activation of the immune system against the tumour, achieving significant increases in disease-free survival and overall survival of patients. The development of BRAF gene kinase inhibitor drugs has improved the results obtained compared to standard therapy in tumours with this mutation. Other treatments targeting the PD-L1 mutation include nivolumab and ipilimumab[315,316]. A new therapy, the combination of relatlimab and nivolumab, arrived in Europe in 2022 and has shown better results than nivolumab monotherapy in PFS. Specifically, the median PFS was 10.1 months (95%CI 6.4-15.7) with relatlimab-nivolumab compared to 4.6 months (95%CI 3.4-5.6) with nivolumab, a median reduction in the risk of progression or death of 25% (HR 0.75, 95%CI 0.62-0.92) (Figure 129)[317].

FIGURA 129. PROGRESSION-FREE SURVIVAL IN MELANOMA PATIENTS TREATED WITH RELAT- LIMAB IN COMBINATION WITH NIVOLUMAB VERSUS NIVOLUMAB



	Nº of events/ Nº of patients	Medium progression-free survival (IC95%) *mo*
Relatimab-Nivolumab	355	10.2 (6.37-15.74)
Nivolumab	359	4.63 (3.38-5.62)

Hazard ratio for progression or death, 0.75 (95%CI, 0.62-0.92), p=0.006

Source: Tawbi (2023)[317]

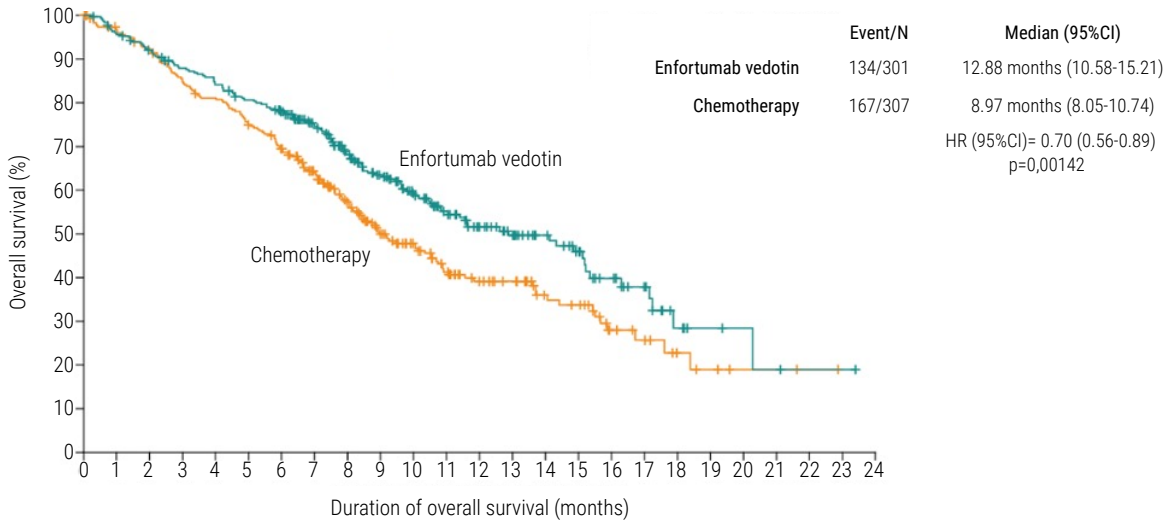
Precision medicine has also reached the treatment of **colorectal cancer**. In this field, the monoclonal antibodies cetuximab and bevacizumab have shown better results than standard chemotherapy-based treatment. For example, in metastatic patients with BRAF V600E mutation, the combination of encorafenib, cetuximab and binimetinib is associated with longer overall survival (9 months) compared to the control group[318]. On the other hand, the combination of bevacizumab plus chemotherapy had better health outcomes than chemotherapy alone. Specifically, the PFS for bevacizumab + chemotherapy was 9.6 months versus 8.4 months for chemotherapy[319]. Similarly, pembrolizumab has demonstrated greater health gains than chemotherapy in patients with microsatellite instability (MSI-H), or changes in one of the mismatch repair (MMR) genes. Specifically, the estimated PFS at 36 months was 42.3% (95% CI 34.0-50.4) for pembrolizumab versus 11.1% (95% CI 6.1-17.9) for the chemotherapy group[320].

Similarly, in kidney cancer, an example of the efficacy of targeted therapies is found in a study of 886 patients, mostly with PD-L1-positive tumours, in the combination treatment of avelumab and axitinib versus standard treatment. The median progression-free survival of the combination therapy was 18.3 months versus 8.4 months for the comparator[321]. On the other hand, other targeted therapies such as sorafenib, sunitinib, pazopanib and everolimus have shown significant benefits on patient health. In this regard, one study analysed the impact of targeted therapies by examining differences in absolute survival and the percentage of survivors treated before (2000-2003) and after (2005-2008) the use of these therapies. It showed that survival over the period increased from 15 to 20 months (p<0.001), and the percentage of survivors from 52.9% to 57.5% (p<0.001), thus concluding that targeted therapy has a positive effect on clinical outcomes in advanced renal cell carcinoma[322]. Also, different combinations of immunotherapy with tyrosine kinase inhibitors (TKIs), such as pembrolizumab + lenvatinib or nivolumab + cabozantinib, among others, have shown benefits in PFS and OS[323,324].

In urothelial cancer, there have also been advances in recent years, including the approval of enfortumab vedotin, an antibody conjugate, by the EMA in 2022[325]. In the pivotal trial, patients treated with enfortumab vedotin achieved an OS of 12.88 months (95% CI 10.58 to 15.21 months) compared to 8.97 months (95% CI 8.05 to 10.74 months) with chemotherapy (Figure 130). Similarly, the estimated 12-month survival rates (95%CI) were 51.5% (44.6-58.0) and 39.2% (32.6-45.6) with enfortumab vedotin and chemotherapy, respectively[326]. Likewise, another monoclonal antibody such as nivolumab in combination with chemotherapy has demonstrated OS benefits over chemotherapy alone. At a median follow-up of 33.6 months, OS was higher with nivolumab combination therapy than with gemcitabine-cisplatin alone (HR: 0.78; 95% CI: 0.63 to 0.96; P= 0.02). PFS was

also longer with nivolumab combination therapy than with chemotherapy alone (HR: 0.72; 95% CI, 0.59 to 0.88; P=.001). At 12 months, progression-free survival was 34.2% and 21.8%, respectively[327].

FIGURA 130. OVERALL SURVIVAL IN PATIENTS TREATED WITH ENFORTUMAB VEDOTIN VERSUS CHEMOTHERAPY IN THE TREATMENT OF UROTHELIAL CANCER

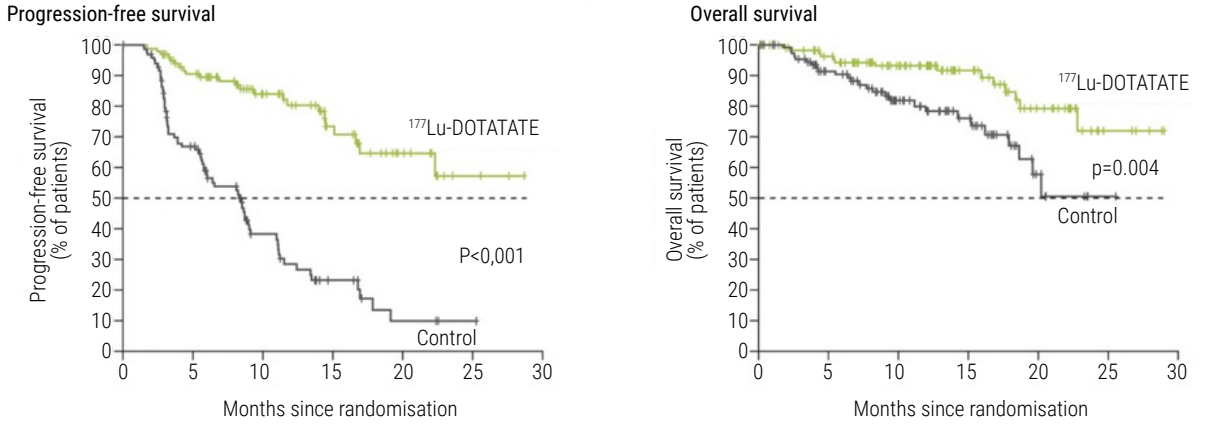


Source: Powles (2021)[326]

As mentioned above, one of the latest advances in cancer treatment is di- rigid therapy with radioligands, which use the specific characteristics of tumour cells as the basis for their mechanism of action. The therapy consists of administering a substance (the radioligand) that combines a precision compound, the cancer cell-locating ligand, with a therapeutic radioactive particle, the radioisotope. In this way, the radioligand locates cancer cells in any part or parts of the body and emits radiation specifically and precisely targeted to those cells. The radioisotope damages the tumour, altering its ability to replicate and/or triggering the cell death mechanism[328].

One example of the efficacy of these therapies is lutetium (177Lu) oxodotreotide, approved by the EMA in 2017 for the treatment of progressive, unresectable or metastatic well-diagnosed **gastroenteropancreatic neuroendocrine tumours**[329,330]. The efficacy of this treatment was assessed in a trial in 229 patients randomised to treatment with intravenous radioligand plus best supportive care or treatment with octreotide alone, demonstrating a clinically relevant effect on PFS (best medians, and gain in months, as well as HR risk reduction, not response rates at 20 months), and a favourable trend in overall survival, although statistical significance was not reached in the observed differences (Figure 131)[331]. In a subsequent longer-term study (follow-up 76.3 months), median overall survival was 48.0 months (95%CI 37.4-55.2) in the treatment group and 36.3 months (25.9-51.7) in the control group (HR 0.84 [95%CI 0.60-1.17]; p=0-30)[332].

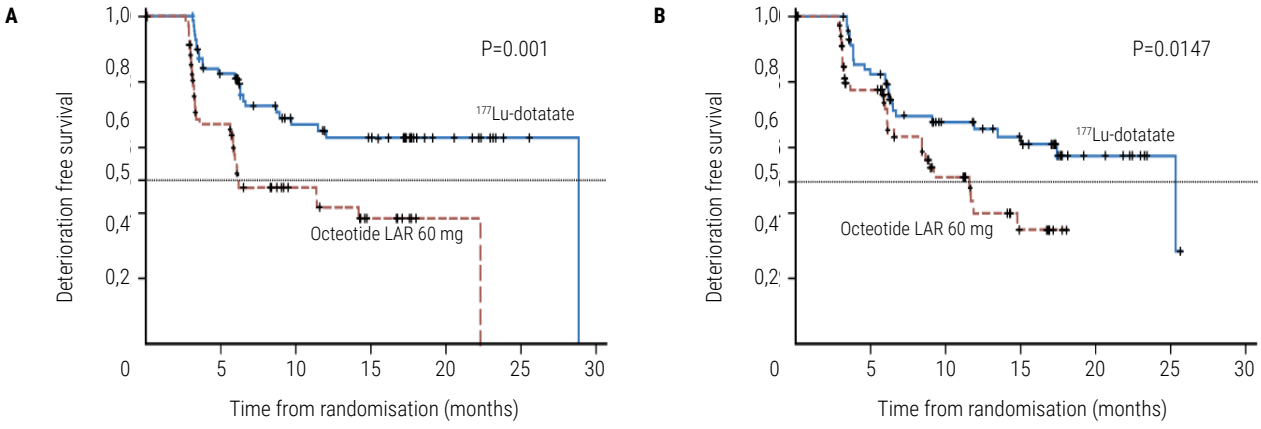
FIGURE 131. PROGRESSION-FREE SURVIVAL (A) AND OVERALL SURVIVAL (B) OF LUTETIUM (177LU) OXODOTREOTIDE IN THE TREATMENT OF GASTROENTEROPANCREATIC NEUROENDOCRINE



Source: Strosberg (2017)[331]

This therapy also demonstrated a positive effect on patients' quality of life versus standard treatment, both in terms of overall health status (HR: 0.41) and physical functioning (HR: 0.52) (Figure 132) and in physical role (HR: 0.58), fatigue (HR: 0.62), body pain (HR: 0.57), diarrhoea (HR: 0.47), disease-related concerns (HR: 0.57) and body image (HR: 0.43). Differences in time to deterioration in quality of life were significant in all domains: 28.8 months versus 6.1 months for general health status, and 25.2 months versus 11.5 months for physical functioning[333].

FIGURE 132. IMPAIRMENT OF LUTETIUM (177LU) OXODOTREOTIDE HEALTH-RELATED QUALITY OF LIFE ON GLOBAL HEALTH STATUS (A) AND PHYSICAL FUNCTIONING (B) IN THE TREATMENT OF GASTRO-ENTEROPANCREATIC NEUROENDOCRINE TUMOURS



Source: Strosberg (2017)[333]

Beyond solid tumours, there have also been very notable advances in the field **of oncohaematology**, especially thanks to advanced therapies, which have brought about a major change in the treatment of patients with acute lymphoblastic leukaemia, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, follicular lymphoma or multiple myeloma, who were refractory or unresponsive to the available therapeutic alternatives[334]. Progress in these areas is detailed in the section on rare oncological diseases.

Finally, it is crucial to emphasize that therapeutic advances in oncology not only extend survival but also improve patients' quality of life[335]. These advances provide treatment options that, in many cases, have a more favourable safety profile and are better tolerated than standard chemotherapy, resulting in significant impro-

vements in patients' quality of life. It is also important to highlight that the true value of innovative oncology drugs will be revealed over time as long-term real-world data become available. Furthermore, it is necessary to consider that a significant portion of the improvements in health outcomes can be attributed to these innovative drugs, while another part of these improvements will come from other preventive, diagnostic, and socioeconomic measures, as well as organizational and process innovations.

Advances in cancer treatment, including chemotherapy, hormone therapy, immunotherapy and targeted therapies, along with early diagnosis of the disease, have led to substantial improvements in survival for almost all types of cancer.

Vaishampayan (2014)[322], Toschi (2017)[301], Lichtenberg (2018)[282]

In recent years, personalised precision medicine and its progress against specific therapeutic targets has revolutionised the therapeutic arsenal for different types of solid and haematological tumours, leading to better health outcomes and quality of life for patients.

Buxbaum (2020)[284], Lichtenberg (2023)[73], Bardia (2021)[297], de Langen (2023)[306], Sartor (2021)[314]

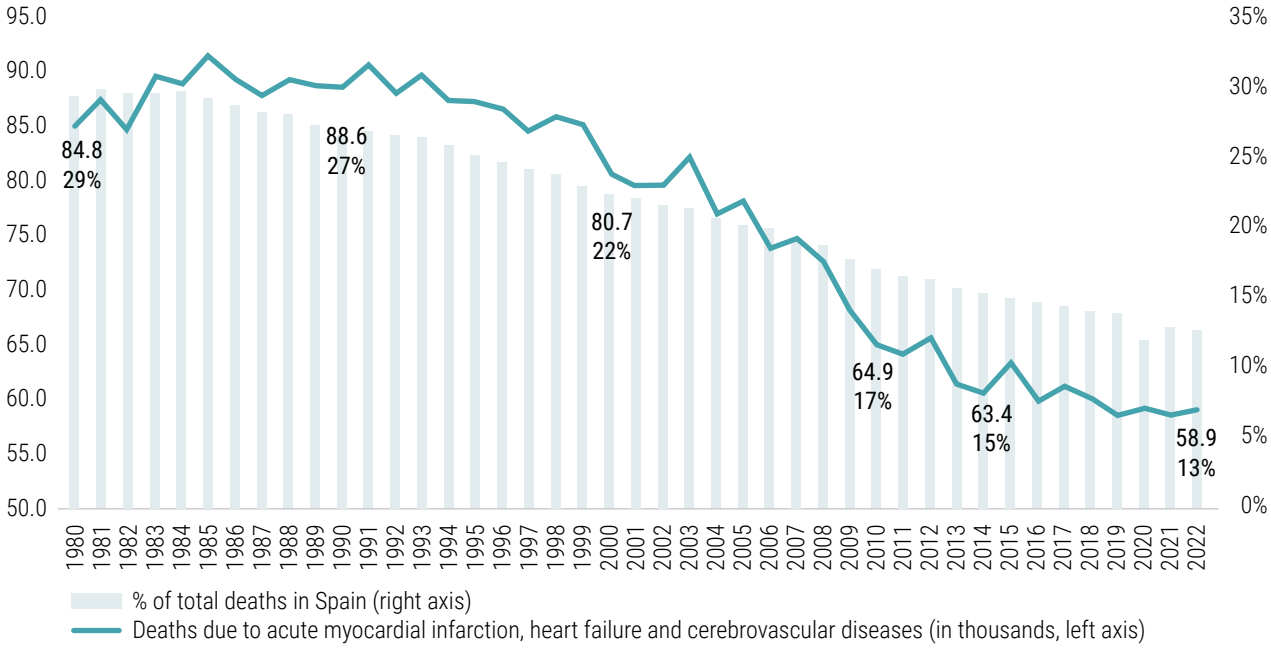
CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVD) comprise a range of disorders affecting the heart and blood vessels, including high blood pressure, coronary heart disease (myocardial infarction), cerebrovascular disease, peripheral vascular disease, heart failure, rheumatic heart disease, congenital heart disease and cardiomyopathies[336]. Obstruction of blood flow to the heart or brain, as well as cerebral haemorrhages or blood clots, are responsible for acute events such as myocardial infarction or stroke[337,338]. These events are often linked to a combination of risk factors, such as smoking, unhealthy diets, obesity, physical inactivity, harmful alcohol consumption, high blood pressure, diabetes and hyperlipidaemia[339].

Cardiovascular diseases are the leading cause of death globally. In 2022, 19.8 million people lost their lives due to these conditions, representing a mortality rate of 2.6%. It is estimated that around 775 million individuals worldwide suffer from these diseases. In particular, ischaemic heart disease, stroke and intracerebral haemorrhage stand out as the leading causes of cardiovascular disease mortality worldwide, accounting for 82% of these deaths in 2022. These three diseases also have the highest rates of years of life lived with disability per 100,000 people affected among all cardiovascular diseases: 2,275, 819 and 923, respectively. Europe contributes 18% of global deaths, with 3.6 million cardiovascular deaths per year on the continent[340].

In Spain, cerebrovascular diseases, heart failure and acute myocardial infarction are among the 10 leading causes of death, with 24,688, 20,584 and 13,643 deaths in 2022, respectively, accounting for 13% of all deaths. However, the number of deaths from these three diseases has decreased by 30% since 1980, when they accounted for 29% of all deaths in the country (Figure 133)[341].

FIGURE 133. EVOLUTION OF MORTALITY FROM SELECTED CARDIOVASCULAR DISEASES, SPAIN,1980-2022



Source: Own elaboration based on INE data (2023)[341]

The approach to cardiovascular disease must address the associated risk factors. In addition to adopting healthy habits, the main therapy involves treating risk factors such as hypercholesterolaemia, high blood pressure and diabetes with medication. It is essential not to overlook the treatment of any risk factor, as their benefits do not add to but rather enhance each other[342–344].

Thus, over the years, a crucial health outcome has been evaluated to measure the effectiveness of both statins and antihypertensives: the incidence of cardiovascular events and the associated mortality rate. In this context, several studies have been conducted, and their findings have been consolidated in various systematic reviews and meta-analyses.

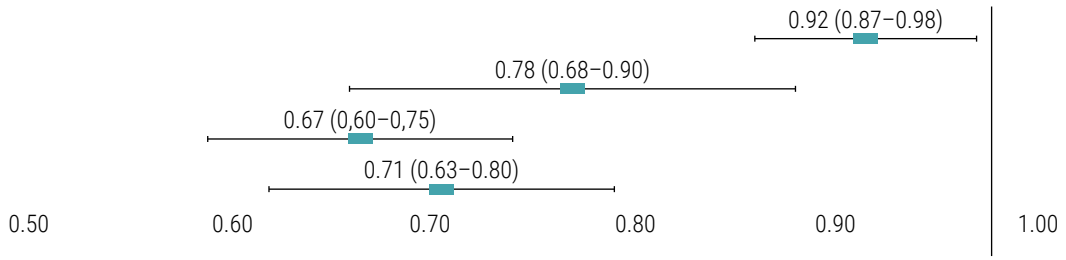
Statins and antihypertensives

An example of this is the meta-analysis by Armitage and colleagues (2019), which concluded that statin use or more intensive statin therapy reduced the risk of major vascular events for each 1.0 mmol/L reduction in low-density lipoprotein (LDL) cholesterol by 21% (RR 0.79, 95% CI 0.77 to 0.81) in people aged 75 years and older. For patients of all ages, the same analysis obtained similar results: statin use reduced the risk of non-fatal myocardial infarction by 24% (RR: 0.76; 95% CI, 0.73 to 0.79), the risk of needing vascular surgery by 25% (RR: 0.75; 95% CI: 0.73 to 0.78) and mortality from cardiovascular events by 12% (RR: 0.88; 95% CI: 0.85 to 0.91)[345].

Similar results have been observed in the SPARCL clinical study, the results of which were published in 2020, on the effects of atorvastatin on vascular events (peripheral, coronary and cerebrovascular). In the 4,731 patients analysed who had suffered a recent stroke or transient ischaemic attack, statin use reduced the 6-year risk of total vascular events by 32% (HR: 0.68, 95% CI: 0.60 to 0.77). It has reduced the risk of coronary (HR: 0.54; 95%CI: 0.42 to 0.70) and peripheral vascular events (HR: 0.56; 95%CI: 0.35 to 0.89) by almost half and the risk of cerebrovascular events by 24% (HR: 0.76; 95%CI: 0.66 to 0.88)[346].

A more recent example is presented in the meta-analysis by Chou et al. in 2022. Their results show that statins reduce the risk of all-cause mortality by 8% (RR: 0.92 [95% CI: 0.87- 0.98]) in patients with a history of cardiovascular disease. In addition, there is a 22% reduction in the risk of stroke (RR: 0.78 [95%CI: 0.68-0.90]), a significant 33% reduction in the risk of myocardial infarction (RR: 0.67 [95%CI: 0.60-0.75]) and a 29% reduction in revascularisation episodes (RR: 0.71 [95%CI: 0.63-0.80]) (Figure 134)[347].

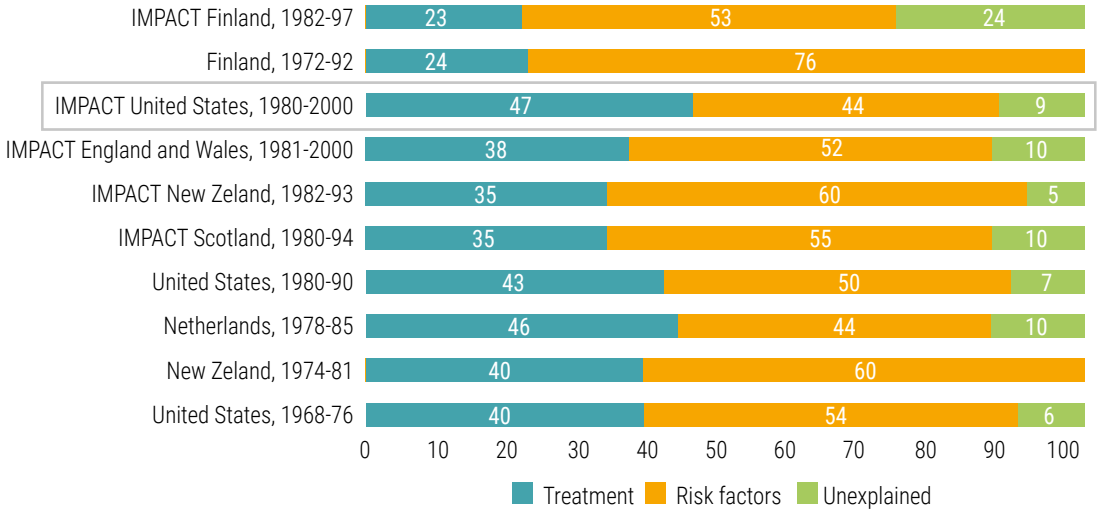
FIGURA 134. RISK REDUCTION IN MORTALITY AND CARDIOVASCULAR EVENTS CAUSED BY STATINS IN PATIENTS WITH A HISTORY OF CARDIOVASCULAR DISEASE



Source: Chou (2022)[347]

A study by Ford et al. (2007) examined the impact of drugs and other medical interventions in reducing the death rate from cardiovascular disease in various countries and time periods, all prior to 2000. According to the results, the range of averted deaths attributed to the therapeutic benefits of pharmacological and surgical treatments was 23% to 47%. In addition, 44% to 60% of averted deaths were associated with improvements in risk factors, while 6% to 24% were attributed to other factors (Figure 135). It is relevant to note that many of the treatments identified were pharmacological, such as statins, suggesting that they played a crucial role in lowering cholesterol and blood pressure. This may indicate that the benefit of drug use could be even more significant in lowering the mortality rate from these diseases[348].

FIGURE 135. PERCENTAGE OF THE DECREASE IN DEATHS FROM CORONARY HEART DISEASE ATTRIBUTED TO TREATMENT AND RISK-FACTORS CHANGES IN VARIOUS POPULATIONS AND TIME PERIODS



Source: Ford (2007)[348]

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Antihypertensive drug therapy has been associated with reduced cardiovascular events, although long-term data on its impact on life expectancy are limited. However, the SHEP (Systolic Hypertension in the Elderly Programme) study stands out as an exception, providing evidence that antihypertensive treatment for 4.5 years significantly prevented cardiac events, including 1 in 2 admissions for heart failure, 1 in 3 heart attacks (fatal and non-fatal) and 1 in 4 cardiovascular events[349].

In a follow-up more than 20 years later, the same participants, whose mean age at baseline was 72 years, were examined, differentiating between those who received treatment and those who received placebo. An increase in life expectancy of 105 days (95% CI 39-242, p=0.07) for all causes of mortality and 158 days (95% CI 36-287, p=0.009) for mortality from cardiovascular events was observed in the treated group. After 22 years, 59.9% of the treated group died compared to 60.5% of the placebo group, with deaths from cardiovascular events being lower in the treated group (28.3% vs. 31.0%). In other words, each month of antihypertensive therapy is associated with an increase of about 1 day in life expectancy[350].

A meta-analysis of 123 studies and 613.815 participants found that each 10 mm Hg reduction in systolic blood pressure produced by the use of antihypertensives significantly reduced the risk of major cardiovascular disease events (relative risk [RR] 0.80, 95% CI 0.77-0.83), coronary heart disease (0.83, 0.78-0.88), stroke (0.73, 0.68-0.77) and heart failure (0.72, 0.67-0.78), which, in the populations studied, resulted in a significant 13% reduction in all-cause mortality (0.87, 95% CI 0.84-0.91)[351].

For each 10 mm Hg reduction in systolic blood pressure produced by using of antihypertensive drugs, the risk of mortality in patients with cardiovascular disease is reduced by 13%.

Ettehad (2016)[351]

Fang et al. conducted a study on the incidence of stroke in patients over 65 years of age in the Medicare programme in the United States between 1988 and 2008. In this analysis, it was observed that, coincident with an increase in the use of statins (from 4% to 41.4%) and antihypertensives (from 53.0% to 73.5%) in this population, the incidence of ischaemic stroke decreased from 927 to 545 per 100,000 individuals, while haemorrhagic stroke decreased from 112 to 94 per 100,000. This decline represents a decrease of about 40% over the two decades[352].

In the context of preventive medication, such as statins and antihypertensives, adherence to treatment plays a key role. It has been observed that up to 60% of patients with hypertension and up to 90% of those with dyslipidaemia show poor adherence to medication. According to a systematic review by Kengne et al. (2024), non-adherence to these medications increases the risk of cardiovascular events by 10-90% (HR: 1.1-1.9) and the risk of mortality by 40-80% (HR: 1.4-1.8) in patients with hypertension and dyslipidaemia[353].

Other drugs in cardiovascular treatment

Several studies have found evidence of health improvements through the use of drugs for the treatment of cardiovascular diseases, other than statins and antihypertensives. An analysis conducted by Szummer et al. (2019) through a systematic literature review reveals that the implementation of various therapies, such as pharmacological reperfusion combined with aspirin, stent placement followed by platelet inhibition, and complementary treatments, halved the one-year mortality rate from coronary syndromes, decreasing from 22% to 11% between 1995 and 2014[354].

Additionally, Hansen et al. (2020), through a meta-analysis, concluded that the use of drugs such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists significantly increased life expectancy in patients with cardio-vascular disease. An increase of 43.7 days (95% CI 20.8 to 66.5) was observed with beta-blockers, 41.0 days (95% CI 18.8 to 63.3) with ACE inhibitors and 41.3 days (95% CI 14.3 to 68.4) with aldosterone antagonists[355].

Another example is a neprilysin and angiotensin receptor inhibitor used to treat symptomatic chronic heart failure with reduced ejection fraction. According to clinical trials, this drug, compared with angiotensin-converting enzyme inhibitors, reduced the risk of mortality, hospitalisation and myocardial infarction by 17% to 20% [HR: 0.80 to 0.83; 95% CI 0.73 to 0.90], and demonstrated improvements in quality of life (+1.13 vs -0.14 points; P<0.001) according to the Kansas City Cardiomyopathy Questionnaire (KCCQ)[356–358].

Among the lipid-lowering therapies with an impact on survival, the new PCSK9 inhibitor monoclonal antibodies, for use in patients with poor response or intolerance to statin therapy, have demonstrated very significant reductions in LDL cholesterol (range of approximately 60% compared to placebo). One such example is evolocumab, whose treatment produced a clinically significant reduction in the risk of cardiovascular events (HR: 0.47, 95%CI 0.28 to 0.78, P=0.003) in patients who had failed to reduce their cholesterol with statin therapy alone[359].

The impact of innovation: the example of Switzerland

A study conducted by Lichtenberg (2015) in Switzerland (in patients aged 65 years and older) assessed the relationship of the impact of cardiovascular drug innovation on the increase in life expectancy of these patients. According to this study, people who took innovative cardiovascular medicines lived longer than those who received older cardiovascular medicines. The most conservative estimates indicated that innovations accounted for almost a quarter of the improvement in longevity for these people, increasing their life expectancy between 2002 and 2012 by almost 3 months, at a cost per life-year gained of less than $10,000[360].

Recent developments in cardiovascular treatment (2020-2023)

In the period between 2020 and 2023, the FDA and EMA have granted approval for six innovative cardiovascular medicines, marking significant milestones in the progress of disease management. Among them is bempedoic acid, approved in 2020 for adults with primary hypercholesterolemia. Ethyl icosapent, which gained approval in 2020 by the FDA and in 2021 by the EMA, is aimed at reducing the risk of cardiovascular events in statin-treated adult patients with high cardiovascular risk and elevated triglycerides. Evinacumab, approved in 2021, is used in conjunction with a low-fat diet and other drugs to lower blood cholesterol levels. Inclisiran and vericiguat, approved in 2020 and 2021, are notable for their applications in the treatment of primary hypercholesterolaemia and chronic heart failure, respectively, while mavacamten has been approved in 2022 and 2023 for the treatment of obstructive hypertrophic cardiomyopathy in adult patients. In addition, nine new indications for existing medicines have been approved by these institutions (Table 7).

TABLE 7: FIRST IN CLASS DRUGS APPROVED BY FDA AND EMA IN THE CARDIOVASCULAR FIELD, 2020-2023

ACTIVE INGREDIENT	INDICATION	FDA	EMA
New substances or "first in class"			
Bempedoic acid	Adults with primary hypercholesterolemia or mixed dyslipidaemia	2020	2020
Ethyl isosapent	Reducing the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk with high triglycerides	2020	2021
Evinacumab	It is used in conjunction with a low-fat diet and other medications to lower blood cholesterol levels	2021	2021
They will include	Adults with primary hypercholesterolemia or mixed dyslipidaemia	2021	2020
Vericiguat	Treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilised after a recent episode of decompensation requiring intravenous therapy	2021	2021
Mavacamten	Treatment of symptomatic hypertrophic obstructive cardiomyopathy (New York Heart Association, NYHA, class II-III) in adult patients	2022	2023

Notes: (1) Three generic medicines were approved in 2023 to treat cardiovascular diseases, which are not listed in the table: Dabigatran Etexilate Accord, Dabigatran Etexilate Leon Pharma, and Ibuprofen Gen.Orph. (2) Although the EMA included Finerenone in the cardiovascular disease category, its indication in both the FDA and EMA is for renal treatment. For this reason, this drug was not included in the table. (3) Although semaglutide and dulaglutide were approved by the FDA for the treatment of cardiovascular diseases, they were only approved by the EMA for the treatment of diabetes mellitus. Therefore, they are not included in the table.

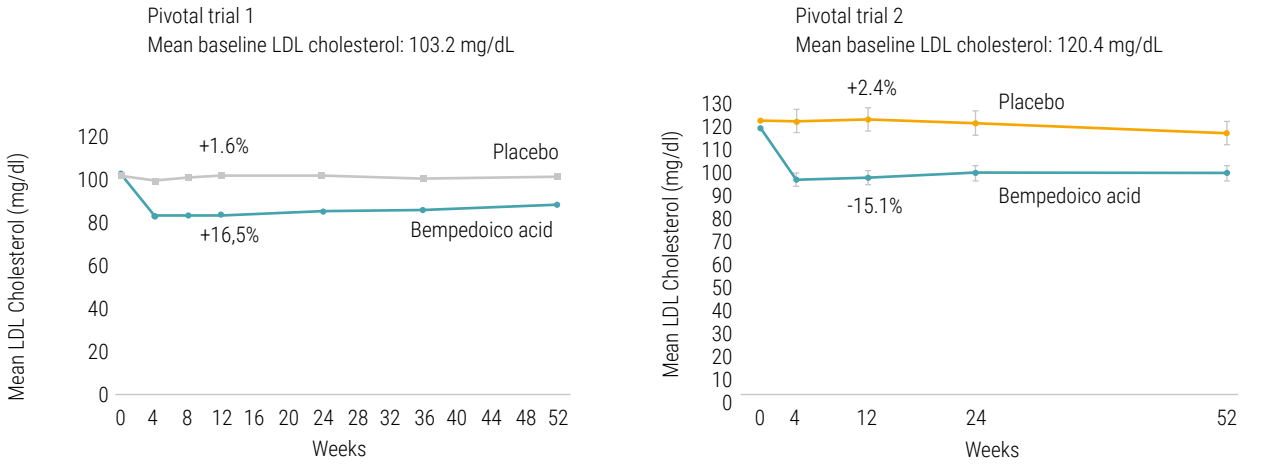
Source: EMA (2020[361], 2021[362], 2022[363], 2023[364]) and FDA (2020[365],2021[366],2022[367])

Bempedoic acid is indicated for patients with primary hypercholesterolaemia or mixed dyslipidaemia, conditions that cause elevated levels of lipids, including cholesterol, in the blood. It is used in combination with a statin, either alone or with other lipid-lowering drugs, in patients whose cholesterol levels have not decreased sufficiently with the maximum statin dose[368,369].

Its efficacy has been demonstrated in two pivotal, randomised, double-blind, placebo-controlled trials in patients with atherosclerotic cardiovascular disease, familial heterozygous hypercholesterolemia or both[368,369].

In the first pivotal trial, which included 2,230 patients (1,488 in the control group and 742 in the placebo group), with an average baseline LDL cholesterol level of 103.2 mg/dl, the drug reduced the average cholesterol level by 19.2 mg/dl at week 12. This represented a -16.2% change from baseline, while in patients in the placebo group, there was a 1.6% increase in cholesterol levels (difference versus placebo in change from baseline: -18.1%; 95%CI, -20.0 to -16.1; p<0.001)368. In the second pivotal trial, which included 779 patients, the baseline cholesterol level was higher than in the first, 120.4 mg/dl. Bempedoic acid significantly reduced LDL-C levels compared to placebo at week 12 (-15.1% vs. 2.4%, respectively; difference, -17.4% [95% CI, -21.0% to -13.9%]; P < 0.001) (Figure 136)[369].

FIGURE 136. EFFICACY OF BEMPEDOIC ACID VS. PLACEBO IN THE TREATMENT OF PATIENTS WITH PRIMARY HYPERCHOLESTEROLAEMIA OR MIXED DYSLIPIDAEMIA, WEEK 12



Note: Treatment of both arms is a combination with statin treatment

Source: Ray (2019)[368] and Goldberg (2019)[369]

Inclisiran has the same indication as bempedoic acid. The difference lies in the form in which it is administered. While bempedoic acid comes in the form of 180 mg tablets, with a recommended dose of one tablet per day, inclisiran is administered by subcutaneous injection, usually in the abdomen, but also in the upper arm or thigh. After the first injection, the next dose is administered after 3 months and every 6 months thereafter.

Three studies involving a total of 3,660 patients showed the efficacy of inclisiran in reducing LDL-cholesterol levels. More than 94% of the participants were also taking statins or other drugs to control blood lipid levels. The studies included patients with familial hypercholesterolaemia and those with elevated LDL-cholesterol levels who had cardiovascular atherosclerotic disease or were at risk of developing it. After 18 months of treatment, the results were consistent across all studies, showing that LDL-cholesterol levels decreased by 51.4% [95%CI (-53.4% to -49.4%); P<0.0001] in patients treated with inclisiran compared to those receiving placebo[370].

Ethyl icosapent is a drug intended to reduce the risk of cardiovascular events, such as myocardial infarction, stroke and other complications resulting from obstructed blood flow. It is used as an adjunct in the treatment of adults already on statin therapy who have elevated blood triglyceride levels. The administration of ethyl icosapent is recommended in patients who either have cardiovascular disease or who have diabetes and another disease that increases the risk of cardiovascular events. Ethyl icosapent also works as an adjunct to statin therapy. According to a publication that evaluated this combination against placebo, all clinical indicators showed significant reductions in adults with high triglyceride levels (150 mg/dl or more): mortality (HR: 0.70, 95%CI 0.55 to 0.90), myocardial infarction (HR: 0.72, 95%CI 0.56 to 0.93) and stroke (HR: 0.63, 95%CI 0.43 to 0.93)[371].

The pivotal efficacy trial included 8,179 patients with established cardiovascular disease or with diabetes and other risk factors, who were receiving statin therapy and who had a triglyceride level of 135 to 499 mg/dl and an LDL cholesterol level of 41 to 100 mg/mg. At a median follow-up of 4.9 years, where the median endpoint was a composite of cardiovascular events, including death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation or unstable angina, 17.2% of patients in the control group had a cardiovascular event, compared to 22.0% of patients in the placebo group, indicating that patients on icosapent style have a 25% lower risk of a cardiovascular event (HR: 0.75; 95%CI, 0.68 to 0.83; P<0.001) (Figure 137)[372].

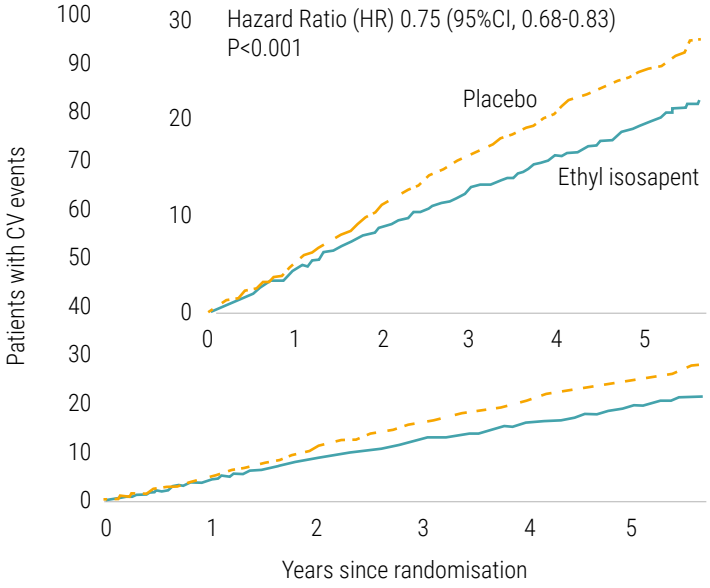
Evinacumab is used in combination with a low-fat diet and other medications to lower blood cholesterol levels. It is indicated for adults, adolescents, and children aged 5 years and older with homozygous familial hypercholesterolaemia, an inherited disease that raises LDL cholesterol levels, a risk factor for cardiovascular disease.

In the pivotal trial, evinacumab was shown to effectively reduce LDL cholesterol levels in adults and adolescents aged 12 years and older with homozygous familial hypercholesterolaemia. The 65 participants received evinacumab or placebo along with other cholesterol treatments. After 24 weeks, mean LDL cholesterol levels in patients treated with evinacumab decreased by about 47% from baseline, compared with an increase of about 2% in the placebo group. This reduction was maintained for another 24 weeks of treatment[373].

Vericiguat is used in the treatment of adults with chronic heart failure with reduced ejection fraction who have recently received intravenous treatment due to worsening symptoms. The efficacy of this medication in managing heartfailure is supported by the results of a pivotal study involving over 5,000 patients. This study, lasting 10.8 months, compared treatment with vericiguat to a placebo, both administered alongside other heart failure medications.

In the control group, 35.5% of patients experienced events resulting in death due to cardiac and circulatory problems or required hospitalization for heart failure. These results contrast with the 38.5% observed in the group of patients who received the placebo and experienced similar events. In other words, patients treated with vericiguat had a 10% lower risk of death from cardiac and circulatory issues compared to those who received the placebo (HR: 0.90; 95% CI: 0.82-0.98; P=0.02) (Figure 138)[374].

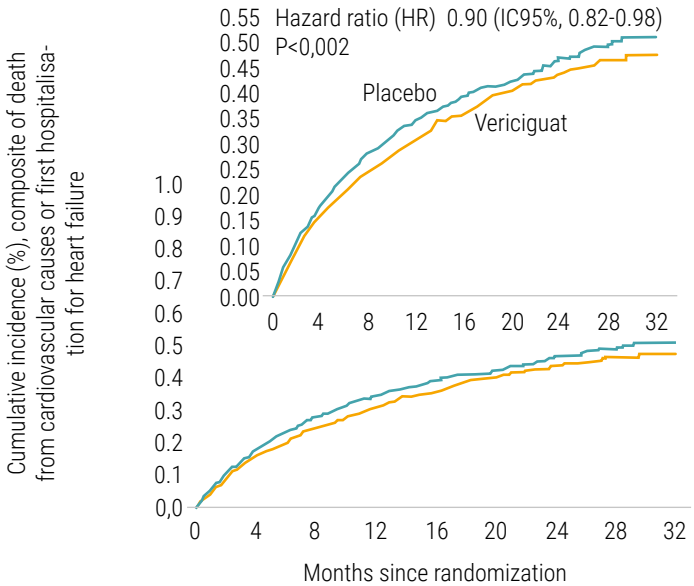
FIGURE 137. EFFICACY OF ETHYL ICOSAPENT ON PATIENTS WITH CARDIOVASCULAR DISEASE OR OTHER FACTORS RISK, 5 YEARS FOLLOW-UP



Note: Treatment of both arms is a combination with statin treatment.

Source: Bhatt (2019)[372]

FIGURE 138. EFFICACY OF VERICIGUAT FOR THE TREATMENT OF CHRONIC HEART FAILURE WITH HEART FAILURE FRACTION REDUCED EJECTION RATE

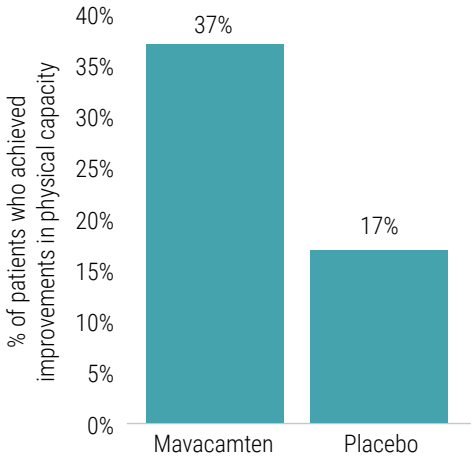


Soure: Armstrong (2020)[374]

Mavacamten is a medication indicated for the treatment of obstructive hypertrophic cardiomyopathy (HCM) in adults. This condition is characterized by thickening or enlargement of the muscle in the heart's main pumping chamber, which can hinder blood flow from the heart to the rest of the body. It is specifically prescribed for adults experiencing symptoms of the disease in Class II or Class III HCM. The "class" designation reflects the severity of the disease, with "Class II" associated with a mild limitation in physical activity, while "Class III" indicates a significant limitation in physical activity.

The effectiveness of this drug was evaluated by comparison with placebo in a pivotal study, which included 251 patients with HOCM, and whose endpoint focused on the proportion of patients who achieved a predefined level of improvement in physical capacity[ii]. After 30 weeks of treatment, 37% of patients treated with mavacamten were found to achieve such improvement, compared to 17% of those receiving placebo (difference vs placebo: +19.4%, 95%CI: 8.7 to 30.1, p=0.0005) (Figure 139)[375]

FIGURE 139. EFFICACY OF MAVACAMTEN FOR THE TREATMENT OF OBSTRUCTIVE HYPERTROPHIC MYOCARDIOPATHY, 30 WEEKS



Note: Increase in physical capacity: an increase of 1.5 mL/kg per minute or more in peak oxygen consumption (pVO2), along with at least one reduction in NYHA functional class, or an increase of 3.0 mL/kg per minute or more in pVO2 without worsening in NYHA functional class.

Source: Olivotto (2020)[375]

In recent decades, the inclusion of drugs such as statins and anti-hypertensives has led to a significant The use of aggressive interventions in the treatment of cardiovascular disease has resulted in significant improvements in health outcomes, including a reduction in the risk of mortality and associated cardiovascular events.

Lichtenberg (2015)[360], Ettehad (2016)[351], Chou (2022)[347]

In recent years, cardiovascular treatment has evolved significantly. New medications have been developed to address the lack of response to maximum statin doses, achieving cholesterol reductions of between 15% and 50%. Additionally, drugs have been approved to treat specific conditions, such as symptomatic chronic heart failure in adults with reduced ejection fraction and symptomatic obstructive hypertrophic cardiomyopathy, which have been shown to reduce associated morbidity and mortality.

Ray (2019)[368], Ray (2023)[370], Bhatt (2019)[372], Armstrong (2020)[374], Olivotto (2020)[375]

ii *The primary endpoint was an increase of 1.5 mL/kg per minute or more in peak oxygen consumption (pVO2), together with at least a reduction in NYHA functional class or an increase of 3.0 mL/kg per minute or more in pVO2 without worsening NYHA functional class*

DIABETES MELLITUS

Diabetes mellitus (DM) comprises a group of metabolic diseases characterised by the presence of hyperglycaemia, resulting from defects in insulin secretion and/or insulin action, which causes significant cardiovascular morbidity and premature mortality worldwide376. Type 1 diabetes (T1D1) occurs when the body's immune system attacks and destroys the insulin-producing cells of the pancreas, while in type 2 diabetes (T2D), the most common type of diabetes, the body produces insulin, but either does not produce enough insulin or is unable to respond to its effects[377].

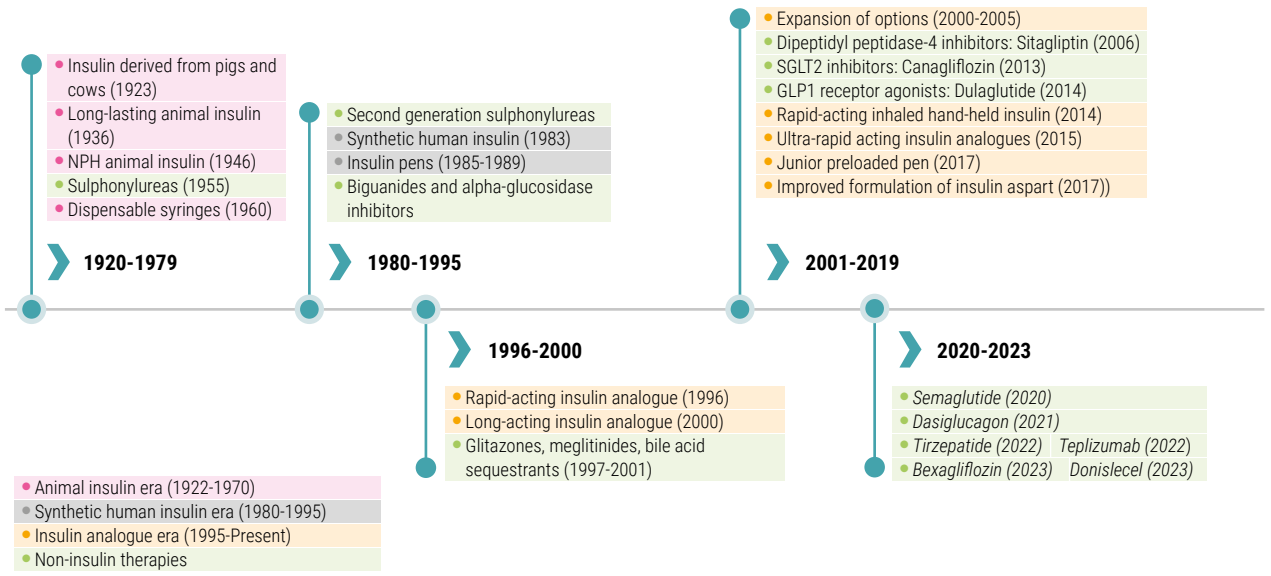
Specific long-term effects of diabetes include retinopathy, nephropathy and neuropathy, among other complications[378]. In addition, a patient with diabetes has up to four times the risk of developing cardiovascular disease compared to a person without the disease[379–381]. Reducing the likelihood of developing complications of diabetes requires better control of blood glucose levels, as well as other cardiovascular risk factors such as hypertension, dyslipidaemia, obesity, and a reduction in tobacco consumption[382–386].

According to WHO, an estimated 537 million adults (aged 20-79 years) worldwide currently have diabetes, and this number is expected to increase to 643 million by 2030 and 783 million by 2045[387]. Excluding the mortality risks associated with the COVID-19 pandemic, an estimated 6.7 million adults lost their lives as a result of diabetes or its complications in 2021. This is equivalent to 12.2% of all deaths worldwide from any cause, with Europe contributing 2% (111,000) of all diabetes-related deaths[388].

With a total of 295,000 children, Europe has the highest number of children and adolescents with type 1 diabetes. In addition, it is estimated that one in eleven adults (61 million) live with diabetes in Europe. In the case of Spain, 5.1 million adults aged 20-79 years have diabetes. In fact, it is estimated that DM affects one in seven adults, ranking as the second highest rate in Europe. It has been reported that the number of people with diabetes has increased in Spain by 42% since 2019[387,388]. It has been estimated that around 25,000 people die each year in Spain due to diabetes and the numbers continue to rise[389]. It is also a disease associated with high under-diagnosis, and it is estimated that almost a third (30.3%) of people living with diabetes in Spain are undiagnosed, which can lead to serious and potentially fatal complications[388].

Treatments for adequate diabetes control have undergone considerable evolution over the last century (Figure 140). The increase in diabetes prevalence in recent years has been accompanied by improved disease control, the development of new forms of insulin and advances in glycaemic control. In addition, governments and policymakers have implemented proven and effective measures to control and prevent the disease, such as promoting healthy lifestyles through public health campaigns and community programmes, as well as measures to strengthen the healthcare infrastructure to provide comprehensive diabetes care, including access to medicines such as insulin and medical glucose monitoring devices[390,391].

IGURE 140. EVOLUTION OF DRUGS TO TREAT DIABETES MELLITUS, 1920-2023



Abbreviations: **GLP1:** glucagon-like peptide-1 receptor; **SGLT2:** sodium-glucose cotransporter 2.

Notes: The chronology shows the main drugs to treat diabetes mellitus by year of their first approval in the US and/or EU market. Animal insulin era: Before 1922, patients with DM died within 2 years. With insulin derived from pigs and cows, life expectancy increases, but is still 25 years less than the general population. Animal NPH insulin allows for more flexible disease management. The first dispensable syringes improve convenience of delivery. Synthetic human insulin era: Lower frequency of injection and allergic reactions. First insulin pens, more portable and convenient, less painful, less room for human error. Insulin analogue era: First rapid-acting insulin analogue (insulin lispro): greater flexibility in administration. First long-acting insulin analogue (insulin glargine): more stable effect, once-daily dosing. Expansion of options. Inhaled rapid-acting portable insulin: more flexibility. Ultra-fast-acting insulin analogues offer 24h coverage and greater flexibility. Junior pre-filled pen: more precision, lower injection force and dose memory function. Improved insulin aspart formulation: greater delivery flexibility. Non-insulin therapies: First generation of sulphonylureas: increased insulin secretion. Second generation: more potent compounds. Emergence of biguanides, which reduce hepatic production and glucose absorption. Alpha-glucosidase inhibitors, which reduce glucose absorption by the digestive tract. Emergence of glitazones: decrease insulin resistance. Meglitinides: stimulate the beta cells of the pancreas to release insulin. Dipeptidyl peptidase-4 inhibitors, GLP1 receptor agonists and SGLT2 inhibitors: reduced risk of cardiovascular death and major adverse cardiovascular events.

Source: Own elaboration based on Feingold (2000)[392], Zinman (2015)[393], Marso (2016)[394], Neal (2017)[395], Deeb (2018)[396], Pratley (2018a[397], 2018b[398]), Tran (2018)[399], PhRMA (2019)[400], Tamborlane (2019)[401], FDA (2018-2023)[365–367,402–404] and EMA (2019-2023)[361–364,405]

We have moved from the era of animal insulin, which lasted until the 1970s, to the era of synthetic human insulin around the 1980s, which has represented a revolution in the treatment of the disease, allowing the reduction of injection frequency and adverse effects, as well as the development of the first insulin pens, which are more portable, less painful and with less margin for human error than previous treatments[406].

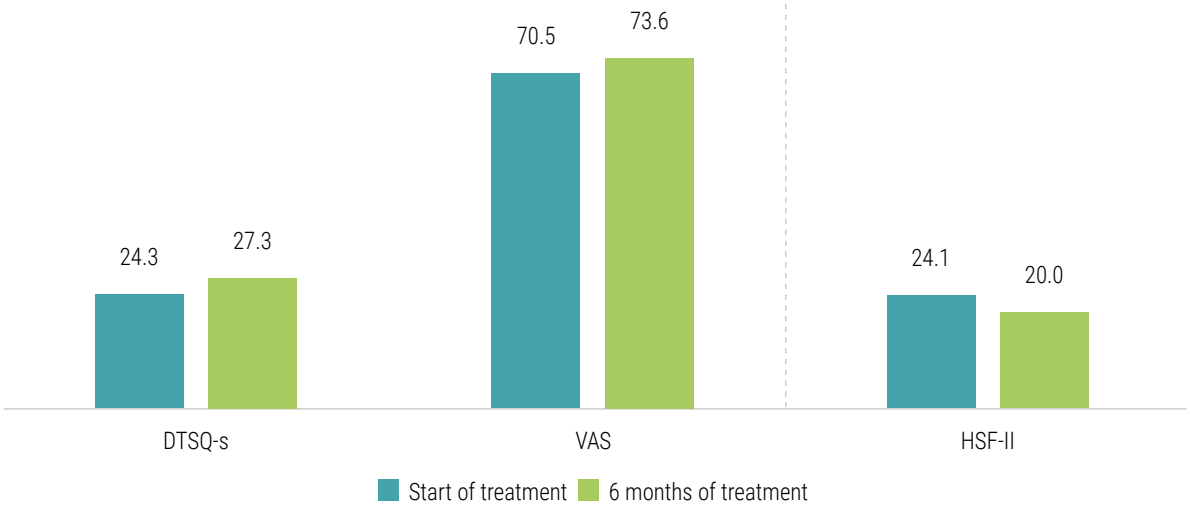
In the mid-1990s, human insulin analogues were developed, with characteristics that improved the utilisation profile of conventional insulins. There are several types of insulin analogues, including slow-acting, intermediate-acting, rapid-acting and long-acting insulin analogues. Rapid-acting insulin analogues have a plasma concentration twice as high and in half the time of regular insulin. In addition, they reduce the long-term risk of cardiovascular complications, allow for greater flexibility in dosing regimens and have less variability in absorption[407]. Long-acting insulin analogues have a higher absorption capacity than conventional long-acting insulins, a slower onset of action and a longer effect, with a nearly constant concentration, as well as a lower risk of hypoglycaemia[408,409].

In addition to the different types of insulin mentioned above, new forms of insulin delivery, such as pre-filled pens, infusion pumps and inhaled insulin, have been developed. These advances have facilitated their use, increased patient satisfaction and raised adherence rates, thereby improving disease control and reducing associated comorbidities. There are many advantages of pens over traditional vials and syringes in terms of clinical outcomes, adherence, accuracy and utilisation[410–413]. In addition, smart insulin pens have been developed that accurately record the timing and dose of insulin injections, allowing these data to be integrated with continuous glucose monitoring. This improves diabetes self-management by addressing an unmet need for patients to be more actively involved in their care. Based on data from their use in real-world clinical practice,

over the lifetime of patients with T1D, the use of these smart pens has been associated with significant improvements in average life expectancy (+0.90 years) and quality-adjusted life expectancy (+1.15 quality-adjusted life years), as well as average cost savings compared to standard care[414].

Insulin therapy is the mainstay of treatment for people with T1D, but side effects such as hypoglycaemia and weight gain are often limiting factors in achieving glycaemic targets and reducing risks of diabetes-related complications[415]. The beneficial effect of new forms of insulin on health outcomes in patients with T1D has been demonstrated, for example, switching from basal insulin therapy to insulin degludec in patients with T1D resulted in several improvements in health and patient-reported outcomes (Figure 141)[416]. In a study of patients in Madrid, at 6 months of treatment with degludec, a 16.5% reduction in fasting basal plasma glucose, a 2.8% reduction in glycated haemoglobin (HbA1c) levels, as well as a significant 70.6% reduction in the number of severe hypoglycaemia episodes were obtained. As shown in Figure 141, these results translated into improvements in treatment satisfaction, quality of life and patient-reported outcomes. There was a 12.3% increase in treatment satisfaction levels as measured by the Diabetes Treatment Satisfaction Questionnaire status version (DTSQ-s), as well as a 4.4% increase in quality of life as measured by the Visual Analog Scale (VAS) of the EuroQol- 5 Dimension (EQ-5D). Fear of hypoglycaemia episodes was also significantly reduced by 17%, as assessed by the Hypoglycaemia Fear Survey type II (HFS-II) instrument.

FIGURE 141. OUTCOMES REPORTED BY DT1 PATIENTS AFTER 6 MONTHS OF TREATMENT WITH INSULIN DEGLUDEC, SPAIN 2018

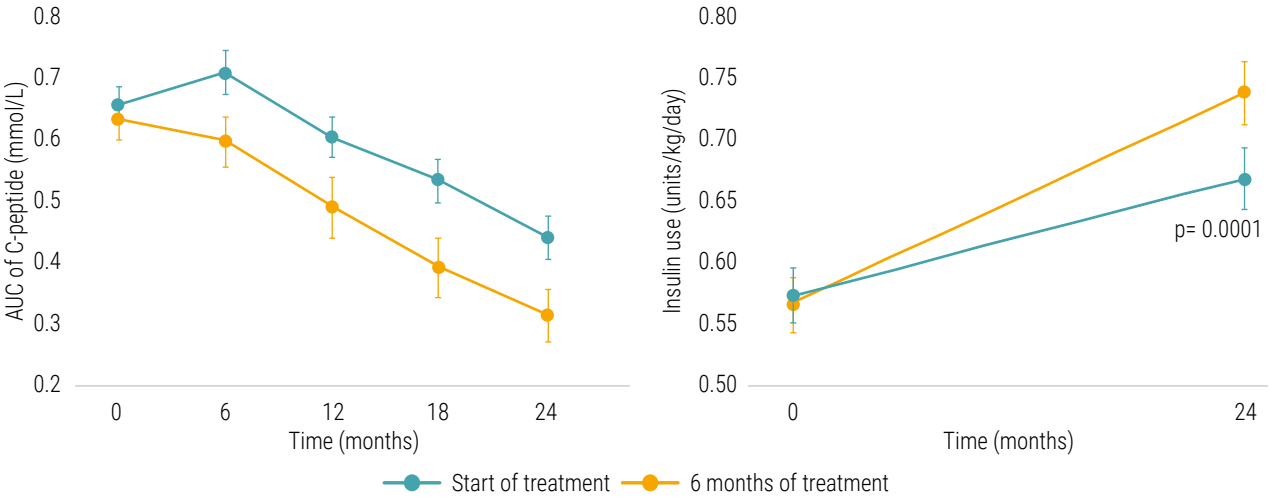


Abbreviations: **DTSQ-s:** Treatment Satisfaction Questionnaire status version; **VAS:** Visual Analog Scale; **HSF-II:** Hypoglycemia Fear Survey type II.

Source: Lecumberri (2018)[416]

Also noteworthy is the FDA approval in 2022 of teplizumab, an innovative therapy designed to modify the course of the disease in patients with T1D. It is the first drug approved to delay the onset of DT1, based on data from multiple clinical trials confirming consistent preservation of insulin-producing cell function as measured by C-peptide. In studies with 2-year data, the decrease from baseline C-peptide levels was 34% and 51% in the teplizumab and control groups, respectively ($p<0.0001$). In addition, significantly lower insulin use (0.66 vs. 0.74 units/kg/day; $p=0.0001$) was observed (Figure 142)[417].

FIGURE 142. OBSERVED MEAN C-PEPTIDE (A) AND INSULIN USE (B) IN CLINICAL TRIALS WITH TEPLIZUMAB TREATMENT COMPARED TO THE CONTROL GROUP IN DT1 PATIENTS



Note: (A) 2-year C-peptide AUC levels from studies with 2-year data. The p-value at 2 years was obtained from ANCOVA for the integrated data observed at 2 years. (B) Mean insulin use at 2 years. The p-value at 2 years was obtained from ANCOVA for integrated data observed at 2 years.

Abbreviations: AUC: area under the curve.

Source: Herold (2023)[417]

Finally, in the advanced therapies section, the benefits of a new therapy approved for TD1 have been described. This is donislecel, the first allogeneic pancreatic islet cell therapy, approved in 2023 by the FDA[418].

The management of T2DD is based on three fundamental pillars: following a balanced diet, regular physical exercise and personalised pharmacological treatment, which may require insulin or another type of pharmacological treatment depending on each patient[419].

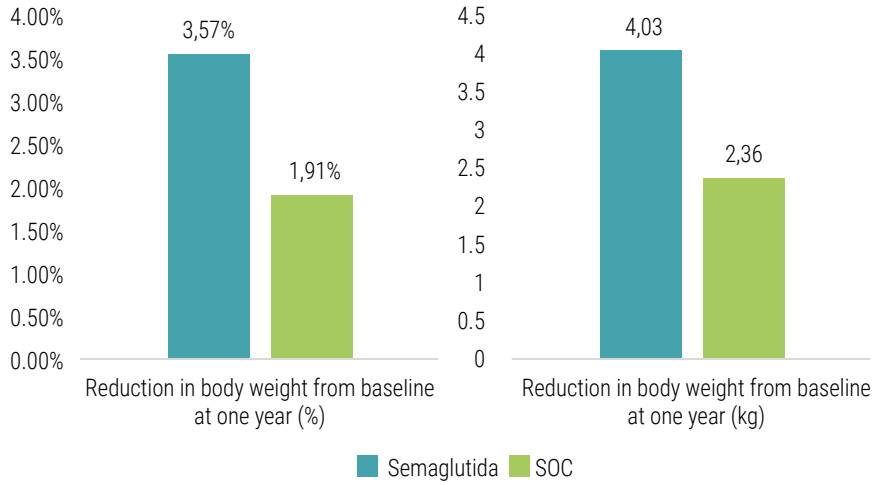
Non-insulin antidiabetic therapies have expanded the therapeutic arsenal available[392]. Among the most important mechanisms of action are dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors, which have been shown not only to control blood glucose but also to reduce the risk of cardiovascular complications.

With regard to GLP-1 receptor agonists, the approval in 2020 of semaglutide to improve glycaemic control as an adjunct to diet and physical exercise in patients with T2DD is noteworthy[361]. The availability of an oral option for this therapeutic group may represent a significant advance in improving the treatment of patients with T2DM by controlling their disease without the need for injections420. Several studies have shown that the use of oral semaglutide is associated with improvements in quality of life (70% gains in the physical and mental component index of the SF-36 questionnaire), when compared to placebo[421–424].

More recently, the SEPRA study, a pragmatic, randomised, open-label, 2-year, pragmatic study, compared the effects of administering subcutaneous semaglutide once a week versus the standard of care of the physician's choice when added to at least two oral antidiabetic drugs for treatment intensification in adults with TD2 in the US (Figure 143)[425]. According to the study results, the use of semaglutide resulted in a significantly higher proportion (p=0.0033) of patients achieving HbA1c <7% (53%, 95%CI: 0.48-0.58) compared to standard treatment (46%, 95%CI: 0.41-0.50). In addition, first-year results showed a weight loss of 4.03 kg with semaglutide compared with 2.36 kg with standard treatment, which consisted mainly of other GLP-1 agonists (71.3%) or SGLT-2 inhibitors (15.5%). The percentage of body weight reduction was significantly higher (p=0.010) in patients receiving semaglutide (3.57% vs 1.91%) (Figure 143). In addition, a lower

proportion of patients receiving semaglutide (52%, SD: 8.2) required additional treatment intensification in year 1 of the study versus the comparator (81%, SD: 13.0).

FIGURE 143. CHANGES IN BODY WEIGHT IN DT2 PATIENTS RECEIVING ONCE WEEKLY SUBCUTANEOUS SEMAGLUTIDE COMPARED TO STANDARD OF CARE



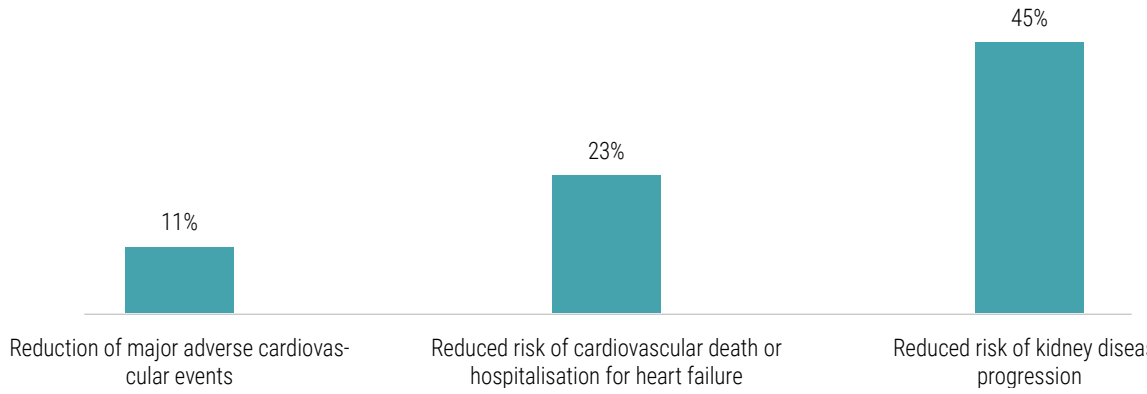
Abbreviation: SOC: standard of care.

Source: Kurtzhals (2023)[425]

Also of note is the approval in 2022 of tirzepatide, the first long-acting dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, designed to improve glycaemic control in T2D2[363,367]. Dual agonist activity may be the mechanism by which tirzepatide significantly reduces HbA1c levels and body weight in patients with TD2, as observed in phase III clinical trials[426]. The SURPASS-4 trial in adults with T2DD and high cardiovascular risk inadequately controlled on oral hypoglycaemic medication reported that, at 52 weeks, mean HbA1c changes with tirzepatide were -2.43% (SD: 0.05) with 10 mg and -2-58% (SD: 0.05) with 15 mg, compared to -1.44% (SD: 0.03) with insulin glargine[427].

On the other hand, among the SGLT2 inhibitors, bexagliflozin will be approved by the FDA in 2023 to improve glycaemic control in T2DD as an adjunct to diet and exercise[404]. This therapeutic group has demonstrated a 23% reduction in the risk of cardiovascular death or hospitalisation for heart failure (HR: 0.77 [95%CI: 0.71-0.84], p<0.0001) regardless of the existence of atherosclerotic cardiovascular disease or a history of heart failure. Furthermore, they reduce the risk of kidney disease progression by 45% (0.55 [0.48-0.64], p<0.0001), with similar benefits in patients with or without atherosclerotic cardiovascular disease (Figure 144)[428].

FIGURA 144. EFFECT ON CARDIOVASCULAR RISK AND RISK OF DISEASE PROGRESSION WITH SGLT2 INHIBITOR TREATMENT IN PATIENTS WITH T2D



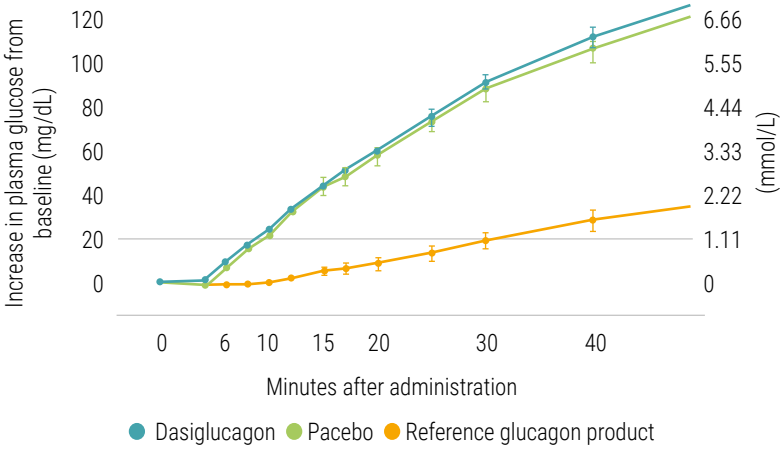
Source: own elaboration based on Zelniker (2019)[428]

Recently, the mechanism of action of SGLT2 inhibitors has been reconceptualised as organ protective rather than antihyperglycaemic agents. They have been described as having a breadth of effects, which can achieve adaptive reprogramming of stressed cells in a way that promotes homeostasis and survival in patients with TD2[429].

New indications have also been approved for some drugs, such as dulaglutide, to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with T2DM with or without established cardiovascular disease[365]. In addition, some indications have been expanded for paediatric patients aged 10 years and older with T2DD, such as dapagliflozin for those whose disease is not sufficiently controlled[362], as well as empagliflozin and metformin hydrochloride as an adjunct to diet and exercise to improve blood glucose[404].

On the other hand, a glucagon receptor agonist in the form of a dasiglucagon injection has been approved in the United States in 2021 to treat severe hypoglycaemia in patients aged 6 years and older with diabetes[366]. In a randomised, double-blind trial involving 170 adult participants with TD1, during controlled insulin-induced hypoglycaemia, mean increases in plasma glucose were observed after 30 minutes. These increases were 90.9 mg/dL for dasiglucagon, compared to 19.1 mg/dL for placebo. For the reference glucagon product, the corresponding mean increase was 88.5 mg/dL. The change in plasma glucose from baseline was found to be significantly greater for dasiglucagon than for placebo at 10, 15, 20 and 30 minutes (p<0.001 for each time point) (Figure 145)[430].

FIGURE 145. MEAN INCREASE IN PLASMA GLUCOSE (MG/DL) SHOWN AS CHANGE FROM BASELINE WITH IC95% AFTER A SINGLE DOSE OF 0.6 MG DASIGLUCAGON, PLACEBO OR 1,0 MG OF THE REFERENCE GLUCAGON PRODUCT IN TREATMENT OF ADULTS DT1



Note: The horizontal line represents the definition of plasma glucose recovery used for the primary endpoint (an increase from baseline of at least 20 mg/dL).

Soure: Pieber (2021)[430]

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There are other recently approved drugs to reduce complications of diabetes such as finerenone to reduce the risk of several serious complications in adults with chronic kidney disease associated with T2D2[366]. This drug has shown strong and consistent renal benefits in patients with impaired liver tests, and profound cardiovascular benefits even in patients with higher fibrosis scores (FIB-4) who were at high risk of developing cardiovascular complications. Specifically, it reduced the risk of any of the following CV events included in the composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for heart failure) versus placebo in the FIB-4 subgroups by 52% (FIB-4 score >3.25), 39% (FIB-4 score >3.25), 39% (FIB-4 score >3.25) and 15% (FIB-4 score >3.25): >3.25), 39% (>2.67) and 24% (>1.30) (p-values for interaction = 0.01, 0.13 and 0.03, respectively)[431].

In addition, new improvements have been made to insulin infusion devices to make them more effective and easier to use. These improvements include a more comfortable design, specific improvements for paediatric devices, memory functions and the addition of continuous glucose monitors[399,414]. This means that there are more and more treatment options that allow people with diabetes to better control their blood sugar by taking fewer pills, needing fewer injections or simplifying their daily routines.

Medicines currently in development for diabetes aim to provide other benefits in addition to improved glycaemic control, including weight loss and/or reduced end-organ damage in the cardiovascular system and liver. Dual agonists with GLP-1 and glucagon receptor activity (e.g. cotadutide), and triagonists with GLP-1, GIP and glucagon receptor agonist activity (e.g. the triple agonist LAPS), are being investigated as promising therapies for patients with non-alcoholic steatohepatitis, many of whom are overweight or obese and have T2D2[432]. Finally, it is worth noting that cell therapies to replace damaged insulin-producing cells could transform the treatment of T1D and form part of a future cure for this disease[433].

Pharmacological progress in diabetes began with the initial discovery of insulin. This has been followed by the development of new insulins and forms of release to improve control of the disease and prevent vascular complications in the medium and long term. Added to this is the diversity of non-insulin anti-diabetic therapies, which have broadened the therapeutic arsenal and offered oral alternatives, improving disease control and quality of life for these patients.

Espinosa (2007)[407], Wang (2003)[408]; Pratley (2018)[397,398]

Recently, in type 2 diabetes, the expansion of indications to pediatric populations and the introduction of drugs offering additional benefits—such as weight loss and reduction of cardiovascular complications, in addition to glycemic control—have been notable advancements. In type 1 diabetes, the approval of the first disease-modifying drug and the first advanced therapy has the potential to change the therapeutic management of this disease and may even lead to a cure in the future.

Radcliffe Department of Medicine (2023)[433], Cho (2023)[426], Herold (2023)[417], FDA (2020-2023)[365–367,404] and EMA (2020-2023)[361–364]

RESPIRATORY DISEASES

Advances in innovative medicines have had a positive impact on the treatment of chronic respiratory diseases, which represent a significant global health burden and are the leading causes of mortality and morbidity worldwide.

In 2019, chronic respiratory diseases (CRDs) were responsible for 4 million deaths, making them the third leading cause of death worldwide, behind only cardiovascular diseases and cancer[434]. The two most common chronic respiratory diseases are chronic obstructive pulmonary disease (COPD) and asthma[435]. Specifically, COPD has been the largest contributor to the global rate of disability-adjusted life years lost (DALYs) and mortality, as it was the leading cause of death during 2019 with 3.3 million deaths, while asthma ranked as the most prevalent chronic respiratory disease, with 262.4 million prevalent cases[436]. Other respiratory diseases include pulmonary hypertension, idiopathic pulmonary fibrosis and various conectivopathies, which can compromise respiratory capacity and overall lung function.

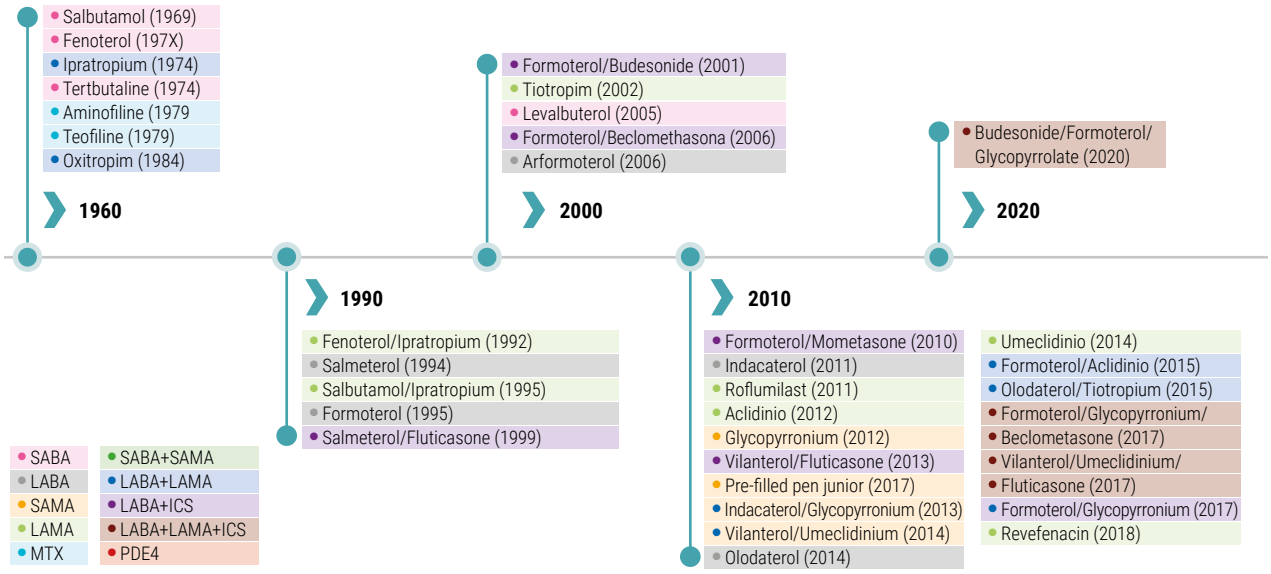
The number of COPD cases is projected to increase by 112 million to a total of 592 million in 2050, corresponding to 9.5% of the total eligible population globally, representing a relative increase of 23.3% from 2020 to 2050 worldwide[437] In Spain, the evolution of prevalence has remained stable at around 3.4% in recent years, with estimates that five out of every 100 men and two out of every 100 women aged 40 years and over suffer from COPD in Spain[438]. In addition, a downward trend in mortality has been reported, specifically, from 2001 to 2019 COPD mortality has decreased by approximately 43%, with a total of 13,808 deaths in 2019 in Spain[439].

Promoting early prevention of COPD through measures such as reducing smoking and exposure to environmental pollutants is essential. As COPD is not currently a curable disease, strategies after diagnosis focus on preventing exacerbations, achieving and maintaining acceptable symptom control and reducing bronchial obstruction[440]. Studies have shown that exacerbations of COPD, in addition to increasing the cost of the disease, lead to a deterioration in health-related quality of life, significantly affect disease progression and increase the risk of death[441,442].

Advances in the understanding of COPD have been accompanied by developments in the pharmacological treatment of the disease. The most commonly used drugs to treat COPD are corticosteroids, to reduce lung inflammation, and bronchodilators with different mechanisms of action (β2-adrenergic agonists, anticholinergics and methylxanthines such as theophylline), both short-acting for mild patients and long-acting for those patients with more severe symptoms. In addition, it has been shown that combining bronchodilators with different mechanisms of action and durations can increase the degree of bronchodilation, with a lower risk of side effects compared to increasing the dose of a single bronchodilator[443,444].

Since their introduction, long-acting bronchodilators have been the mainstay of COPD treatment. These drugs are divided into long-acting anticholinergics and long-acting β2-adrenergic agonists (LAMA and LABA, respectively), first used alone and, in recent years, also in combination[442,445]. Long-acting inhaled bronchodilators are convenient and more effective in relieving symptoms than short-acting bronchodilators, improving health status and reducing exacerbations and associated hospitalisations[446]. The emergence of LAMAs was one of the most important paradigm shifts in COPD treatment, with tiotropium standing out as the first long-acting bronchodilator to be administered as a once-daily inhaler[447]. This drug has been shown to reduce COPD exacerbations and improve lung function, inspiratory capacity and symptoms at rest and with exercise, improving quality of life[448]. The evolution of COPD treatments can be visualised in (Figure 146)[449,450].

FIGURE 146. EVOLUTION OF FREQUENTLY USED MAINTENANCE MEDICATION IN COPD



Note: The chronology shows the leading COPD medicines by class and year of first approval in the US and/or EU market.

Abbreviations: **SABA:** Short-acting β2-agonists; **LABA:** Long-acting β2-agonists; **SAMA:** Short-acting muscarinic antagonists; **LAMA:** Long-acting muscarinic antagonists; **MTX:** Methylxanthines; **LABA+LAMA:** Long-acting β2-agonists+Long-acting muscarinic antagonists; **LABA+ICS:** Long-acting β2-agonists+Inhaled corticosteroids; **LABA+LAMA+ICS:** Long-acting β2-agonists+Long-acting muscarinic antagonists+Inhaled corticosteroids; **PDE4:** Phosphodiesterase 4 inhibitors.

Source: Own elaboration adapted from van Haarst (2019)[449] and Chronic Obstructive Lung Disease (2023)[450]

Regarding other LAMAs, aclidinium bromide and glycopyrro-nium bromide in inhalation devices were marketed in Spain in 2013. The former was developed for the maintenance treatment of COPD and has demonstrated benefits in terms of improved lung function, quality of life and transitional dyspnoea index[451]. Glycopyrronium bromide demonstrated an improvement in lung function versus placebo, as well as a 34% reduction in the risk of flare-ups[452,453]. Subsequently, in 2014, umeclidinium bromide was marketed in Spain and has shown, both alone and in combination with a LABA (vilanterol), an improvement in lung function, health-related quality of life and frequency of exacerbations[454]. Finally, revefenacin was approved in the United States in 2018, making it the only LAMA approved for once-daily nebulised administration. Until its approval, only two LABAs (arformoterol and formoterol) and the anticholinergic agent glycopyrrolate were the only long-acting bronchodilators available for nebulised administration, and all required twice-daily administration[455].

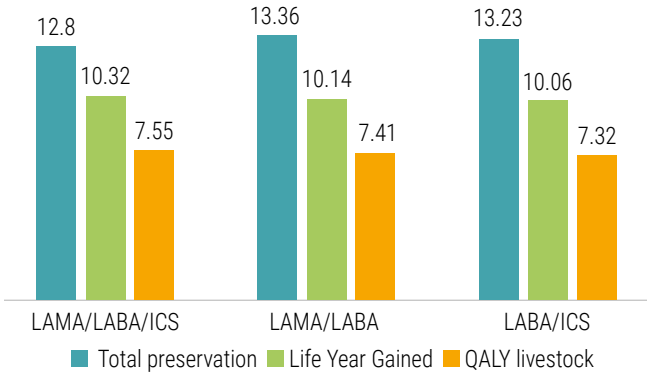
Similarly, major advances have been made in the evolution of LABAs with some ultra-long-acting drugs. A relevant example is olodaterol, which has a rapid onset of action, and when added to tiotropium potentiates improvement in lung function, quality of life and reduction of dyspnoea. In addition, the combination of tiotropium with olodaterol represents a new perspective in the treatment of COPD[448]. The beneficial effects of this long-acting dual bronchodilation have been demonstrated in several pivotal studies[456–459]. On the other hand, vilanterol is noteworthy as the first LABA approved only for use in combination with other respiratory medicines. In general, LABAs have been shown to improve quality of life indicators and reduce hospitalisations compared to placebo. However, there is no significant impact on exacerbations or mortality, based on the combined results of 26 studies involving approximately 15,000 participants[460,461].

According to the recommendations of the 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD)[450]. treatment with LABA/LAMA/ICS triple therapy has been shown to improve lung function, symptoms and patient quality of life, as well as reduce exacerbations in patients with chronic obstructive lung disease compared to LABA/ICS combination therapy or LAMA monotherapy[462–468]. In addition, the most recent evidence suggests that triple inhaled therapy outperforms LABA/LAMA combinations in reducing mortality in patients with symptomatic COPD and a history of frequent and/or severe exacerbations[469].

An increase in the number and severity of exacerbations is associated with an increased risk of subsequent exacerbations, all-cause mortality and COPD-related mortality[470]. For this reason, reducing exacerbations is a key treatment goal for many COPD patients[471]. In this regard, a study in patients with moderate-severe COPD in Spain has shown that LABA/LAMA/CSI triple therapy is associated with a lower rate of exacerbations (12.80) than dual therapy with LAMA/LABA (13.36) and LABA/ICS (13.23), as well as with more life years gained (10.32 vs. 10.14 and 10.06, respectively) and QALYs (7.55 vs. 7.41 and 7.32, respectively) (Figure 147)[472].

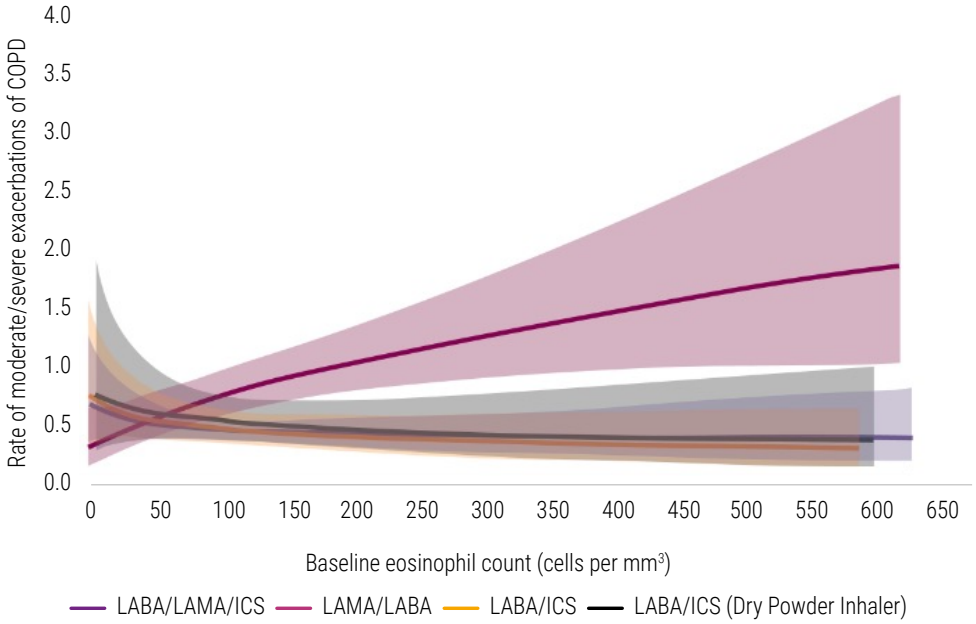
The budesonide/formoterol/glycopyrrolate combination is the most recent triple therapy approved by the EMA. The benefits of this LABA/LAMA/ICS triple therapy in reducing moderate/severe exacerbation rates relative to glycopyrrolate/formoterol (LAMA/LABA) dual therapy have been demonstrated even among COPD patients with no history of exacerbations in the previous year[473]. The impact of corticosteroid therapy on the reduction of moderate/severe exacerbations was observed for all preparations containing budesonide (Figure 148)[473].

FIGURE 147. EFFECTS OF LABA/LAMA/ICS THERAPY VERSUS LAMA/LAMA AND LABA/ICS ON TOTAL EXACERBATIONS, LIFE YEARS AND AVAC GAINED PER PATIENT



Source: Trigueros (2022)[472]

FIGURE 148. RATE OF MODERATE/SEVERE EXACERBATIONS IN PATIENTS REPORTING NO PREVIOUS EXACERBATION AS A FUNCTION OF BASELINE EOSINOPHILS AND TREATMENT GROUP (LABA/LAMA/ICS THERAPY VS. LAMA/LABA AND LABA/ICS)



Source: Martinez (2021)[473]

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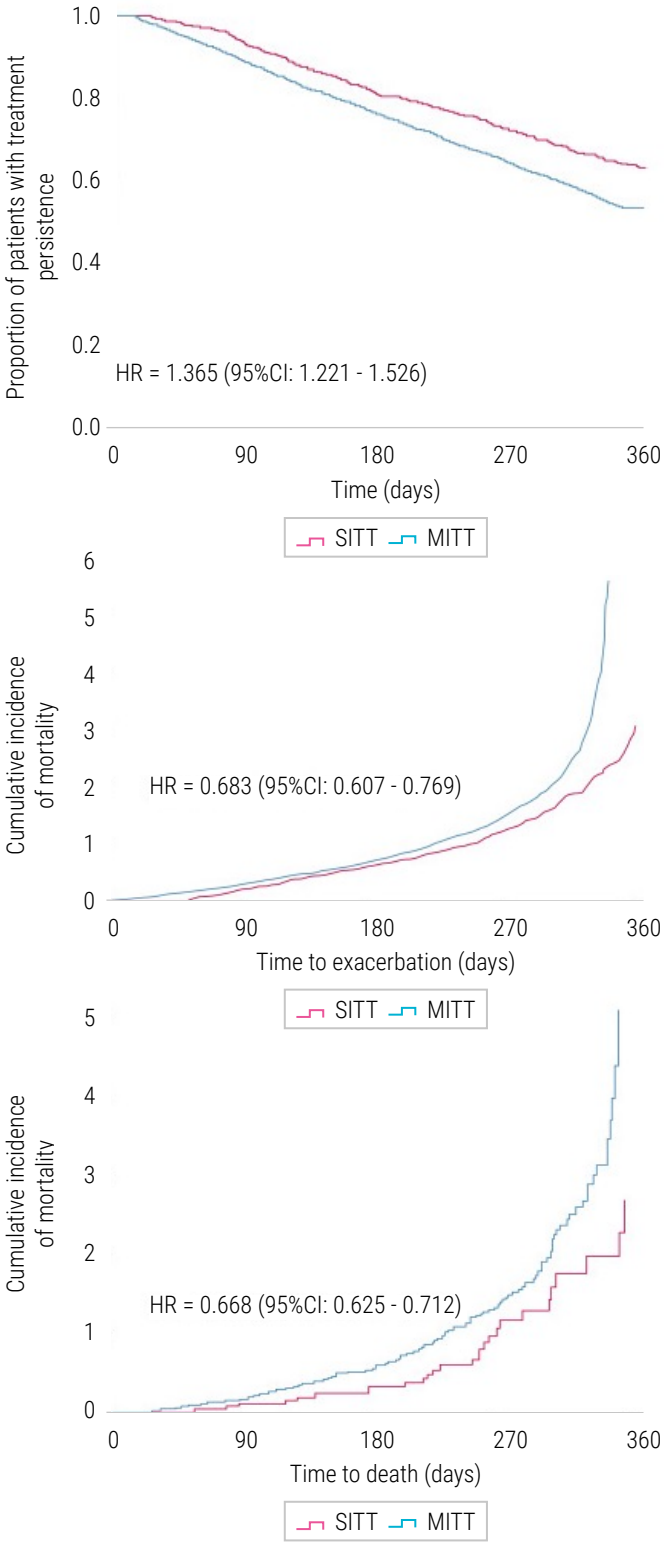
The success of inhaled therapy and its impact on quality of life is directly dependent on adherence to the prescribed regimen. Indeed, it has been reported that the overall St George's Respiratory Questionnaire (SGRQ) score as a measure of quality of life was significantly worse in patients with intermediate/poor adherence (p=0.036), according to a cross-sectional study of 318 COPD patients on inhaler therapy in the last 3 months from 53 community pharmacies[474].

In this regard, the use of single inhalers compared to multiple inhalers for delivery of triple therapy has shown significantly better adherence[475]. In addition, increased persistence (treatment discontinuations <60 days) to treatment has been reported, along with a decreased risk of exacerbations and mortality[476]. This has been verified in a study conducted in Spain where it has been reported that therapeutic persistence is higher with single inhaler versus triple therapy with multiple inhaler, while the cumulative incidence of major/severe exacerbations and mortality are lower (Figure 149)[477].

In addition to the efficacy of triple therapy, there is evidence to support the efficacy of the combination of LABA and LAMA as an effective approach to enhance bronchodilation. These combinations offer proven benefits in both short- and long-term treatment for patients with asthma or COPD. In addition, they reduce the need to increase the doses of the individual components, which in turn reduces the risk of adverse events[478].

Prevention of exacerbations in COPD patients is crucial, as their frequency and severity increase with the degree of obstruction, and a previous history of exacerbations is the main risk factor for future crises. Most exacerbations are caused by viral or bacterial infections and are a major cause of hospitalisation. In severe COPD, the incidence of viral infections may exceed 40%, with influenza virus being the second most common after rhinovirus. Therefore, non-pharmacological re-commendations in COPD patients include vaccination, notably pneumococcal vaccination, which reduces the incidence of lower respiratory tract infections, and annual influenza vaccina-

FIGURA 149. EFFECT OF SINGLE INHALER TRIPLE THERAPY ADMINISTRATION COMPARED TO MULTIPLE INHALERS ON A) TREATMENT PERSISTENCE B) EXACERBATIONS AND C) MORTALITY IN COPD PATIENTS, SPAIN



Abbreviations: SITT: Single Inhaler Triple Therapy; **MITT:** Multiple Inhaler Triple Therapy; **HR:** Hazard ratio; **CI:** Confidence Interval.

Source: Alcázar-Navarrete (2022)[477]

tion, essential to reduce cardiovascular morbidity and mortality and prevent serious infections, especially in patients with comorbidities. In addition, vaccination against SARS-CoV-2 is crucial in these patients where COVID-19 disease is associated with increased mortality and higher rates of mechanical ventilation. Finally, in recent years, vaccination against respiratory syncytial virus (RSV) has gained importance as it is associated with respiratory infections such as bronchiolitis and pneumonia[479].

On the other hand, in addition to the respiratory difficulties derived from the pathology itself, COPD patients often suffer from other problems related to the disease, such as diabetes, anaemia and cardiovascular or metabolic problems, among others[480]. Cardiovascular problems are of particular concern, as COPD is associated with a 2- to 3-fold higher cardiovascular mortality than the general population[481].

Recently, a link between statin use and improved outcomes, such as reduced exacerbations and mortality, has been observed in observational studies of patients using statins for cardiovascular and metabolic indications in the context of COPD. In addition, vitamin D supplementation reduced exacerbation frequency in patients with low baseline vitamin D levels[450].

COPD research has provided a clearer and more precise understanding of the characteristics of the disease, which is represented by different phenotypes and pathobiological mechanisms. As with other diseases, precision medicine and the search for molecules that target specific populations are opening up new possibilities for treating the disease. New dual-acting compounds that are both muscarinic antagonists and β2-agonists (MABA) are being developed for the treatment of patients with stable COPD. In addition, as α1-antitrypsin deficiency has been associated with COPD, new compounds of enhanced intravenous recombinant human α1-antitrypsin and inhaled recombinant α1-antitrypsin are being developed. Finally, the development of new inhaled antivirals is noteworthy as early administration of antiviral agents at the onset of a respiratory viral infection may have the potential to reduce the severity or even prevent exacerbations of COPD[482].

More recently, on the premise that ICS may have beneficial effects in a subset of COPD patients and that blood eosinophil count predicts response to ICS therapy in COPD, but is not a perfect biomarker, it has been proposed that RNA sequencing may help to better predict response to corticosteroid therapy, but this needs to be confirmed in future studies. To date, using genome-wide gene expression profiling in the SYMBEXCO trial, nine genes were identified as differentially expressed in COPD patients who developed an early exacerbation after ICS withdrawa[478].

Existing treatments and combinations for COPD have significantly reduced both the risk of exacerbations and the risk of COPD-related mortality, as well as reducing symptoms and improving patients' quality of life.

Kerwin (2012)[452], Jones (2012)[451], Burguel (2014)[456], Singh (2016)[468]

The latest approved treatments for COPD and single inhaler administration methods have shown to improve adherence, reduce exacerbations, and enhance disease control. However, the future of treatment lies in the search for targeted molecules and biomarkers that open up a new range of possibilities for treating the disease and predicting the response to treatments.

Soltz (2023)[478], Lin (2023)[476] y Alcázar-Navarrete (2022)[477]

Asthma is another chronic respiratory disease whose main symptoms are coughing, wheezing and dyspnoea, among others[483–485]. In general, it has a major clinical and economic impact, is associated with high morbidity and has a significant impact on work activity, as more than 25% of asthma sufferers have some episode of work incapacity due to asthma during the year, and it is one of the 11 most frequent causes of incapacity[486]. Currently, asthma affects an estimated 262.4 million people worldwide[436] and in 2019 caused 461,000 deaths. In addition, having the disease, especially among children under 15 years of age, increases mortality by 46%[486].

Significant variability in the overall prevalence of asthma has been reported between different geographical areas. A recent study has shown variability in asthma prevalence between autonomous communities in Spain, estimating prevalence from 1% to 18% in different regions. In this sense, the recent introduction of highly effective biologic drugs for a subgroup of patients with severe uncontrolled asthma highlights the importance of knowing this prevalence in order to estimate how many patients could benefit from this therapeutic option[487].

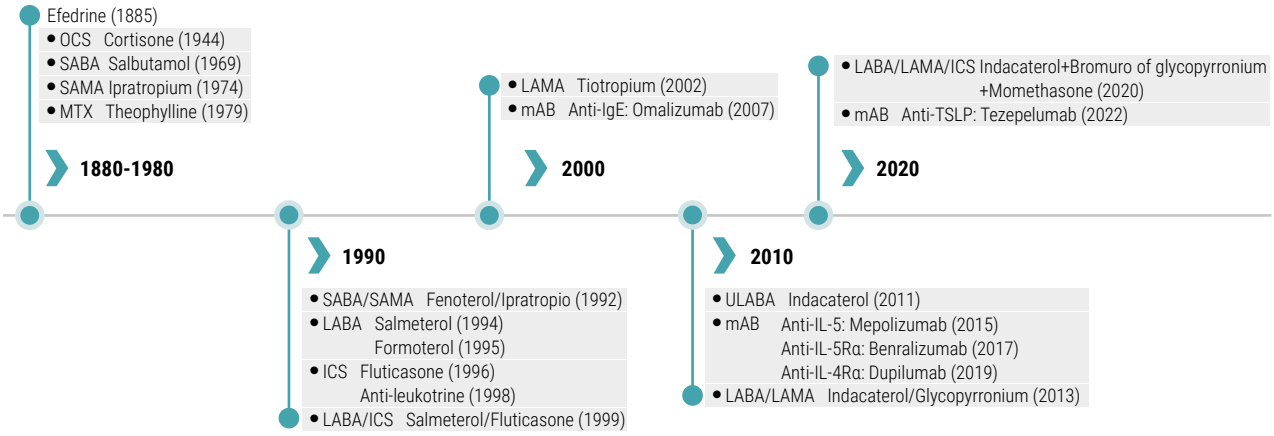
The main goal of treatment has evolved from controlling the symptoms of bronchospasm to treating inflammation to seeking clinical remission as soon as possible, as well as preventing exacerbations, chronic airflow obstruction and reducing mortality, avoiding adverse effects of treatment and allowing a normal lifestyle to be achieved[488–491].

Although the term "control" is broad and can encompass all clinical and pathophysiological aspects of asthma, for practical purposes it includes the clinical features of the disease (symptoms and exacerbations) and lung function tests. Disease control largely reflects the appropriateness of asthma pharmacological treatment for the individual patient, which allows on the one hand to control daily symptoms (current control domain) and, on the other hand, to prevent exacerbations and excessive loss of lung function (future risk domain). These goals can be achieved in most patients with appropriate pharmacological management, which may include control/maintenance or relief/rescue therapies.

Drugs to treat asthma are classified as controller or maintenance, and reliever, also called "rescue". Control or maintenance drugs, which must be given continuously for prolonged periods, include inhaled (ICS) or systemic corticosteroids, leukotriene receptor antagonists (LTRAs), long-acting β2-adrenergic agonists (LABAs), tiotropium and, more recently, monoclonal antibodies (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab).

The evolution of asthma treatments involves the use of common strategies with COPD such as inhaled bronchodilators which are essential for the optimal treatment of asthma patients, in particular ICS are the cornerstone of the therapeutic approach to asthma[450,490]. Historically, therapeutic management of the disease began with the use of ephedrine to prevent and treat bronchospasm, evolved with molecules with anti-inflammatory properties such as anti-leukotriene and, in recent years, monoclonal antibodies have been developed, with tezepelumab being the most recent to offer for the first time a treatment option for asthma patients without biomarker limitations[489]. Also notable is the recent approval of indacaterol/glycopyrronium/momethasone triple therapy, making it the first fixed-dose LABA/LAMA/ICS combination for the treatment of asthma (Figure 150)[492].

FIGURE 150. EVOL UTION OF ASTHMA TREATMENTS



Note: The chronology shows some of the asthma medicines by class and year of first approval in the US and/or EU market.

Abbreviations: **OCS:** oral corticosteroids; **ICS:** inhaled corticosteroids; **IL:** interleukin; **LABA:** long-acting β2-agonists; **LABA+ICS:** long-acting β2-agonists+inhaled corticosteroids; **LABA+LAMA:** long-acting β2-agonists+long-acting muscarinic antagonists; **LABA+LAMA+ICS:** Long-acting β2-agonists+long-acting muscarinic antagonists+inhaled corticosteroids; **mAb:** monoclonal antibody; **MTX:** methylxanthines; **SABA:** short-acting β2-agonists; **SAMA:** short-acting muscarinic antagonists.

Source: own elaboration based on Nolasco (2023)[489] y van Haarst (2019)[449]

Regular use of corticosteroids has been shown to be effective in reducing symptoms, improving lung function, decreasing bronchial hyperresponsiveness and reducing the number of exacerbations[493–496]. The use of ICS was a breakthrough in the treatment of the disease, as it has confirmed a decrease in the frequency and severity of disease symptoms, as well as a reduction in the need for emergency inhalers and exacerbations requiring emergency room visits or hospitalisation[497]. For example, according to one study, regular use of ICS can prevent between 5 and 27 hospital readmissions per 1,000 asthma patients per year in the long term[494]. In addition, other studies have shown an association between the arrival of these medicines and disease-related mortality[498,499].

Regular use of LABAs, such as salmeterol or formoterol, can improve asthma control and reduce exacerbations[500–502]. For example, according to one study, adding formoterol to budesonide asthma treatment reduces the annual number of exacerbations by 2.3 times compared to budesonide maintenance treatment[503]. For LAMA, tiotropium, added to background treatment with at least one ICS or LABA/ICS dual therapy, significantly improved lung function and reduced exacerbation rates[504].

The use of monoclonal antibodies opened up a new avenue of treatment for patients with asthma, especially in patients who did not respond to conventional therapy or whose exacerbations were uncontrolled. In this regard, a whole arsenal of therapeutics is now available to target the different pathways causing lung inflammation. Omalizumab (anti-IgE) has been approved for patients with allergic asthma who have elevated serum IgE values. In addition, mepolizumab, reslizumab and benralizumab (anti-IL-5/Rα) are used to treat patients with severe eosinophilic asthma. In addition, dupilumab (anti-IL-4Rα) is used in patients with elevated eosinophils and/or elevated FeNO, a biomarker whose elevated levels may indicate airway inflammation

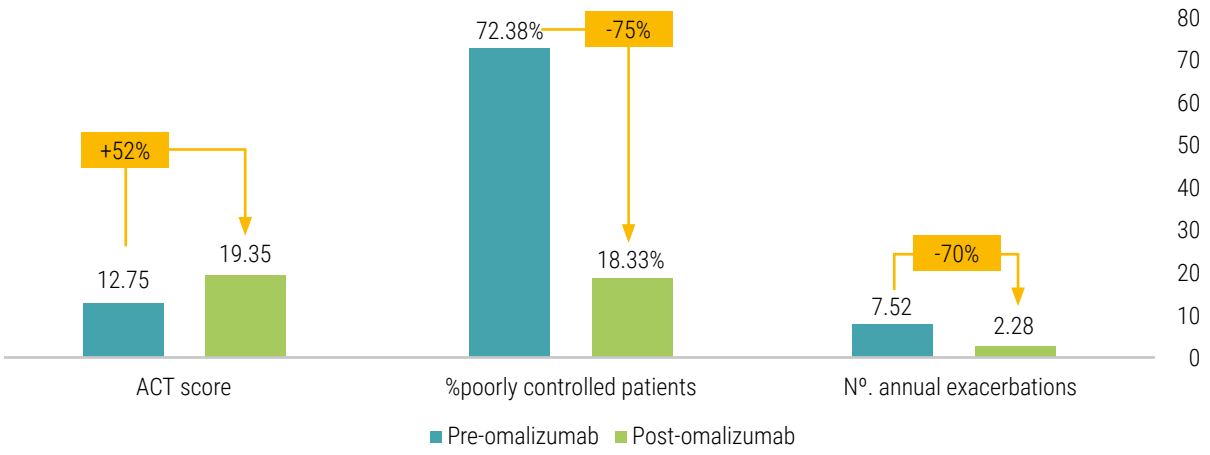
Severe uncontrolled asthma has a clinical impact in terms of exacerbations in uncontrolled patients[488,505,506]. In this regard, several studies have shown that monoclonal antibodies can be used to treat asthma such as omalizumab, mepolizumab and benralizumab, among others, have reduced exacerbations in patients with asthma[507–510]. In addition, biologic therapy has been shown to be particularly effective in severe uncontrolled asthma, defined as asthma disease that remains poorly controlled despite treatment with a combination of high-dose ICS together with a long-acting β2-adrenergic (LABA) (+/-LAMA) in the past year, or oral corticosteroids for at least six months of the same period. Overall, these drugs have demonstrated significant benefits

for people with uncontrolled asthma, including reductions in asthma attacks and emergency department visits, as well as improvements in lung function and health-related quality of life[511].

The most recently approved biologic therapy, tezepelumab, has been shown to be effective in reducing exacerbations in patients with severe uncontrolled asthma, both with high and low blood eosinophil counts. In addition, when administered in conjunction with medium to high doses of the dual LABA/ICS combination, it has shown a significant decrease in exacerbation rates, improving asthma control, lung function and health-related quality of life, regardless of baseline blood eosinophil level[504,512].

Omalizumab has also been shown to be effective in the treatment of severe asthma as an adjuvant to reduce oral corticosteroid doses and is associated with fewer exacerbations (13% vs. 31% in the fixed-dose steroid phase and 16% vs. 30% in the suppression phase), less use of rescue medication and a decrease in asthma severity[513,514]. According to a study in Spain, omalizumab treatment improved the Asthma Control Test (ACT) asthma control score by 52%, while reducing the percentage of poorly controlled patients and the number of annual exacerbations by 75% and 70%, respectively (Figure 151)[509].

FIGURE 151. EFFECTIVENESS OF OMALIZUMAB IN THE TREATMENT OF PATIENTS WITH ASTHMA IN SPAIN

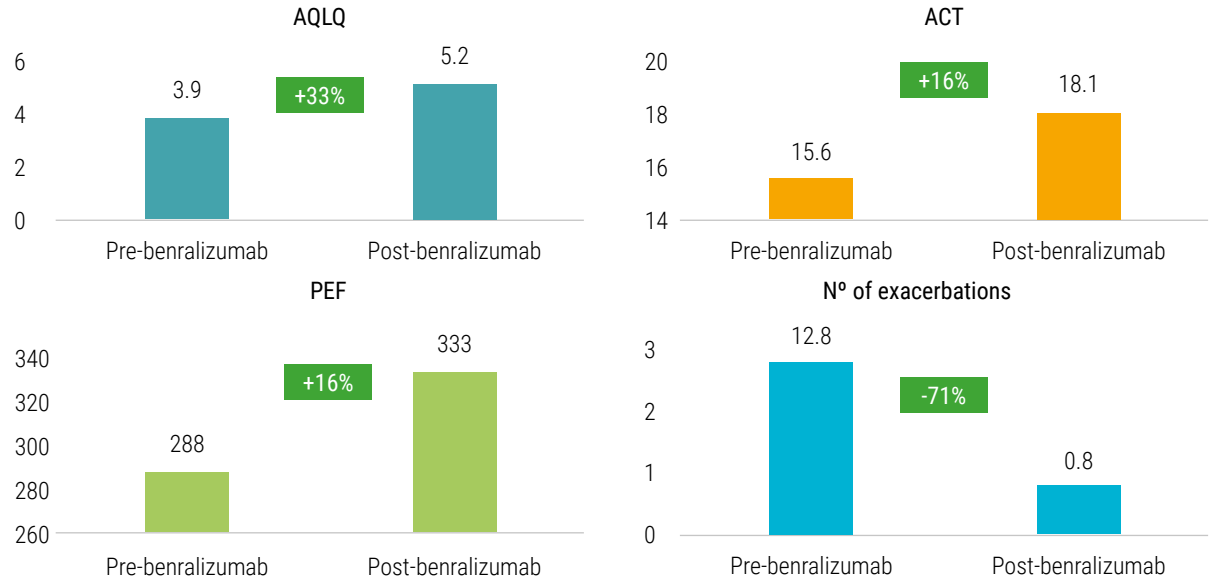


Abbreviations: ACT: Asthma Control Test.

Source: Martínez-Moragón (2019)[509]

Similarly, the use of benralizumab has been shown to improve patient-reported outcomes and functional parameters in patients with severe difficult-to-treat asthma. Specifically, a 33% increase in asthma quality of life questionnaire (AQLQ) scores and a 16% increase in ACT scores were observed. Patients reported less limitation in activities such as working, talking, walking and participating in social activities. In addition, the drug improved functional outcomes and significantly reduced the number of exacerbations requiring courses of oral corticosteroids by 71% (Figure 152)[515].

FIGURE 152. EFFECT OF BENRALIZUMAB ON AQLQ SCORE, ACT SCORE, PEF AND NUMBER OF EXACERBATIONS IN ASTHMA MANAGEMENT



Abbreviations: **AQLQ:** Asthma Quality of Life Questionnaire; **ACT:** Asthma Control Test; **PEF:** peak expiratory flow.

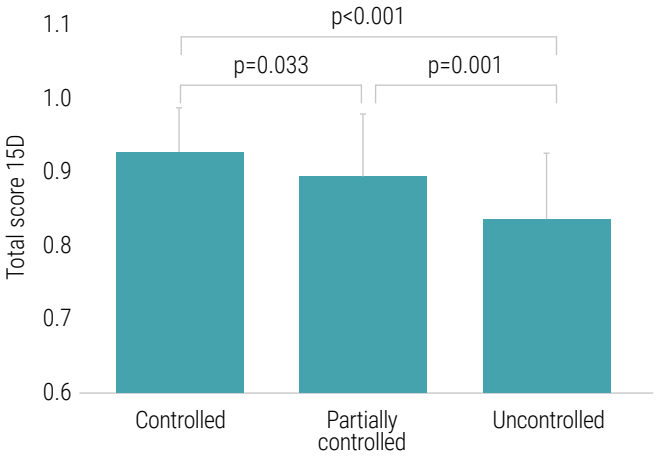
Source Di Bona (2020)[515]

Some asthmatic patients experience a mild/moderate form of the disease that is effectively managed with the use of inhaled corticosteroids and β2-agonists. However, other asthmatic patients face difficulties in disease control, even with high doses of inhaled corticosteroids or even oral corticosteroids. Several inflammation-related mechanisms have been considered to be responsible for the development of the relative corticosteroid resistance observed in these patients[516].

The degree of disease control is a determining factor in the quality of life of asthma patients. For example, an observational study in Spain revealed significant differences between controlled and uncontrolled patients in terms of comorbidities, healthcare resource use, and health-related quality of life[517]. Similarly, some international studies also support the positive effect of ICS on improving patients' quality of life compared to pre-treatment levels.

In a study involving 203 adult asthma patients, it was shown that those with uncontrolled and partially controlled asthma had a lower generic health-related quality of life, as determined by the 15D instrument, compared to the controlled group (Figure 153)[521]. More specifically, statistically significant differences were found between patients with controlled and uncontrolled asthma in 10 of the 15 dimensions measured by the 15D instrument. These included mobility, breathing, sleep, usual activities, mental function,

FIGURE 153. AVERAGE QUALITY OF LIFE OF THE PATIENT WITH ASTHMA, ACCORDING TO THE DEGREE OF CONTROL OF THE DISEASE



Note: The 15D is a generic, comprehensive, standardised and self-administered measure of 15 dimensions of health-related quality of life (HRQoL).

Source: Ilmarinen (2019)[521]

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discomfort and symptoms, depression, distress, vitality, and sexual activity, all of which were lower in patients with uncontrolled asthma.

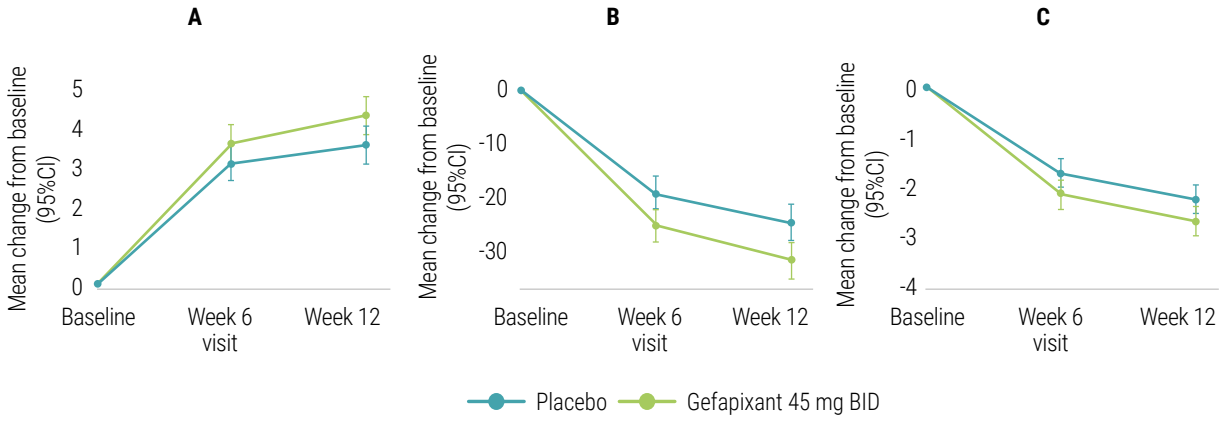
Biomarker assessment is critical in the process of creating a personalised treatment. For example, an elevated FeNO concentration (> 50 parts per billion [ppb]) in adults is associated with responsiveness to ICS. FeNO has also been identified as a predictor of response to biologics, for example, the anti-IgE drug omalizumab has shown a greater reduction in exacerbations in patients with a high FeNO concentration (≥ 19.5 ppb) compared to those with a low FeNO concentration (< 19.5 ppb)[504].

However, so far, only patients with severe asthma receiving monoclonal antibodies benefit from a more personalised approach, where biomarker measurement and comorbidity assessment are crucial for prescribing and predicting treatment response[489]. Only when all recommended inhaled and oral therapies are ineffective, phenotyping and biomarker testing are recommended to determine the most appropriate therapy using a shared decision-making approach with the patient[504].

On the other hand, it is noteworthy that chronic cough, traditionally considered as a persistent symptom of other conditions, is now classified as a specific clinical condition in the International Classification of Diseases, 11th revision (ICD-11)[522]. It has been defined as a persistent cough lasting more than 8 weeks in adults and more than 4 weeks in children, without significant improvement and unresponsive to conventional treatment. In this context, it is relevant to note the approval of gefapixant as the first authorised treatment in the European Union for adults suffering from refractory or unexplained chronic cough, including patients who do not respond to treatment for underlying conditions such as asthma or gastro-oesophageal reflux[523].

In patients with chronic cough, when the efficacy of gefapixant was compared with placebo, it was shown that the drug resulted in improvements in cough frequency, cough severity as measured by the visual analogue cough severity scale and quality of life as measured by the Leicester Cough Questionnaire (LCQ) (Figure 154)[524].

FIGURE 154. IMPACT ON EFFICACY ENDPOINTS OVER 12 WEEKS WITH GEFAPIXANT TREATMENT COMPARED TO PLACEBO IN PATIENTS WITH CHRONIC COUGH



Notes: **A)** LCQ total score over 12 weeks; **B)** Mean weekly cough severity VAS score over 12 weeks; **C)** Mean weekly cough severity Diary score over 12 weeks.

Abbreviations: **BID:** twice daily; **VAS:** visual analogue scale; **MC:** least squares; **LCQ:** Leicester Cough Questionnaire.

Source: McGarvey (2023)[524]

Recently, some researchers have suggested the possibility of using a personalised approach to severe asthma even in patients with mild asthma. This innovative approach aims to prevent airway remodelling and disease progression, aiming for complete remission of the disease. Indeed, the introduction of biologics in severe as-

thma has allowed some patients to completely reverse airflow obstruction, which was previously considered irreversible. This highlights the crucial difference between a "fixed" obstruction, caused by structural changes that do not respond to current treatments, and a "reversible" obstruction, which normalises during treatment with biologics, something that was not achieved with high doses of systemic corticosteroids[525].

Today, precision medicine to address the underlying inflammatory processes is opening new horizons in the treatment of asthma. The future therefore looks bright for both patients with severe asthma, who will benefit from more effective therapies, and for physicians, who will be better informed to understand and manage the disease[489].

The therapeutic approach to asthma has evolved from symptomatic relief with bronchodilators to a more personalised approach to inflammation with biologic therapies, which have been shown to reduce exacerbations and improve functional outcomes and quality of life in patients with severe uncontrolled asthma.

Di Bona (2020)[515]; Edris (2019)[508] and Rabe (2018)[505]

Recent advances in asthma treatment have suggested the feasibility of a personalised approach even in patients with mild forms of the disease, aiming to prevent airway remodelling and disease progression towards complete remission.

Varrichi (2022)[525]

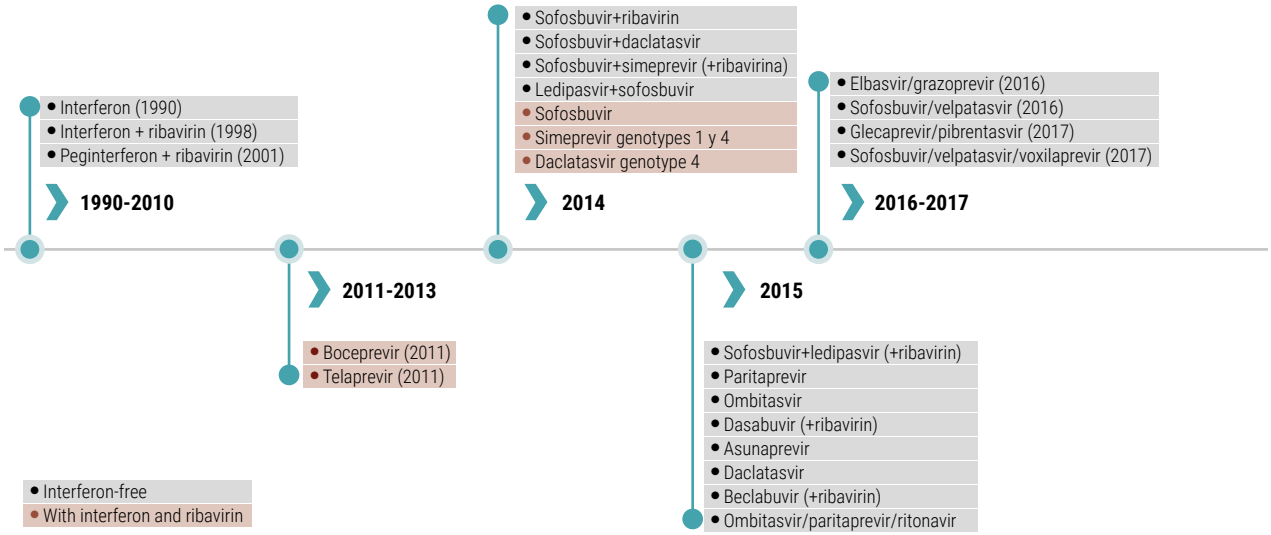
HEPATITIS C

Hepatitis C virus (HCV), discovered in 1989, can cause acute and chronic hepatitis, ranging in severity from mild to severe lifelong disease including liver cirrhosis and cancer. Currently, it is estimated that around 58 million people worldwide are infected with HCV, with an estimated 1.5 million new infections annually, and 290,000 disease-related deaths[526]. In Spain, it is estimated that there are currently approximately 55,000 people with active hepatitis C, of whom 29% are undiagnosed[527].

During the 1990s and 2000s, the main goal of HCV treatment was to prevent complications and ultimately to prevent death, although until 2011 the sustained viral response (SVR) rate of available treatments was less than 50%[528]. Standard therapy consisted of a combination of weekly injections of pegylated interferon alpha and oral ribavirin for a variable period of 24-72 weeks, which was associated with clinically relevant adverse events and marginal response rates in patients with advanced disease[529].

From 2011 onwards, the therapeutic landscape began to change radically, thanks to a better molecular understanding of the virus' life cycle. The new interferon-free antiviral drugs, known as direct antiviral agents (DAAs), were then marketed, which marked a turning point in the treatment of the hepatitis C virus, becoming a paradigmatic case of successful pharmaceutical innovations (Figure 155). The year 2014 was momentous, with the approval of a series of interferon-free DAAs that represented an unprecedented milestone in the treatment of the disease, as they were able to eliminate viral replication in a sustained manner in between 85% and 100% of cases[530–534].

FIGURE 155. EVOLUTION OF APPROVED HEPATITIS C VIRUS TREATMENTS IN EUROPE, 1990-2023



Source: own elaboration from Webster (2015)[531], EMA (2016)[535], EASL (2016)[536] and EMA (2024)[537]

Direct-acting antivirals are associated with much greater efficacy than their predecessors, with significantly higher viral response rates. In addition, the new agents have fewer adverse effects, shorten treatment duration and require little monitoring[531].

Thus, the efficacy and safety of sofosbuvir, incorporated into the Spanish public therapeutic arsenal in November 2014[538], was tested in several clinical trials, with overall sustained viral response rates of 94% in naïve patients and 90% in patients who did not respond to previous treatments[530]. Moreover, its high effectiveness has also been proven in clinical practice, where it has achieved SVR rates of over 80%, even among patients with complicated profiles[539,540].

In 2014, another next-generation DAA, simeprevir, was also approved in Spain, associated with much higher response rates than interferon-ribavirin combinations (80% vs 50%)[538,541,542]. From 2015, new combination therapies for less common forms of HCV - genotypes 3, 4, 5 and 6 - were approved, providing the option of oral interferon-free treatment for all forms of hepatitis C. The combination of ombitasvir, paritaprevir and ritonavir, in addition to being the first interferon-free oral treatment available for patients with genotype 4, has been shown to achieve 100% SVR rates in clinical trials[543]. The ledipasvir/sofosbuvir combination was also approved for treatment of genotypes 1,3,4,5 and 6, allowing for a shortened treatment duration for genotype 1 naïve patients (94% SVR)[544]. In real-world clinical practice data, ledipasvir/sofosbuvir has achieved 12-week SVR rates of over 89% or 92% in the subgroup of HCV genotype 1 patients545[545].

In June 2016, the first fixed-dose combination of sofosbuvir and velpatasvir was approved, ushering in a new era in DAA therapy by allowing almost unique management for all HCV genotypes and simplifying the diagnostic process by avoiding the need for pre-treatment genotyping[546]. The ASTRAL-1-5 studies have confirmed the pan- genotypic efficacy of this combination (95% SVR at 12 weeks of treatment (95% CI 89%-99%)), as well as its efficacy in HCV co-infection with HIV and liver disease[547]. These efficacy results have been verified in a study based on real-life data in Canada, based on administrative data from 2,821 patients, who achieved No SVR of 93.7% for genotype 3 and 96.4% for genotype 2, demonstrating the high effectiveness of treatment[548].

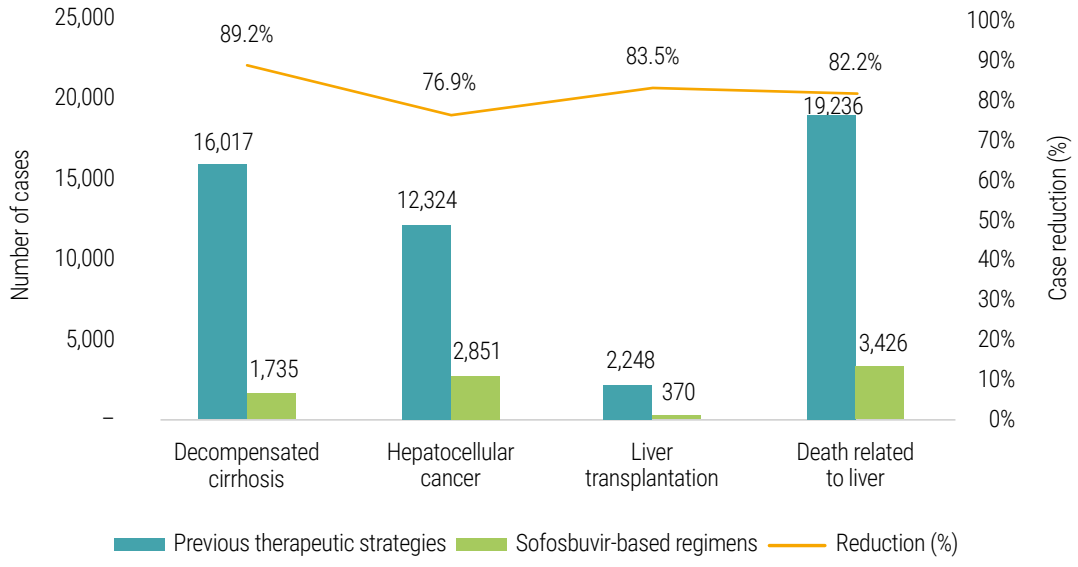
In 2017, the EMA approved two new drugs for the treatment of chronic hepatitis C for patients who have failed or are unable to use previously available therapies for chronic hepatitis C. Both drug combinations (glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir) are direct-acting HCV antivirals that have changed the way this chronic infection is treated[549,550]. The combinations demonstrated a sustained viral response of more than 90% at 12 weeks after completion of treatment[551,552]. In actual clinical practice, SVR rates for glecaprevir/pibrentasvir use were higher than in the trial, reaching 98% overall, according to a study of 2,036 patients in nine countries, including Spain[553].

The promising results of sofosbuvir/velparasvir therapy have also been confirmed in a Spanish study in patients with more advanced disease (presence of compensated cirrhosis), where SVR rates of 91-96% were observed at 12 weeks of treatment[554].

These disruptive results have allowed the prevalence of the disease to fall by more than 40% since the introduction of the new treatments[555,556].

The value of sofosbuvir-based regimens in Spain has been demonstrated in a real-life study in a target population of 85,959 patients with chronic hepatitis C treated during 2015-2019. Compared with previous therapy, sofosbuvir-based regimens reduced the occurrence of decompensated cirrhosis by 89%, hepatocellular carcinoma by 77%, liver transplantation by 84% and liver-related mortality by 82% (Figure 156)[557].

FIGURE 156. NUMBER OF CLINICAL EVENTS AND REDUCTION IN CLINICAL EVENTS BETWEEN PATIENTS TREATED WITH SOFOSBUVIR-BASED AAD AND PREVIOUS THERAPEUTIC STRATEGIES, SPAIN 2015-2019



Source: Esteban (2022)[557]

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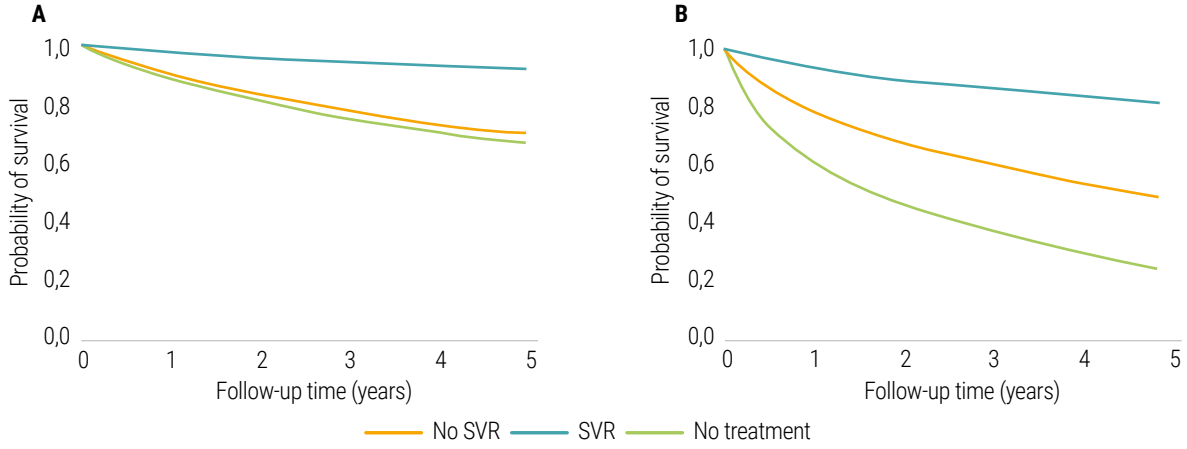
In Spain, the real-life effectiveness and safety of DAAs in chronic HCV-infected patients who started treatment between 2015 and 2019 has also been analysed. Of the 279 patients analysed, 97.8% achieved sustained viral response, with six virologic failures confirmed. In a subgroup analysis according to the presence or absence of cirrhosis, HIV co-infection and genotype, effectiveness was close to or above 90%. Treatment was safe and with low toxicity, leading to the conclusion that DAAs were highly effective, equal or even superior to those reported in clinical trials, even in difficult-to-treat subpopulations[558].

Another interesting real-life international example is a recent study that evaluated the effect of sustained viral response (SVR) on mortality in a cohort of 10,851 people treated in Canada with DAA versus a similar cohort without treatment, with a follow-up period of 2.2 years[559]. The all-cause mortality rate was 19.5 per 1,000 people in the treated cohort, compared to 86.5 per 1,000 people in the comparison cohort. Thus, SVR was associated with a significant reduction in all-cause (HR 0.19; 95% CI 0.17-0.21), hepatic (HR 0.22; 95% CI 0.18-0.27) and treatment-related (HR 0.26; 95% CI 0.21-0.32) mortality compared to no treatment. Older age and cirrhosis were associated with an increased risk of liver-related mortality (Figure 157)[559].

FIGURE 157. ALL-CAUSE SURVIVAL CURVES FOR PATIENTS WITH HEPATITIS C, OVERALL (A) AND FOR PATIENTS WITH CIRRHOSIS (B), CANADA 2017-2019



Source: Janjua (2021)[559]

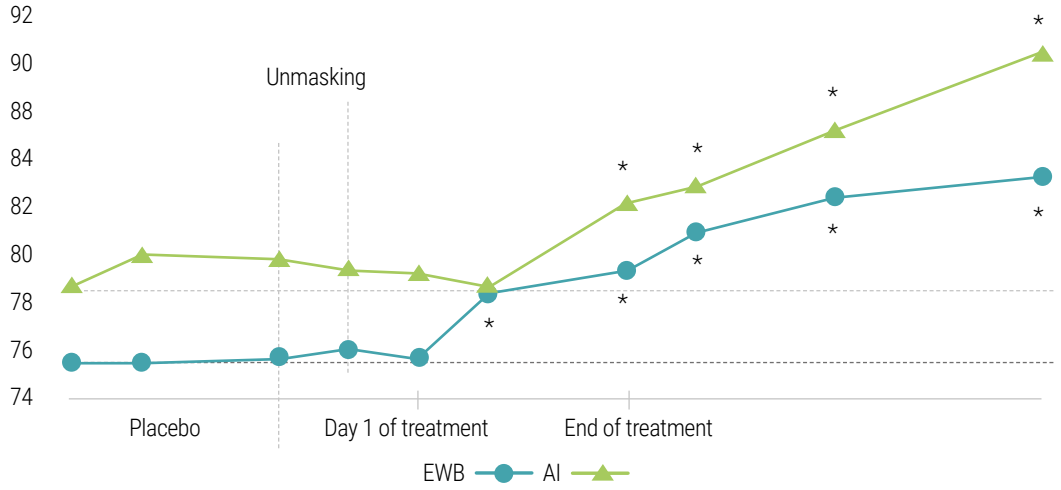
In conclusion, the entry of new drugs and different combinations to tackle the different genotypes of the disease has made it possible to halve the prevalence of hepatitis C in Spain, which means a total disruption in the disease in terms of health outcomes and quality of life[560]. Thus, the Ministry of Health estimates that 165,731 people with HCV were treated with DAAs in Spain between January 2015 and September 2023 and estimates that the percentage of treated patients with a viral response 12 weeks after completing treatment is 94.81%[527]. In addition, it is estimated that DAAs in Spain will prevent an estimated 8,667 cases of cirrhosis, 5,471 cases of hepatocellular cancer and 1,137 long-term liver transplants[561].

From a quality of life perspective, not only the consequences of the disease itself (cirrhosis, portal hypertension, hepatic decompensation and development of hepato- celiac carcinoma) and the potential adverse effects of treatment play an important role, but also the mental component and the social stigmatisation of patients[531].

In this regard, one study shows that, after undergoing antiviral therapy, there was only an improvement in health-related quality of life (HRQoL), as measured by the SF-36, in HCV-infected patients who responded to treatment. Among patients with sustained viral response, HRQoL improved by 6.1 points, while among treatment non-responders, HRQoL decreased by 6.3 points[562]. Other determinants of HRQoL were liver disease severity, age, gender and centre of residence.

In a In a study regarding the latest approved therapies, patients reported significant improvements in quality of life after a 24-week follow-up following different quality of life questionnaires such as the SF-36, the Work Productivity and Activity Impairment Questionnaire (FACIT) or the Work Productivity and Activity Impairment Questionnaire (WPAI). The greatest improvements perceived by patients were found in emotional well-being and work activity impairment (Figure 158)[563].

FIGURE 158. QUALITY OF LIFE REPORTED BY HEPATITIS C PATIENTS TREATED WITH AAD THERAPY



Note: * p<0.05 with respect to baseline.

Abbreviations: **IA** activity impairment at work; **EWB:** emotional well-being.

Source: Younossi (2019)[563]

A more recent meta-analysis showed results along the same lines, demonstrating that at 12 months of treatment with DAA, improvements were obtained in all dimensions of the SF-36 questionnaire, except for bodily pain (mean difference: 1.16; 95%CI: -0.43-2.74) and role-emotional limitations (mean difference: 4.10; 95%CI: -1.32-9.52), compared to the pre-treatment period. At 24 weeks follow-up, there were improvements in all items of the SF-36 questionnaire, except for the domain role-emotional limitations[564].

Direct antiviral agents approved between 2014 and 2017 have ushered in a new era in hepatitis C virus treatment, achieving a very high sustained viral response, even among patients with the most difficult-to-treat profiles.

Webster (2015)[531], Gaetano (2014)[532], Wyles (2017)[547], Spengler (2017)[552]

In recent years, real-life data have demonstrated a change in the prognosis of the disease, with a reduction in the morbidity and mortality associated with this disease, which is so prevalent in Spain, and which causes cirrhosis and decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, total mortality and liver-related mortality, as well as a clear improvement in the quality of life of patients in both the short and long term.

Janjua (2021)[559], Esteban (2022)[557], He (2022)[564]

MENTAL DISORDERS

Mental disorders refer to a series of pathologies characterised by a combination of alterations in the thinking, perception, behaviour and emotions of the sufferer[568]. All these symptoms have a great impact on work and personal relationships, which has a very significant negative effect on the quality of life of those affected[566-568]. These are diseases with high morbidity that not only damage health in themselves, but also have a reduced life expectancy, mainly due to the increased risk of death from unnatural causes (accidents or suicide) and cardiovascular death due to the high frequency of associated risk factors in this population[569,570].

There has been an increase in mental disorders globally of 48.1% between 1990 and 2019. In addition, the proportion of global disability-adjusted life years (DALYs) lost attributed to mental disorders in this period increased from 3.1% to 4.9%. Specifically, in 2019, depressive disorders accounted for the highest proportion of global DALYs lost due to mental disorders (37.3%), followed by anxiety disorders (22.9%) and schizophrenia (12.2%). It should be noted that, in 2020, the number of people suffering from anxiety and depressive disorders increased considerably due to the COVID-19 pandemic. In fact, estimates show an increase of 26% and 28%, respectively, of anxiety and major depressive disorders in just one year[569].

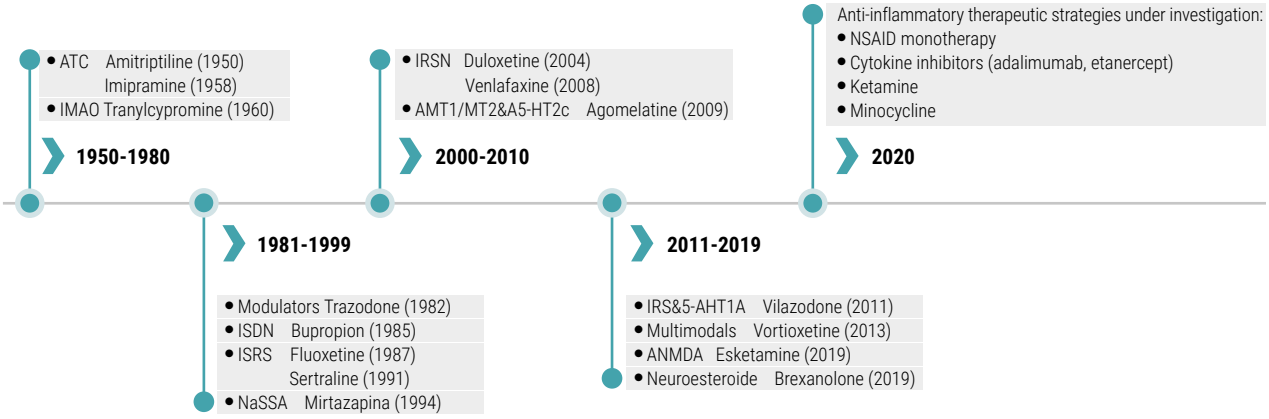
Mental disorders are linked to premature mortality, affecting various diagnoses in a cross-cutting manner. To address inequalities in the life expectancy of people with mental disorders, it is crucial to implement comprehensive, multi-level intervention approaches[571]. The management of these illnesses requires a multidisciplinary and integrated team of psychiatric physicians, nurses, psychologists, educators and social workers, occupational therapists and other professionals. Also, depending on each case, it requires the administration of psychotropic drugs as a palliative method for the most pronounced symptoms. Community treatment orders have been shown to reduce mortality in people with mental disorders, and these orders involve ensuring that the patient follows a treatment plan, including adherence to any medication and psychiatric outpatient visits. In a population-based record analysis study of all patients with community treatment orders in Western Australia over an 11-year period, 2,958 patients with community treatment orders and 2,958 matched controls (patients with psychiatric disorders who had not received a community treatment order) were included. The study showed that, compared to controls, patients with community treatment orders had significantly lower all-cause mortality at 1, 2 and 3 years, with an adjusted hazard ratio of 0.62 (95% CI 0.45-0.86) at 2 years[572].

Effective treatments are now available to control the symptoms of mental disorders and to improve the quality of life of those who suffer from them. Due to the heterogeneity of both symptoms and their causes, it is necessary to analyse the health outcomes of innovative drugs separately for each of the major diseases.

Among mental illnesses, one of the most prevalent and associated morbidity is **major depressive disorder** (MDD)[573]. According to WHO data, in 2021, about 246 million people were affected by MDD worldwide (compared to 193 million in 2019, the period before the pandemic caused by COVID-19). Furthermore, in 2019, depression was the leading cause of DALY loss of all mental disorders[574]. In Spain, depressive disorder appears in 4.1% of the population, with a female predominance in adults (3 times more) and its prevalence increases with age[575].

The evolution of drugs for the treatment of MDD began in the 1950s with the advent of tricyclic antidepressants (TCAs). Later, monoamine oxidase inhibitors (MAOIs) were introduced. (MAOIs), although their safety and tolerability profile represented a limitation in their use. For this reason, the real therapeutic innovation for these patients came in the 1980s with the introduction of selective serotonin reuptake inhibitors (SSRIs) (Figure 159)[576].

FIGURA 159. EVOLUTION OF ANTIDEPRESSANT TREATMENTS



Note: The chronology shows the main antidepressant drugs by class and year of first approval in the US and/or EU market.

Abbreviations: **TCAs:** Tricyclic antidepressants; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **NNSAIDs:** Non-competitive N-methylamine receptor antagonist; **NSAIDs:** Nonsteroidal anti-inflammatory drugs; **NSAIDs:** Nonsteroidal anti-inflammatory drugs. til-D-aspartate; **AMT1/MT2&A5-HT2c:** Melatonin receptor agonist (MT1 and MT2) and serotonergic 5-HT2c receptor antagonist; **IRS&5-AHT1A:** Serotonin reuptake inhibitor and 5-HT1A receptor partial agonist; **MAOIs:** Monoamine oxidase inhibitors; SSRIs: Selective serotonin reuptake inhibitors; **SNRIs:** Serotonin and norepinephrine reuptake inhibitors; **SNRIs:** Dopamine and norepinephrine reuptake inhibitors; **NaSSA:** Specific serotonergic and noradrenergic antidepressants.

Source: own elaboration adapted from Roman and Irwin (2020)[577], Li (2021)[578] and Pilc (2022)[579]

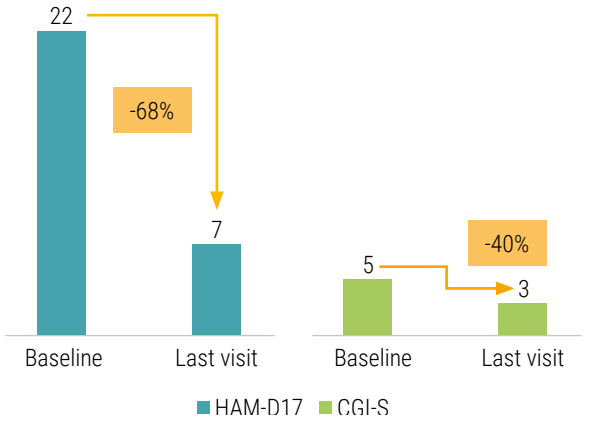
Overall, the efficacy of antidepressants has been demonstrated in a systematic review with a meta-analysis that examined 522 clinical trials conducted with 21 antidepressant drugs versus placebo and other drugs in 116,477 adult subjects with MDD. All antidepressants included in the analysis showed significantly superior efficacy to placebo, and SSRIs such as escitalopram, paroxetine and sertraline had a relatively higher response and lower dropout rate than the other antidepressants[580].

SSRIs share the ability to reduce depressive symptoms with other antidepressants, although they stand out for their greater selectivity in the process, resulting in fewer physical side effects, such as dry mouth, drowsiness or cardiac arrhythmia[581–583]. According to the results of a randomised, pragmatic, double-blind, controlled trial conducted in 550 adult patients aged 18-74 years with MDD, in 179 primary care centres in the UK, with 6 weeks of follow-up, it was concluded that sertraline versus placebo reduces symptoms of depression in these patients by 13%, as measured by the **Patient Health Questionnaire**, 9-item version (PHQ-9)[584].

Another treatment for MDD with a different mechanism of action to other antidepressants is agomelatine. In a French observational study, conducted over 12 months, a significant decrease in the mean total score on the Hamilton Assessment Scale for Depression (HAM-D17) and the Clinical Global Impression of Severity Scale (CGI-S) was observed, with reductions of 68% and 40%, respectively (Figure 160). In addition to benefits in depressive symptomatology, there was evidence of improvement in quality of life and daily functioning in patients receiving agomelatine[585].

Despite the numerous treatment options currently available for MDD (major depressive disorder), a significant proportion of patients—up to one-third—do not respond adequately to pharmacological therapies, and up to 20% are considered non-responders, even with good adherence and treatment administered for a sufficient duration and at an appropriate dose[586]. In recent years, new antidepressant drugs have been developed with the potential to address this unmet medical need for treatment-resistant depression. In 2019, the FDA and EMA approved the use of esketamine in the form of a nasal spray for the treatment of MDD in adults resistant to other medications[405,587]. To date, this treatment represents the only therapeutic option for these patients and has been shown to provide a rapid and sustained reduction in depressive symptoms, reduce the risk of relapse, and exhibit a favorable tolerability profile[588].

FIGURE 160. MEAN CHANGE IN HAM-D17 AND CGI-S FROM BASELINE TO LAST VISIT FOR PATIENTS WITH MAJOR DEPRESSIVE DISORDER WHO RECEIVED AGOMELATINE



Abbreviations: HAM-D17: Hamilton Assessment Scale for the Depression; **CGI-S:** Clinical Global Clinician Impression-Severity Scale.

Source: Gorwood (2020)[585]

The TRANSFORM 1-3 clinical trials conducted to assess the efficacy of esketamine have shown positive results in terms of change in the Montgomery-Asberg Depression Rating Scale (MADRS) score, specifically, it has been reported that in patients treated with esketamine plus antidepressant the change in MADRS score was significantly greater than in the group treated with antidepressant plus placebo at day 28 (least squares mean difference= 24.0; SE = 1.69; IC95% = 27.31; 20.64)[589–591]. In addition, in the SUSTAIN-1 clinical study, intranasal esketamine, when combined with an oral antidepressant, was shown to reduce the risk of relapse by 51% for patients in stable remission and 70% for those with stable response, compared to those receiving an intranasal antidepressant and placebo[592]. On the other hand, the SUSTAIN-2 study corroborated the safety and tolerability of intranasal esketamine plus an oral antidepressant in the long term, showing that 76.5% achieved response and 58.2% of patients achieved remission, according to the MADRS score[593].

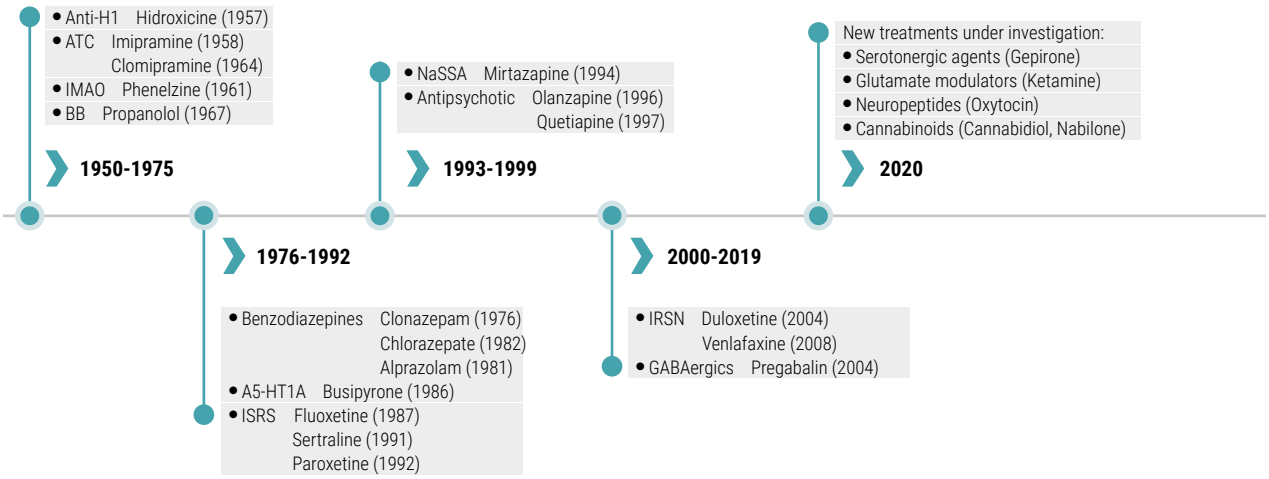
Beyond treatments for MDD, it is worth noting the 2019 approval of brexanolone for the treatment of postpartum depression. In clinical trials, this intravenous therapy has been shown to reduce depressive symptoms by decreasing scores on the HAM-D17 Scale compared to placebo. In one of the treatment groups of the studies, the mean decrease in HAM-D score was 21.0 points, compared to a reduction of 8.8 points in the control group. In addition, throughout treatment and follow-up, more patients achieved a 50% or greater reduction in depressive symptoms in the treatment group compared to placebo[594]. Some studies highlight the fact that while antidepressants are effective in reducing the severity of symptoms caused by depression, and may even make them disappear, this is not sufficient to restore standard levels of quality of life and maintain them over time after treatment has ended[595].

The next disease with the highest burden in DALYs is **generalised anxiety disorder** (GAD). Anxiety is usually associated with other psychiatric disorders such as panic, major depressive or dysthymic disorder, social phobia and other specific phobias[596–598]. Over a prolonged period of anxiety and worry, GAD patients may experience a wide range of symptoms such as restlessness, asthenia, difficulty concentrating, irritability, sleep disturbances and somatic symptoms[599,600]. Therefore, GAD is a major contributor to the loss of quality of life in those who suffer from it, with negative consequences in several areas of their lives, such as more reported days of disability, impairments in psychosocial activity or loss of work productivity[597,601–603].

A lifetime prevalence of GAD has been estimated at 4.3% in the general population[604]. As with depression, GAD is more common among women than among men (8.8% vs. 4.5%). In Spain, it has become the most frequent mental health problem, affecting 6.7% of the population[575].

In the past, anxiolytics such as benzodiazepines used to be the main pharmacological treatment for GAD. However, clinical evidence suggests that antidepressants of different classes: TCAs such as imipramine; serotonin and norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and SSRIs such as paroxetine are more effective, proving superior to placebo in treating GAD. More recently, new serotonergic agents, glutamate modulators and other types of therapeutic strategies with neuropeptides and cannabinoids are being investigated (Figure 161)[600].

FIGURE 161. EVOLUTION OF ANTI-ANXIETY TREATMENTS



Note: The chronology shows the leading anxiety medicines by class and year of first approval in the US and/or EU market.

Abbreviations: **ATC:** Tricyclic antidepressants; **Anti-H1:** Anti-H1 antihistamine; **A5HT-1A:** 5-HT1A receptor agonist; **MAOIs:** Monoamine oxidase inhibitors; **SSRIs:** Selective serotonin reuptake inhibitors; **SNRIs:** Serotonin and norepinephrine reuptake inhibitors; **NaSSA:** Specific serotonergic and noradrenergic antidepressants.

Source: own elaboration adapted from Garakani (2020)[605]

Pharmacological treatment has been shown to be effective in improving quality of life in anxiety disorders, and the greater the reduction in symptoms, the greater the impact on quality of life[606]. Furthermore, treatments that reduce anxiety symptoms not only improve quality of life, but are also associated with improvements in disability and patient-reported outcomes[607].

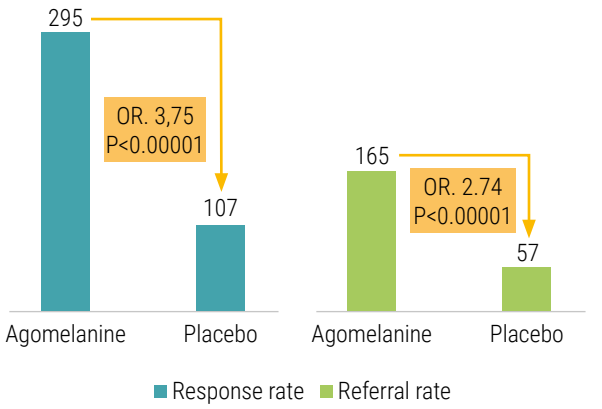
The efficacy of drug treatment for GAD has been proven in a systematic review with meta-analyses[608]. This analysis included 89 clinical trials, representing 25,441 adult patients with GAD. Apart from 1 of the 22 drugs analysed, all the drugs used had positive results compared to placebo, and 16 of them were statistically significant, with changes in the Hamilton Anxiety Scale (HAM-A) between -7.9 and -0.77 (95%CI -14.68 to -0.19). The authors concluded that there are several effective treatment options for GAD, across all drug classes analysed, and that failure of initial drug therapy should not be a reason for abandonment of the drug treatment strategy.

Among the options for the pharmacological treatment of anxiety, there are treatments for depression that have also demonstrated improvements in the quality of life of patients with GAD. For example, a multicentre prospective clinical study analysed 682 patients diagnosed with MDD and GAD over a period of 9 months, concluding that the use of SSRIs (fluoxetine, paroxetine and escitalopram) resulted in improvements in the quality of life and satisfaction index (from 12-17% at baseline to 43-49% at the end of the treatment period) and sleep quality (sleep problems index from 59.7-63.9 at baseline to 21.1-24.9 at the end of the treatment period) and sleep quality (sleep problems index from 21.1-24.9 at baseline to 21.1-24.9 at the end of the treatment pe-

riod), 7-63.9 at baseline to 21.1-24.9 at the end of the treatment period) of these patients compared to their baseline situation, as measured by the Quality of Life and Satisfaction Questionnaire Short Form (Q-LES-Q SF) and Medical Outcomes Study sleep scale (MOS), respectively[609].

More recently, a meta-analysis on the efficacy of agomelatine, an antidepressant approved in 2009, for GAD has been published[610]. Agomelatine demonstrated a significant improvement in Hamilton Anxiety Rating Scale-A (HAM-A) total scores compared to placebo (standardised mean difference = -0.56, p = 0.004). In addition, a patient is approximately 3.75 times more likely to respond to treatment with agomelatine than with placebo. Likewise, a patient is approximately 2.74 times more likely to achieve remission of GAD with agomelatine than with placebo (Figure 162)[610].

FIGURE 162. EFFECT ON RESPONSE AND REMISSION RATES IN AGOMELATINE-TREATED TAG PATIENTS COMPARED TO THOSE WHO RECEIVED PLACEBO



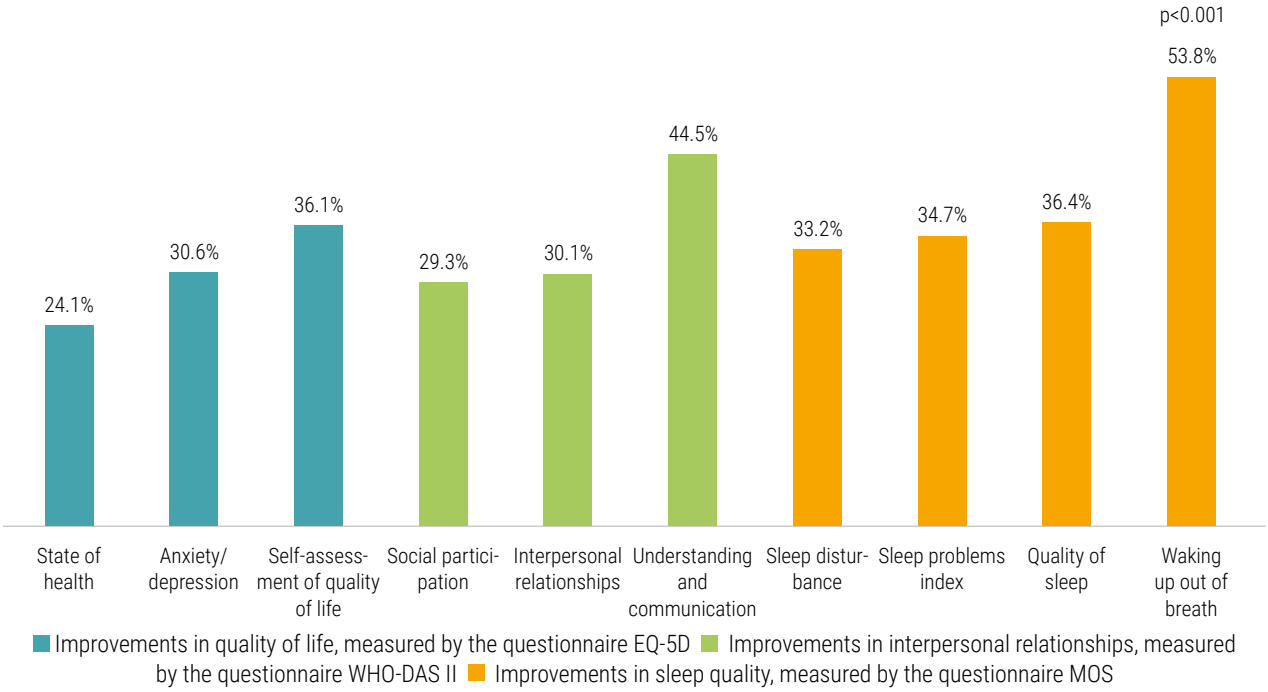
Abbrevaions: OR: Odds ratio.

Source: Wang (2020)[610]

Among the pharmacological options for anxiety, benzodiazepines have traditionally been used, but their side-effect profile and risk of dependence have led to the exploration of alternatives such as quetiapine, an atypical antipsychotic. There is debate as to whether the benefits of benzodiazepines are being underestimated and that the current bias against benzodiazepines may not be justified, referring to an overestimation of the risks and highlighting their value when used with an appropriate and tailored dosing regimen. Furthermore, it has been argued that the anxiolytic properties of benzodiazepines that prompted their initial approval continue to maintain this class of drugs as a highly effective treatment for anxiety[611].

On the other hand, anticonvulsants such as pregabalin and gabapentin, which have GABAergic properties, can also be used in the treatment of anxiety disorders. Although research on their use in treating anxiety is limited, there is evidence to support the efficacy of pregabalin in GAD. A meta-analysis of multiple clinical trials has demonstrated its superiority over placebo and comparable effects to benzodiazepines in the treatment of this disorder[612]. In addition, the inclusion of pregabalin as an add-on therapy for adult patients partially responding to SSRIs has shown positive effects on quality of life indicators in a study conducted in Spain[613]. According to this study, the inclusion of pregabalin produced improvements of between 24% and 54% compared to the previous standard treatment in the different indicators used, which included sleep quality, social relationships, aspects related to communication and comprehension, and self-assessment of quality of life and health status (Figure 163)[613].

FIGURE 163. IMPROVEMENTS IN OUTCOMES REPORTED BY TAG PATIENTS AFTER 6 MONTHS OF USING PREGABALIN AS AN ADJUNCT TO STANDARD TREATMENT, SPAIN



Abbreviations: **MOS:** Sleep Scale. **WHO-DAS II:** WHO Disability Assessment Questionnaire; **EQ-5D:** EuroQoL-5D; **EQ-VAS:** Visual Analogue Scale. p < 0.001

Source: own elaboration based on Álvarez (2015)[613]

A comprehensive approach that addresses both anxiety symptoms and underlying factors can have a significant positive impact on the quality of life of affected individuals[614]. In this regard, it has been observed among people with comorbidities such as social phobia and MDD that those who achieved remission of MDD following pharmacotherapy had significant improvements in quality of life and functioning than those who did not achieve remission of MDD[615]. Thus, depression as a comorbidity may be particularly relevant to quality of life outcomes in the treatment of anxiety disorders.

Recently, new therapeutic strategies for GAD are being investigated, including: serotonergic agents such as gepirone, an antidepressant that has shown anxiolytic properties; glutamate modulators such as ketamine, which has reported benefits in patients with depression and anxiety; neuropeptides such as oxytocin, which may have overall positive effects on anxiety depending on the frequency and context of administration; and cannabinoids such as cannabidiol, the most studied for anxiety[605].

Schizophrenia is a mental illness characterised by inappropriate and/or intrusive distortions of thought, perception and affect without impairment of consciousness or intellectual abilities[575]. Sufferers may experience hallucinations, delusions, incoherence in speech and disturbances in emotions, such as apathy or disconnection between stated emotions and their objective manifestations. This disease is associated with significant disability, with a high probability of affecting educational and occupational performance. People with this pathology have twice the risk of dying at an early age than the population. In a meta-analysis of 109 studies from 24 countries or regions, including 12,171,909 patients with mental disorders, schizophrenia spectrum disorders showed a loss of potential years of life (YPLL) of 15.37 years (95% CI 14.18-16.55), ranking third in terms of YPLL among all mental disorders included in the study[571].

Schizophrenia affects approximately 24 million people, i.e. 1 in 300 (0.32%) worldwide[616]. In Spain, the disorder is estimated to occur in 3.7% of the population[575]. Although the disease affects a smaller proportion of the world's population than depressive and anxiety disorders, the burden of disability for an acute episode of psychosis was

the highest, according to the Global Burden of Disease (GBD) study analysing the burden of 12 mental disorders in 204 countries and territories over the period 1990-2019[569].

Although it is a disease that affects several psychosocial areas and to date no cure has been developed, a significant percentage of patients can lead a relatively normal life with pharmacological treatments[617]. Similar to treatments for other mental disorders, the emergence of pharmacological therapies for schizophrenia dates back to the 1950s, with the so-called first-generation antipsychotics, such as chlorpromazine, haloperidol, perphenazine and fluphenazine, whose efficacy had to be balanced with extrapyramidal effects, such as neurological problems. Later, in the 1990s, the introduction of second-generation antipsychotics brought improvements in efficacy and a reduced side effects[618,619]. The efficacy of antipsychotics has been reported in a meta-analysis in which 402 clinical studies were examined, looking at the efficacy of 32 antipsychotics on 53,463 adult patients with schizophrenia[620]. The analysis has suggested, based on effect estimates, that all antipsychotics reduced symptoms of schizophrenia to a greater extent than placebo.

In the evolution of treatments for schizophrenia, it is worth highlighting the appearance of extended-release injectable formulations (ILP), which emerged to improve adherence with the associated potential to reduce the risk of relapse. The first ILP antipsychotics were marketed in Spain in the 1970s, pioneered by fluphenazine enanthate in 1966 and fluphenazine decanoate in 1968. Non-compliance with medication is one of the main reasons for relapse in individuals with schizophrenia, affecting more than 40% of patients[621,622]. In addition, improved adherence has been found to be linked to greater symptom remission, psychosocial improvement and more successful integration into the community. However, although these drugs have been available for several decades and have potential advantages, their use is much less common in the treatment of schizophrenia compared to the use of oral antipsychotics[623].

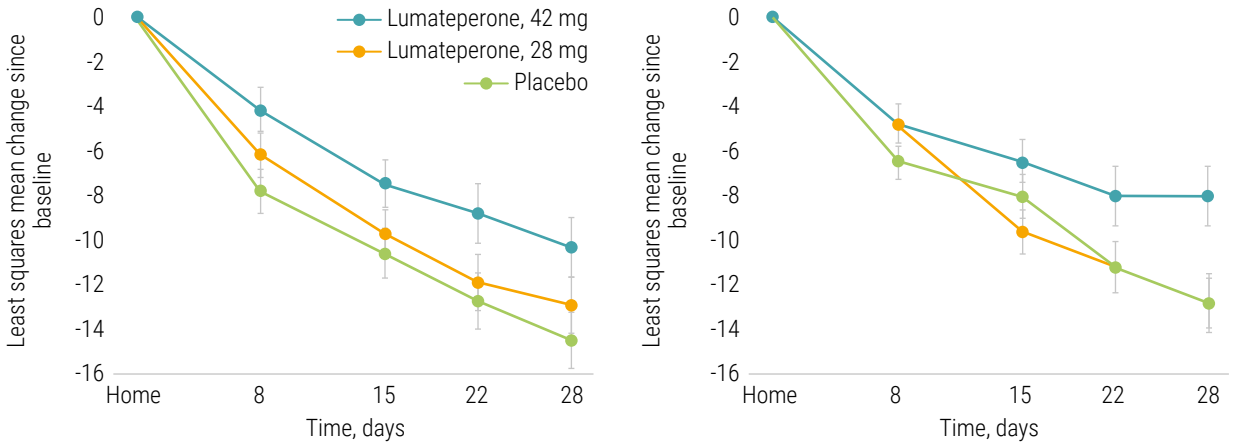
In a systematic review and meta-analysis of the relative risk and factors aggravating or attenuating schizophrenia symptoms, it has been reported that antipsychotic use was protective against all-cause mortality compared to no antipsychotic use (RR=0.71, 95% CI: 0.59-0.84, n=11), with the most significant effects observed for antipsychotics in second-generation ILP formulations (RR=0.39, 95% CI: 0.27-0.56, n=3), clozapine (RR=0.43, 95% CI: 0.34-0.55, n=3), any ILP formulation (RR=0.47, 95% CI: 0.39-0.58, n=2), and any second generation antipsychotic (RR=0.53, 95% CI: 0.44-0.63, n=4)[624].

Among the most prominent therapeutic innovations for schizophrenia, in the early 2010s, the loxapine inhaler, the first non-injectable therapy for the treatment of agitation associated with schizophrenia and bipolar disorder, was approved. Its therapeutic efficacy was tested in more than 1,600 patients in two clinical trials, demonstrating statistically significant reductions in agitation compared to placebo[625,626]. They also highlighted the rapidity of the effects, with statistically significant differences already within the first 10 minutes of administration compared to the control group.

Later in 2018, aripiprazole lauroxil, a long-acting intramuscular injection and pro- longed release indicated for the treatment of adults aged 18-65 years with schizophrenia, was approved[627]. Aripiprazole lauroxil was the first and only long-acting atypical antipsychotic with three dosing periods and the ability to initiate treatment at any dose or duration. The efficacy of the drug was validated in a clinical trial with 622 adult patients, showing a statistically significant improvement when compared to placebo, with score changes ranging from -11.9 to -10.9 (95% CI: -15.4 to -7.3) on the Positive and Negative Syndromes Scale (PANSS)[628].

Subsequently, in 2019, the FDA approved lumateperone, a new molecular entity atypical antipsychotic, for the treatment of schizophrenia[587]. Clinical trials have demonstrated the efficacy and safety of treatment by comparing therapy with placebo for 4 weeks in adult patients with schizophrenia[629,630]. Efficacy has been measured through mean changes in PANSS and Clinical Global Impression of Severity of illness (CGI-S). Specifically, treatment with 42 mg lumateperone demonstrated a statistically significant improvement from baseline to day 28 in PANSS total score versus placebo (least squares mean difference [LSMD], -4.2; 95% CI, -7.8 to -0.6) and in CGI-S score (LSMD, -0.3; 95% CI, -0.5 to -0.1) (Figure 164)[630].

FIGURE 164. CHANGES IN THE TOTAL SCORE OF THE (A) POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) AND (B) CLINICAL GLOBAL IMPRESSION-SEVERITY OF ILLNESS (CGI-S) IN PATIENTS WITH SCHIZOPHRENIA WITH LUMATEPERONE TREATMENT AT DIFFERENT DOSES VERSUS PLACEBO



Notes: A) p< 0,05 vs. placebo. B) p< 0,01 vs. placebo.

Abbreviations: **PANSS:** Positive and Negative Syndrome Scale; **CGI-S:** Clinical Global Impression-Severity of Illness

Source: Correll (2020)[630]

More recently, in 2021, the FDA approved the combination of olanzapine and samidorphan to treat schizophrenia and aspects of bipolar disorder[366]. In a study conducted between 2015 and 2017, the effect of this therapy was analysed in adults with clinically diagnosed schizophrenia who were experiencing an acute episode of psychosis. The results showed a significant improvement in PANSS and CGI-S scores within 4 weeks in patients receiving the combination of olanzapine and samidorphan versus placebo[631].

People with schizophrenia have quality of life parameters between 6% and 32% lower than those of the general population in the four health domains considered in the WHO Quality of Life Measurement Abbreviated Version[632]. For this reason, symptom control contributes to stabilising and improving patients' personal and social relationships[633].

In this context, an observational study of patients with schizophrenia in the UK analysed quality of life outcomes associated with antipsychotic therapy over a 3-year period, concluding that mean EuroQoL-5D (EQ-5D) scores increased over time, with the greatest improvement occurring in the first 6 months, with a mean increase of 0.19 points[634]. In addition, people who were older or who had been ill longer had worse EQ-5D scores at baseline.

Finally, **bipolar disorder** is a chronic and recurrent illness characterised by abnormal mood swings. It is classified as a type of affective psychosis and is characterised by distinct cycles, which may include hypomanic, manic and depressive episodes, significantly interfering with the day-to-day life of these patients, with a major impact on their health and quality of life[635].

The WHO estimates that in 2019 approximately 40 million people were affected by this pathology worldwide[568]. In Spain, it has been estimated that around 1 million people suffer from bipolar disorder, representing 2% of the population[636,637].

As discussed throughout the chapter, antidepressants, anxiolytics and antipsychotics are medicines used in the treatment of various mental health conditions. These medications are known as psychotropic drugs, which also include mood stabilisers. In fact, the first-line treatment of bipolar disorder is with mood stabilisers and, occasionally, their combination with antidepressants and antipsychotics. In general, people with bipolar disorder continue treatment with mood stabilisers for a long period of time. Lithium was the first of these drugs to be approved by the FDA in the 1970s for the treatment of manic and depressive episodes[619]. In

Europe, the use of lithium for the treatment of bipolar disorder also began in the 1970s, and its acceptance and regulation has varied from country to country in Europe.

Some anticonvulsants are also used as mood stabilisers, such as valproic acid, carbamazepine, lamotrigine and oxcarbazepine. The most common antipsychotics used to treat bipolar disorder, often as add-on therapy, are olanzapine, aripiprazole, risperidone, ziprasidone and clozapine. Clozapine is generally used for people who do not respond to lithium therapy[619].

The efficacy of mood stabilisers has been demonstrated in the study by Oya et al. (2019)[638,] in which they synthesised the few existing double-blind, randomised, controlled trials of lithium (2 trials, n=218) and lamotrigine (4 trials, n=706) versus placebo in people with bipolar disorder. Both drugs were superior to placebo, reducing relapse rates associated with any episode of mood disturbance by 19% to 48% (Lithium: RR 0.52, 95% CI 0.41 to 0.66, P<0.00001. Lamotrigine: RR of 0.81; 95%CI 0.70 to 0.93, P=0.004). In addition, it has been reported that treatment with mood stabilisers can positively influence quality of life in patients diagnosed with bipolar disorder[639].

Some antidepressants are also used with the aim of improving the symptoms of people with bipolar disorder, such as fluoxetine, paroxetine and sertraline, although there is controversy about their effect. In fact, one study has shown that antidepressants were no more effective than placebo in helping to treat depression in people with bipolar disorder who were receiving a mood stabiliser[619].

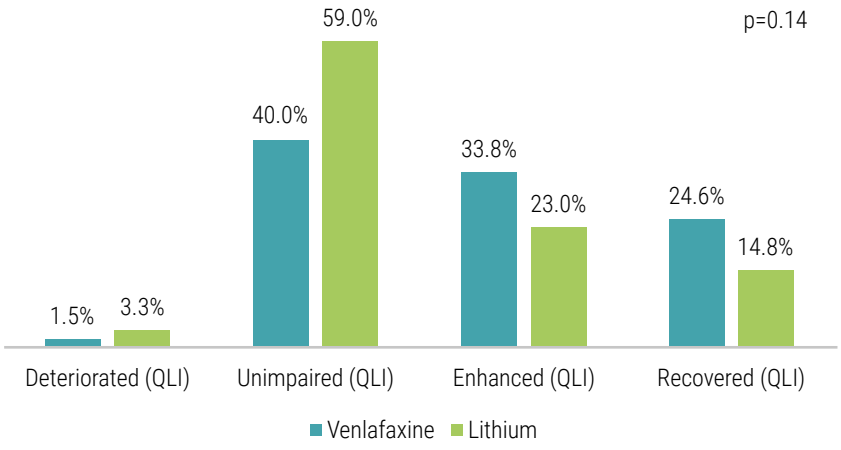
Regarding antipsychotics, studies by Prajapati et al. (2018)[640] and Keramatian et al. (2019)[641] have examined the effects of extended-release injectable antipsychotics, concluding that these drugs provided improvements in symptoms in people with bipolar disorder when compared to placebo. More recently, the study by Keramatian et al. (2021) is a review that provides an overview of recently published randomised controlled trials on the efficacy and safety of atypical antipsychotics in bipolar disorder. In particular, it highlights quetiapine which achieved significantly greater improvement in depressive symptoms, as well as higher rates of recovery and remission, compared to placebo in bipolar disorder[642].

Among the latest developments for the treatment of bipolar disorder are the 2018 FDA approvals of existing compounds for the treatment of paediatric patients with bipolar disorder[627]. As discussed above, the combination of olanzapine and samidorphan approved in 2021 to treat schizophrenia has also been indicated to treat aspects of bipolar disorder and is therefore prescribed in combination with drugs such as lithium or valproate[643]. However, this therapy has not yet been approved in Europe and currently the treatment of bipolar disorder remains unsatisfactory[644].

Although bipolar disorder has a significant impact on quality of life, even more than other mood or anxiety disorders, research on how antipsychotics affect patients' quality of life is limited. In most cases of bipolar disorder, depressive episodes predominate over manic episodes, with the latter being a major contributor to morbidity and mortality.

One of the studies on the impact of drugs on quality of life and, specifically, on the reduction of depression in patients with bipolar disorder, has been conducted by Lorenzo-Luaces et al. (2018), showing that venlafaxine is superior to lithium treatment in reducing depressive symptoms in patients with bipolar disorder and, consequently, a higher proportion (58.4% versus 37.8%) of venlafaxine patients reported an improvement in quality of life at the end of treatment (Figure 165)[645].

FIGURE 165. OUTCOMES REPORTED BY PATIENTS WITH BIPOLAR DISORDER AFTER 12 WEEKS OF TREATMENT WITH LITHIUM AND VENLAFAXINE, AS MEASURED BY THE QUALITY OF LIFE INDEX (QLI), %

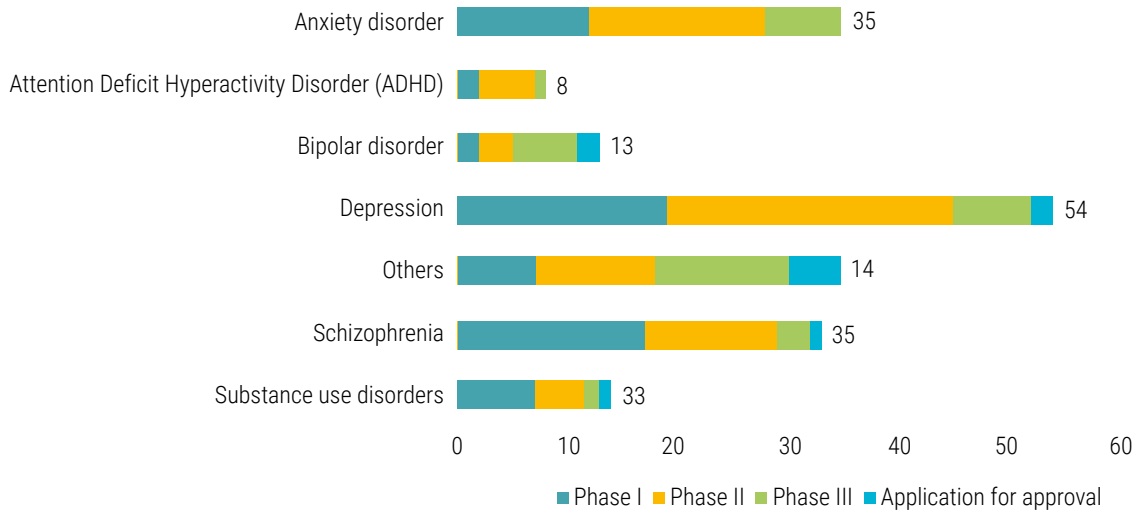


Abbreviation: QLI: Quality of Life Index.

Source: Lorenzo-Luaces (2018)[645]

Finally, it is worth noting that more than 160 drugs are currently being developed for mental illnesses, including 54 for depression, 35 for schizophrenia, 35 for anxiety disorders and 13 for bipolar disorders[646,647]. These treatments are intended to provide therapeutic advances for patients who do not benefit from conventional therapeutic strategies or who experience negative side effects with current therapies (Figure 166)[647].

FIGURE 166. MEDICINES IN DEVELOPMENT FOR MENTAL DISORDERS, 2023



Source: Adapted from PhRMA (2023)[647]

Among the most notable advances in the treatment of mental disorders is the use of biomarkers, which are being investigated to improve diagnosis and assess patient response to therapies, as well as to identify new therapeutic targets[648]. It is hoped that advances in the identification of peripheral biomarkers can improve the effectiveness of mental health care and address some of the unmet needs in the clinical management of severe mental disorders[649].

Psychotropic drugs such as antidepressants, antipsychotics and mood stabilisers, for the treatment of mental disorders such as major depressive disorder, generalised anxiety disorder, schizophrenia and bipolar disorder, have shown significant improvements in symptoms and quality of life of those who suffer from them.

Cipriani (2018)[580], Slee (2019)[608], Huhn (2019)[620]

Existing medicines for mental disorders, such as antipsychotics, reduce mortality in people with schizophrenia, while drugs in development expand therapeutic possibilities for these illnesses. In addition, some of the recently introduced drugs improve prospects for treatment-resistant depression and postpartum depression.

PhRMA (2023)[647]; González-Pinto (2020)[589]; Cornett (2021)[594]; Correl (2022)[624]; Potkin (2020)[631]; Correll (2020)[630]

PARKINSON'S DISEASE

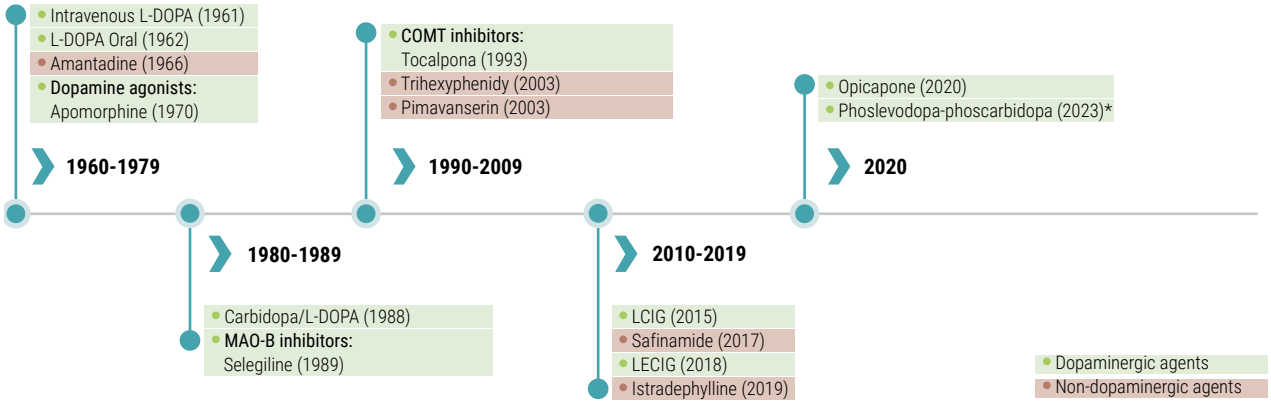
Parkinson's disease (PD) is a chronic degenerative disorder caused by the destruction of dopaminergic neurons in the central nervous system, affecting the transmission of information essential for proper movement control. Symptoms include tremor, rigidity, slowness of movement and postural instability[650]. Although previously thought to affect only the motor system, it is now recognised that it also causes alterations in the autonomic (changes in sweating, gastrointestinal problems), limbic (emotion and behavioural processing) and the somatosensory system (responsible for perceptions such as touch, temperature and pain) systems[651].

In recent years, PD has experienced more rapid growth in prevalence and disability than other neurological disorders and has become one of the leading causes of disability worldwide. Globally, the prevalence of the disease has increased by 160% in the period 1990-2019[652]. In Spain, the prevalence of PD is also on an upward trend, estimated to double by 2028 and to triple by 2050[653]. Currently, about 10,000 new cases of PD are diagnosed each year in Spain, reaching about 160,000 people affected by 2021[654].

The evolution of the therapeutic management of PD began with the introduction in the 1960s of treatment with levodopa, the metabolic precursor of dopamine. Due to side effects caused by the use of levodopa monotherapy, such as dyskinesias, motor fluctuations and nausea, the use of the levodopa-carbidopa combination was introduced in 1988. To control side effects and increase the activity of levodopa, from the late 1990s onwards, levodopa started to be administered together with other dopaminergic agents, such as dopamine agonists, catechol-O-methyltransferase (COMT) or monoamine oxidase B (MAO-B) inhibitors.

In the period between 2015 and 2020, the EMA has approved two new agents to reduce off-episodes in levodopa-carbidopa treatment (safinamide, approved in 2015, and opicapone, in 2016). For its part, the FDA has approved new treatments for PD such as istradephylline in 2019 (rejected by the EMA in 2022) and another that has received neither approval nor opinion from the EMA, namely an atypical antipsychotic for the treatment of PD psychosis (pimavanserin, in 2016). Formulations that increase the bioavailability of levodopa have also been developed with a new form of administration: levodopa-carbidopa intestinal gel, approved by the EMA in 2005 and by the FDA in 2015; and levodopa-carbidopa-entacapone intestinal gel, approved in 2018 in Sweden and subsequently in other European countries[655]. Finally, by the end of 2023, the National Institute for Health and Care Excellence (NICE) in England has recommended the prodrug foslevodopa-foscarbidopa as a treatment option for advanced PD (Figure 167)[656,657].

FFIGURE 167. EVOLUTION OF TREATMENTS FOR PARKINSON'S DISEASE



Note: The chronology shows the main antidepressant drugs by class and year of first approval in the US and/or EU market. *Approved in England.

Abbreviations: **L-DOPA:** Levodopa; **MAO-B:** monoamine oxidase B; **COMT:** catechol-O-methyltransferase; **LCIG:** levodopa-carbidopa intestinal gel; **LECIG:** levodopa-carbidopa-entacapone intestinal gel.

Source: own elaboration adapted from Charvin (2018)[657] and NICE (2023)[656]

Beyond the motor symptoms of PD, it must be taken into account that more than 50% of Parkinson's patients suffer from psychosis at some point, with symptoms of hallucinations and delusions, which can cause great distress to sufferers and their caregivers, as they are difficult to treat, increase the likelihood of needing residential care, and are associated with increased mortality[658]. Different antipsychotics have been tried before, however, their efficacy in these patients has not been proven for several reasons, such as poor tolerance, worsening of parkinsonism, adverse events or lack of significant improvement in symptoms[659,660].

Pimavanserin, approved under the category of "innovative therapy" by the FDA in 2016, has a different mechanism of action to that of classical antipsychotics, as it acts as a blocker of a specific serotonergic nerve receptor, known as THT2A or 5HT2A. Its efficacy has been tested in a randomised, controlled study of 199 patients aged 40 years or older with Parkinson's disease psychosis, during a 43-day period of treatment with this drug versus placebo. After the treatment period, a reduction of 5.79 points on the positive symptom rating scale for Parkinson's disease (SAPS-PD) was observed in the pimavanserin group compared to -2.73 in the placebo group (difference of -3.06; 95%CI -4.91 to -1.20, p=0.001)[661].

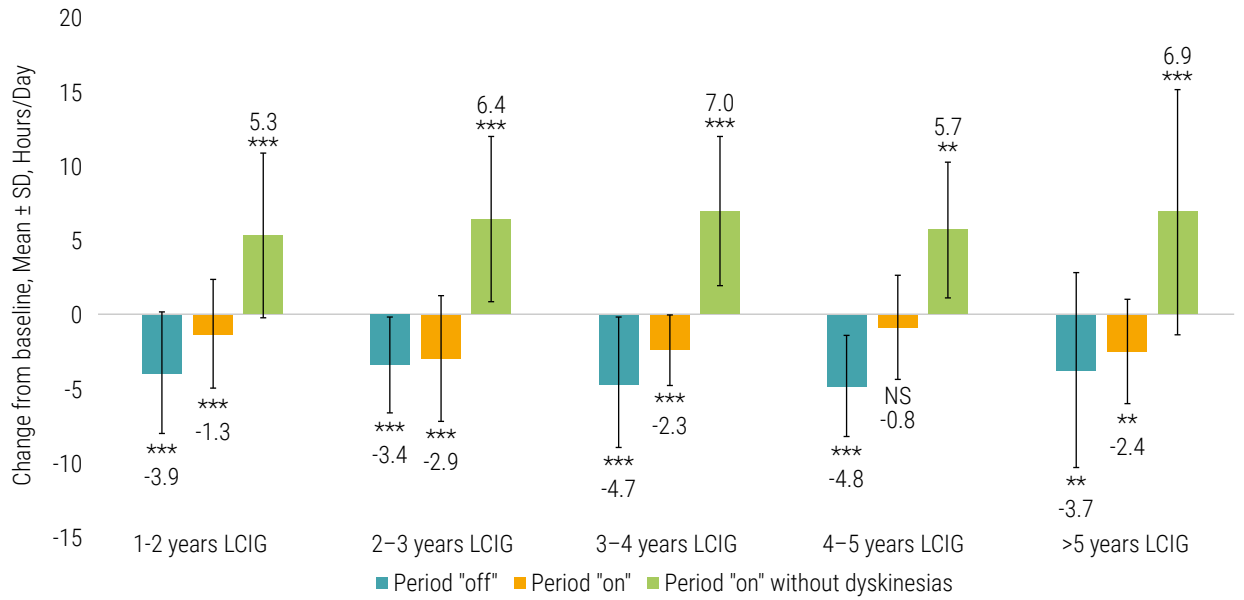
Levodopa remains the most effective drug for the treatment of PD[662]. Despite this, its use is often delayed until later stages of the disease, because its long-term administration produces so-called motor fluctuations, periods when the medication takes effect (on periods) and periods when it does not (off periods). This means that the doses have to be higher and higher and, consequently, the side effects produced by the medication itself increase (psychological disorders, increased sexual appetite, orthostatic hypotension, gastrointestinal

alterations, etc.) and even the appearance of dyskinesias or abnormal and excessive involuntary movements, typical of the on periods[663,664].

For its part, the levodopa-carbidopa intestinal gel (LCIG) approved in 2015 consists of an invasive method in which, through direct communication with the intestine, the medication is administered from a programmable pump. Intraduodenal administration of levodopa maintains stable dopamine levels, reducing motor fluctuations and improving dyskinesias, achieving better clinical control, administered as a single drug[665].

LCIG treatment results in an increase in on-state time of day and a reduction in off-state time[666]. This has been confirmed by the results of an international, prospective study that evaluated the efficacy of LCIG treatment over a 54-week period in 354 PD patients aged 30 years and older, who had off periods equal to or greater than 3 hours per day[667]. These patients saw their off period reduced by 4.4 hours per day (65.6%) and noted a significant increase in the on period without dyskinesia (+4.8 hours per day, 62.9% increase), with a slight increase in the on period with dyskinesia (+0.4 hours per day, 22.5%). More recently, LCIG has also been shown to work in the long term in reducing motor symptoms, according to a multinational, retrospective, cross-sectional, post-marketing observational study of 387 patients from 14 countries, stratified into 5 groups according to treatment duration, from 1-2 to > 5 years. During the visit, a significant reduction in effective medication off time was observed in all groups ($p < 0.001$). There was also a decrease in the duration of dyskinesia in all groups ($p < 0.001$), except in the 4-5 year LCIG therapy group ($p = 0.1378$). On the other hand, time on effective medication but without dyskinesia increased in all groups ($p < 0.0001$ for all except for 4-5 years LCIG [$p = 0.0002$]) (Figure 168)[668].

FIGURE 168. CHANGE FROM BASELINE OF "OFF" TIME AND "ON" TIME WITH AND WITHOUT DYSKINESIA DURING WAKING HOURS FROM LCIG INITIATION TO PATIENT VISIT ACCORDING TO DURATION OF LCIG TREATMENT IN PATIENTS WITH PARKINSON'S DISEASE



Note: Significance for change from baseline as follows: NS: $p > 0.05$; **$p < 0.001$; ***$p < 0.0001$.
Abbreviations: SD: standard deviation; **NS:** not significant; **LCIG:** levodopa-carbidopa intestinal gel

Source: Fasano (2023)[668]

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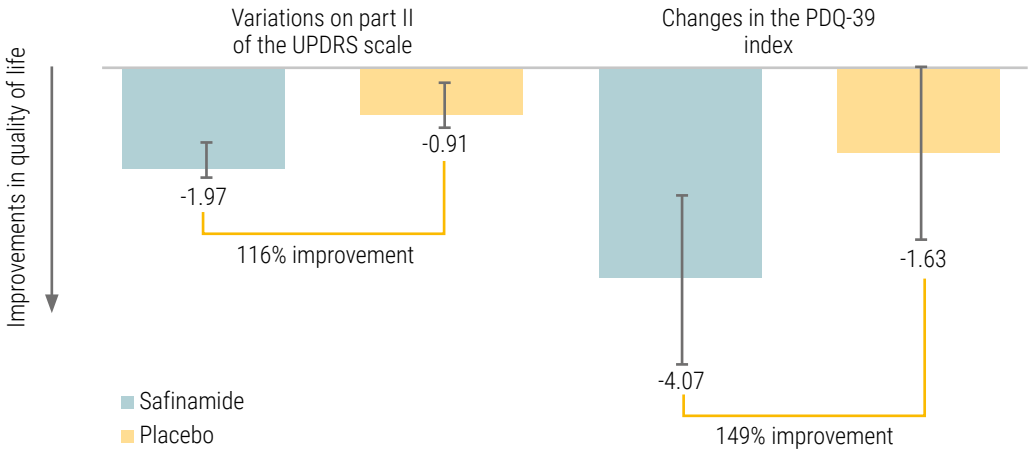
Off periods can cause motor fluctuations, such as tremor and rigidity, as well as non-motor fluctuations, such as anxiety, fatigue or depression. They affect 40% of people with Parkinson after 4-6 years of treatment, and almost all patients after 10 years, with a significant impact on the quality of life of sufferers[669,670]. For this reason, pharmacological advances have focused on reducing these effects through both dopaminergic and non-dopaminergic mechanisms of action.

Safinamide, marketed in Spain since 2015, is a multimodal drug with a mechanism of action that includes reversible inhibition of MAO-B and modulation of glutamate, which is the main excitatory neurotransmitter in the brain. A study of 352 PD patients showed that treatment with this drug reduced off periods by 67% versus placebo, with significant improvements in quality of life of between 116% and 149%. Following the use of this drug, there was a 1.97 point reduction (95% CI -2.11 to -1.40, p=0.0068) in part II (activities of daily living) of the Unified Parkinson's Disease Rating Scale (UPDRS), compared with a 0.91 point reduction in the placebo group (95% CI -1.11 to -0.28, p=0.0390, p=0.0068). On the PDQ-39 questionnaire, specifically to measure quality of life in people with PD, the observed reductions were -4.07 in the safinamide group (95%CI -5.68 to -2.45, p=0.0390) and -1.63 in the placebo group (95%CI -3.29 to 0.03, p=0.0390) (Figure 169)[671,672].

FIGURE 169. EFFECT OF SAFINAMIDE TREATMENT VERSUS PLACEBO ON QUALITY OF LIFE IN PATIENTS WITH PARKINSON'S DISEASE AND OFF EPISODES. VARIATIONS IN PART II OF THE UPDRS SCALE AND THE PDQ-39 QUESTIONNAIRE. INDIA, ROMANIA, ITALY



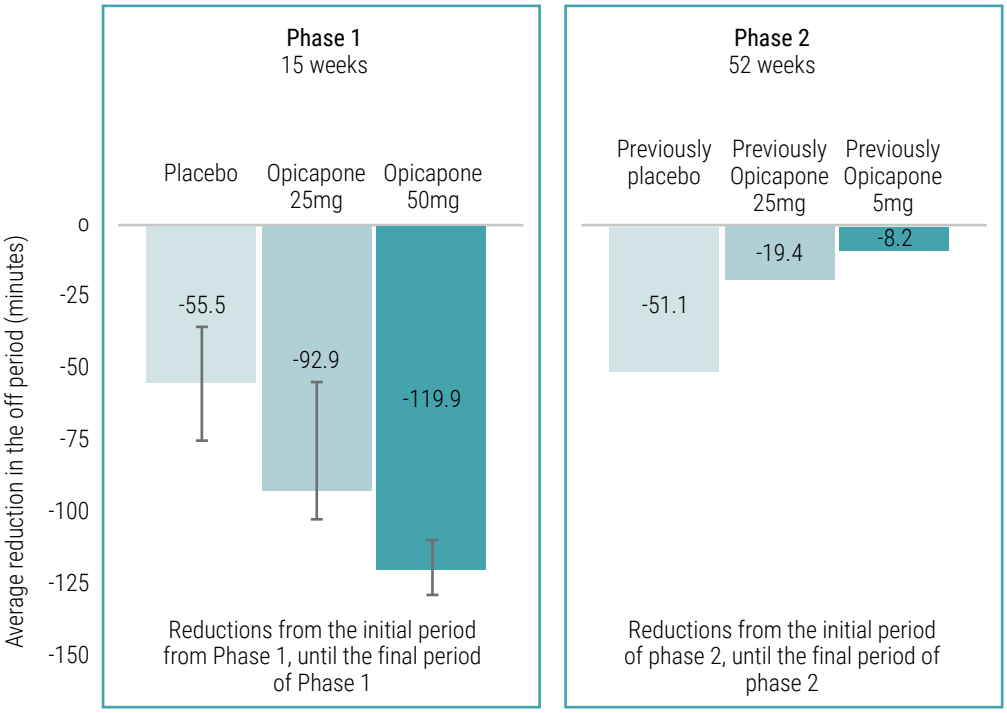
Abbreviations: UPDRS: Unified Parkinson's Disease Scale; **PDQ-39:** Parkinson's Disease Quality of Life Questionnaire.

Source: Own elaboration based on Cattaneo (2020)[672]

Istradephylline is a non-dopaminergic, adenosine A2A receptor antagonist, which is also aimed at reducing off periods in PD patients. Its efficacy has been proven in a study in Japan (the first country to approve this drug) with 476 patients[673]. Reductions in the off-period were observed in 38.2% of the patients studied, and improvements in the symptoms presented during the off-period in almost half (44.7%) of the people who participated in the study. Similarly, the mean score of part III (motor aspects examination) of the UPDRS scale improved by 10%, from 33.7 at baseline to 30.3 at the end of the treatment period.

Opicapone, a COMT inhibitor marketed in Spain since 2017, has been shown to produce significant reductions in off-time in PD patients in two studies (BIPARK-I and BIPARK-II), each comprising two distinct phases[674,675]. In the aggregate analysis of the effects of these two studies, they observed that, in the first phase, the use of opicapone reduced the off time of these patients by 119.9 and 92.9 minutes from baseline for the 25mg and 50mg doses respectively, compared to a reduction of only 55.5 minutes for the placebo group[676]. In the second phase, patients previously in the placebo group were observed to have a significant reduction in off time (51.1 minutes) with the use of opicapone. Patients who were on the 25mg dose in the first phase benefited from treatment optimisation (additional 19.4 minutes of reduction), while patients who started the study on 50mg have maintained their initial reduction times (additional reduction of 8.2 minutes) (Figure 170)[676].

FIGURA 170. LONG-TERM EFFICACY OF OPICAPONE USE IN ADULT PATIENTS WITH PARKINSON'S DISEASE, MEASURED BY REDUCTION IN OFF TIME. AGGREGATE ANALYSIS OF TWO BIPHASIC, MULTICENTER, MULTI-COUNTRY STUDIES



Notes: Study 1: 71 centres and 12 countries (Belgium, UK, Israel, Estonia, Czech Republic, Russia, South Africa, Australia, South Korea, India, Argentina and Chile). Study 2: 106 centres and 20 countries (19 in Europe + Russia)

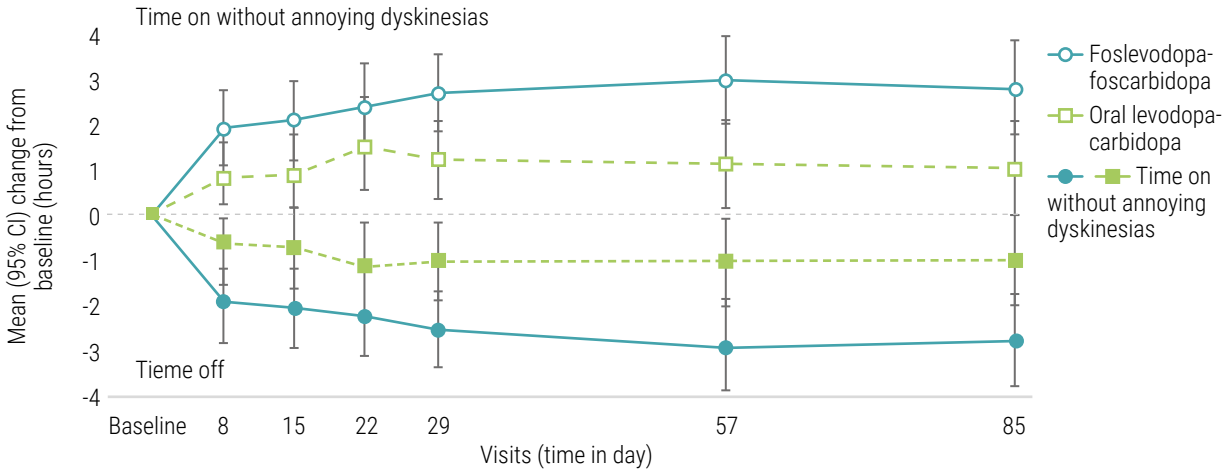
Source: own elaboration based on (2019)[676]

Combining LCIG infusion with an oral COMT inhibitor has been shown to reduce LCIG dose by at least 20%, while maintaining stable levodopa concentrations and motor function. In this context, the approval in 2018 of levodopa-carbidopa-entacapone intestinal gel (LECIG), which includes the COMT inhibitor entacapone, is noteworthy. Due to the presence of entacapone, the bioavailability of levodopa from LECIG infusion is higher than from LCIG infusion and therefore reduced total daily doses of levodopa can be administered to achieve the same effective and stable plasma levels of levodopa[677]. Initial "real world" clinical experience to date with LECIG infusion in Sweden has been evaluated in an observational study of 24 PD patients. According to the results, most patients reported an improvement in their ability to perform daily activities and in their assessed quality of life with LECIG infusion therapy and a high proportion of patients (70%) who had not previously used any type of levodopa infusion perceived that their symptoms had improved[678].

Finally, in England, foslevodopa/foscarbidopa was approved in 2023 for use in patients with advanced PD[656]. According to the results of a randomised, double-blind, 12-week study with a total of 114 PD patients, the new

treatment administered by continuous subcutaneous infusion has been shown to improve motor fluctuations, with benefits both in the on-period without bothersome dyskinesias and in the off-period. Compared to oral levodopa-carbidopa, treatment with foslevodopa/foscarbidopa showed a significant improvement (decrease) in the off period at week 12 compared to oral levodopa-carbidopa (mean change [standard deviation] based on the model from baseline: -2.75 [0.50] vs -0.96 [0.49] hours; difference -1.79 hours, 95%CI (-3.03 to -0.54); p=0.0054) (Figure 171)[679]. The therapy with foslevodopa/foscarbidopa was safe and well tolerated, in line with the well-established safety profile of levodopa-containing medications.

FIGURE 171. LEAST SQUARES MEAN (IC 95%) CHANGE FROM BASELINE IN MEAN DAILY DWELL TIME WITHOUT PROBLEMATIC DYSKINESIA AND REST TIME IN PATIENTS WITH EP WITH FOSLEVODOPA-FOSCARBIDOPA TREATMENT COMPARED WITH ORAL LEVODOPA-CARBIDOPA



Source: Soileau (2022)[679]

Thus, although there is currently no cure for PD, disease-modifying treatments have the potential to delay the onset of motor symptoms and improve the quality of life of patients with the disease. Treatments targeting specific biological pathways involved in the disease process, such as alpha-synuclein, a protein that accumulates in the brains of PD patients, are currently being investigated. On the other hand, there has been growing interest in the design of micro- and nanosystems that can improve the transport of drugs into the brain through their ability to circumvent the blood-brain barrier, improving the pharmacological and therapeutic characteristics of both conventional and novel drug molecules[680].

Treatments for Parkinson's disease introduced in recent decades have achieved significant reductions in off periods and symptoms of psychosis, as well as improving the quality of life of these patients.

Cummings (2014)[661], Fernandez (2015)[667], Ferreira (2019)[676], Cattaneo (2020)[672]

New gel formulations of levodopa-carbidopa and their combination with other drugs that increase their bioavailability are the main therapeutic innovation in recent years for Parkinson's disease, together with a prodrug that has become an effective, safe and well-tolerated new therapeutic option for patients in advanced stages.

Nyholm (2022)[677]; Fasano (2023)[668]; Soileau (2022)[679]

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, degenerative neurological disease of the central nervous system (CNS) that causes a range of symptoms that impair patients' health and quality of life. Some of the most common symptoms are inflammation, pain, vision and mobility problems, fatigue and cognitive dysfunction. In addition, MS frequently causes episodes of neurological dysfunction lasting days or weeks, known as flare-ups, which usually subside partially or completely, especially in the early stages of the disease. In fact, only a small percentage of patients, around 10%, have an onset of progressive neurological deterioration without flares[681].

It is the most common neurological disease in young adults after epilepsy and is the leading cause of disability in this population group, with a higher prevalence in women[682,683]. An estimated 2.8 million people worldwide suffer from MS and its prevalence is increasing[684]. In Europe it affects around 700,000 people and in Spain its prevalence has also been increasing over time, currently affecting around 55,000 people, with 2,500 new cases diagnosed each year[683,685].

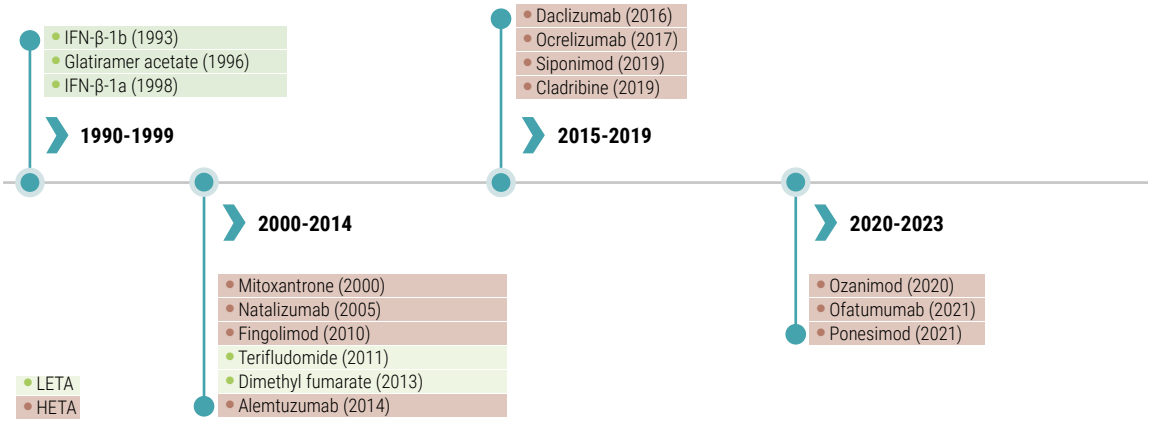
Currently, there is neither a cure for MS nor an effective strategy to prevent its onset. Therefore, the therapeutic management of the disease is based on reducing the inflammatory burden, including relapses and inflammatory CNS lesions, as increased inflammation and lesions lead to long-term physical disability, fatigue and cognitive impairment, which significantly reduces the patient's quality of life and life expectancy[686].

In the last two decades, the field of MS has been transformed by the rapidly expanding arsenal of new disease-modifying therapies (DMTs) aimed at modulating immune responses to reduce inflammation and improve the long-term prognosis of these patients[687]. Current recommendations are aimed at early initiation of treatment in patients with active MS to avoid the production of irreversible CNS lesions and to try to prevent the progression of disability[681].

Until the mid-1990s, steroids were the central MS treatment to slow disease progression, allowing faster recovery after relapse, controlling symptoms, but not modifying the long-term course of the disease[688]. The year 1993 marked a change in the treatment of the disease with the arrival of the first drug aimed at modifying the course of the disease, interferon β-1b[689]. Its main objective was to reduce the frequency of outbreaks, as well as to reduce the disability associated with them, and to prevent the accumulation of lesions in the brain and spinal cord.

There are currently more than 20 drugs approved as SMTs for use in MS[690]. They are usually divided into low to moderate efficacy therapeutic agents (LETA), traditionally used as first line (interferons, glatiramer acetate, teriflunomide, fumarates), and high efficacy therapeutic agents (HETA) with different mechanisms of action, including S1P receptor modulators such as fingolimod, siponimod, ozanimod and ponesimod; immunosuppressants such as mitoxantrone; different types of monoclonal antibodies such as natalizumab, alemtuzumab, ocrelizumab and ofatumumumab; and other drugs such as cladribine (Figure 172)[687,690].

FIGURE 172. EVOLUTION OF THE MOST RELEVANT DISEASE-MODIFYING THERAPIES FOR MS



Note: The chronology shows the leading multiple sclerosis medicines by class and year of first approval in the US and/or EU market. *Daclizumab was withdrawn for safety in the EU in 2018.

Abbreviations: LETA: low to moderate efficacy therapeutic agents; **HETA:** high efficacy therapeutic agents.

Source: Own elaboration adapted from Selmaj (2024)[690] and Melamed (2020)[687]

In clinical trials, LETAs have been shown to be effective in reducing flares and their clinical consequences. For example, interferon β-1a has been shown to be useful in reducing the frequency of relapses in patients with relapsing remitting multiple sclerosis (from an annual rate of 0.90 with placebo to 0.61) and in delaying the progression of disability as measured by the Expanded Disability Status Scale (EDSS)[691–693]. The main clinical study of patients with active relapsing MS treated with glatiramer acetate estimates that the treatment reduced the number of flares by 29%[694].

Oral treatment with dimethyl fumarate provided a new, effective and more convenient treatment option for MS patients by substantially improving inflammation (90% reduction in inflammatory lesions on MRI) and neuroprotection (53% fewer flares and 38% less disability progression)[695]. Studies on the effects in real clinical practice have confirmed its effectiveness by showing that it reduces the annual relapse rate by more than 76%, while improving quality of life at a follow-up of more than one year[696].

On the other hand, in actual clinical practice, oral treatment with teriflunomide for 24 months has been shown to be able to stabilise patients' perceived quality of life, as measured by changes in SF-36 scores from baseline to the last visit. This positive perception of the treatment is due to the fact that relapse activity decreased significantly compared to the period prior to the start of treatment ($p<0.001$). In addition, the convenience and side effects domains of the Medication Satisfaction Questionnaire (MSTQ) had the highest mean scores, indicating the acceptability of oral teriflunomide in this cohort [697].

Compared to MS patients receiving no treatment, use of SMT was associated with a 26% lower risk of mortality (Adjusted Relative Risk 0.74, 95%CI 0.56-0.98)[698]. In an international retrospective observational study, treatment outcomes were compared according to the time of initiation of HETA therapy: 0-2 years (early group, n=213) versus 4-6 years (late group, n=253). Disability outcomes were assessed at 6-10 years. At year 6 after disease onset, the mean EDSS score (ordinal scale 0-10, with higher scores indicating greater disability) was 2.2 in the early treatment group and 2.9 in the delayed treatment group. The superiority of early treatment persisted at each year of follow-up until year 10. The adjusted mean difference in the EDSS score between groups over the entire follow-up period (6-10 years after disease onset) was - 0.98 points (95%CI: - 1.51 to - 0.45; p < 0-000.1)[699].

Recently, early treatment with HETA has been proposed as a strategy for the management of MS for most patients, with the aim of stopping the inflammatory pathological process as early as possible to avoid

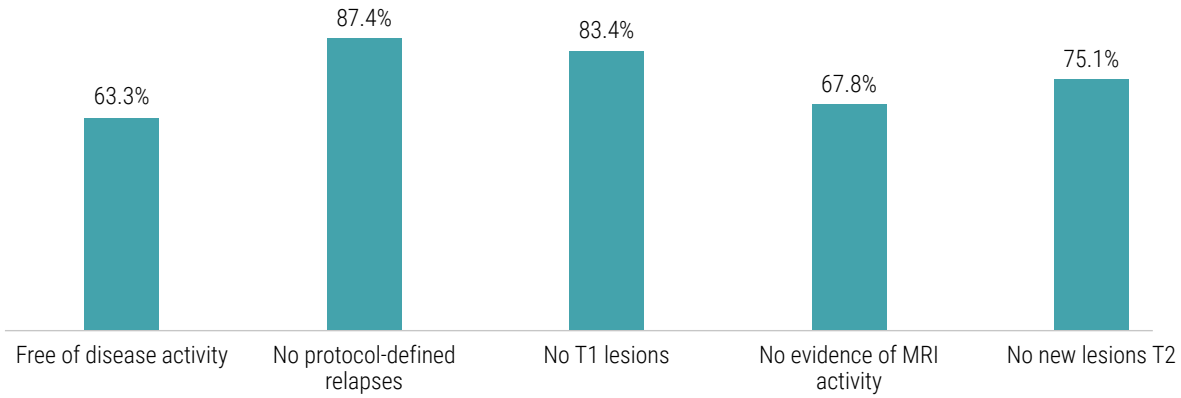
the accumulation of tissue damage and disease burden in all forms of MS. Most HETAs suppress focal inflammatory processes more effectively than moderately effective drugs. However, this approach has not yet become widespread in most patients due to extensive debate. On the one hand, it is crucial to consider safety by involving the patient in decision-making to assess the benefits and risks in each individual case. In addition, concerns arise about the loss of salvage treatment options when less effective treatments are not successful[690].

Oral DMTs have advantages for patients in terms of patient comfort and adherence to treatment and represent advances in disease management. The first HETA-approved oral DMT was fingolimod, which was shown in clinical trials to reduce the relapse rate (up to 60%), the risk of disability progression over 2 years (-70%) and cumulative lesions700. In an example of real clinical practice in Spain, treatment with fingolimod reduced the relapse rate by more than 83% after 3 years of treatment. Furthermore, the percentage of relapse-free patients after 12 and 24 months of fingolimod treatment was 78.2% and 69.2%, respectively, while 66.4% of patients were relapse-free during the study period, confirming its long-term effectiveness[701].

The last two decades have seen a growing interest in gaining a deeper understanding of patients' perceptions of their quality of life and health experiences, especially in pathologies such as MS where patients' quality of life is affected by the progressive accumulation of physical and cognitive disability over time. There are HETAs for the treatment of MS through other routes of action such as humanised monoclonal antibodies that have been shown to be effective in reducing relapses and generating tangible benefits in the quality of life of MS patients[702]. For example, with natalizumab treatment in a cohort of real-life MS patients, statistically significant improvement was observed in 9 out of 12 NeuroQoL domains, addressing key aspects such as mood, sleep and anxiety[703].

For secondarily progressive forms with activity, the available drugs are INF β-1b, INF β-1a and siponimod. In 2018, the EMA authorised ocrelizumab for the treatment of primary progressive forms. The PRO-MSACTIVE study, conducted in patients with active relapsing multiple sclerosis (RMS) receiving ocrelizumab, is a French Phase IV, multicentre, open-label clinical trial. The study found that 267/422 (63.3%, 95%CI 58.5, 67.9%) of patients were free of disease activity at week 48 of the study. The majority of patients, 67.8%, had no signs of activity on brain MRI, including no gadolinium-enhanced (GoE) T1 lesions (83.4%) and no new/enlarged T2 lesions (75.1%) (Figure 173). In addition, the patient-reported outcome questionnaires (PROs) used to assess disease severity, quality of life, impact on work productivity and satisfaction with patient treatment showed a stable trend in total and per dimension scores on all scales from baseline to the end of the study[704].

FIGURE 173. PATIENTS WITH NO DISEASE ACTIVITY (PRIMARY ENDPOINT) WITH ACTIVE RELAPSING MULTIPLE SCLEROSIS (EMR) TREATED WITH OCRELIZUMAB



Note: Protocol-defined relapses were defined as symptoms attributable solely to MS in the absence of fever or infection, persistent for more than 24 h, preceded by neurological stability for ≥ 30 days, accompanied by objective neurological worsening consistent with an increase of at least: 0.5 step on the Expanded Disability Status Scale (EDSS), or 2 points on one of the following EDSS functional system scores (pyramidal, ambulation, cerebellar, brainstem, sensory or visual), or 1 point on each of ≥ 2 EDSS functional system scores on the previously described FSS (pyramidal, ambulation, cerebellar, brainstem, sensory or visual).

Abbreviations: MRI: Magnetic Resonance Imaging.

Source: Manchon (2022)[704]

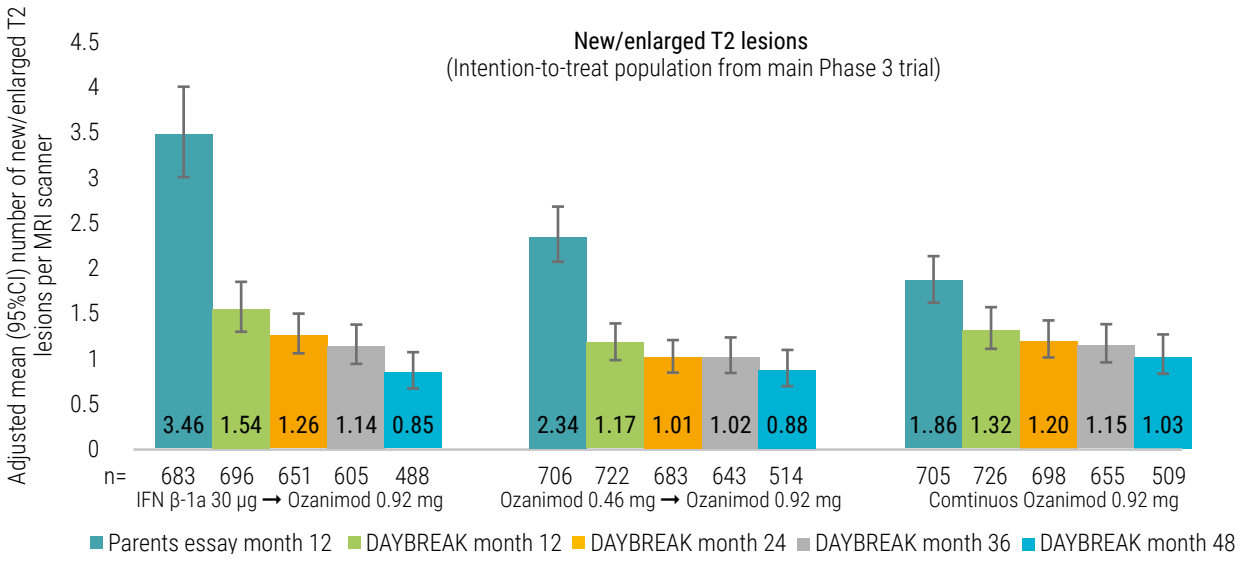
Finally, ofatumumab, the first fully human anti-Ti-CD20 immunoglobulin G1 (IgG1) monoclonal antibody, received EMA approval in 2020 for the treatment of RMS. Data from the ALITHIOS open-label extension study showed that annualised relapse rates remained low (<0.05) for up to five years after starting continuous treatment with ofatumumab. Patients with RMS experienced profoundly suppressed relapse rates, reduced brain magnetic resonance imaging lesions and high rates of no evidence of disease activity[705].

Regarding other mechanisms of action, in the case of sphingosine-1-phosphoinositide receptor blockers, siponimod has been licensed by the EMA in 2020 for the treatment of MS in advanced disease[706]. In the pivotal trial, siponimod demonstrated improvements versus placebo in both the percentage of patients with new MRI-recognised T1 (0% siponimod vs 67% placebo) and T2 (43% siponimod vs 63% placebo) lesions[707]. In patients with active disease, siponimod was compared with placebo and demonstrated a statistically significant relative reduction of 31% (HR 0.69, 95%CI 0.53-0.91) and 37% (HR 0.63, 95%CI 0.47-0.86) in the risk of disability progression at 3 (primary endpoint) and 6 months (secondary endpoint), respectively. In absolute terms, the proportion of patients with confirmed progression at 6 months on the Expanded Disability Status Scale (EDSS) was 19% on siponimod and 28.1% on placebo[708]. Over the lifespan, the effect of siponimod vs. no treatment was favourable in terms of life years gained (7.9 vs. 4.9) and quality-adjusted life years (4.2 vs. 2.0 QALYs) in patients with secondary progressive MS[709].

Among the compounds in this therapeutic class, ozanimod in 2020[710] and ponesimod in 2021[711] have also received a positive response for marketing by the EMA. Ozanimod had shown a lower relapse rate (0.17) than interferon β-1a (0.28) as well as 42% fewer T2-recognised lesions compared to inferferon[712]. Ponesimod was shown to reduce the cumulative number of new GoE lesions compared to placebo[713]. The annualised flare rate (ABR) has been used as the primary endpoint in pivotal studies evaluating these drugs. In the SUNBEAM and RADIANCE studies, ozanimod has demonstrated a significant 48% and 38% reduction in AAR, respectively, over treatment periods of at least 12 months and 24 months, compared to intramuscular interferon β-1. It has also demonstrated a significant reduction in the number of active lesions on MRI compared to intramuscular interferon β-1, with a relative reduction of 48.3% at 12 months and 42.4% at 24 months[714]. Meanwhile, ponesimod in the OPTIMUM study has shown a 30.5% relative reduction in TAB compared to teriflunomide. In addition, it reduced the cumulative number of single active lesions combined (LAUC) by 56%, with a mean number of 1.41 LAUC per year compared to 3.16 in the teriflunomide group ($p < 0.0001$)[715].

To assess the long-term safety and efficacy of ozanimod, an open-label extension study called DAYBREAK, a single-arm, open-label, phase 3 trial, was conducted. This analysis included 2,494 participants with RMS who had completed a baseline trial. According to the results, the adjusted annualised relapse rate in these patients was 0.103 (95%CI 0.086-0.123). Over 48 months, 71% of patients remained relapse-free. Among the treatment subgroups in the main trial, 35.0% of the interferon β-1a group and 37.7% of the ozanimod 0.46 mg and 0.92 mg groups were free of new/extended T2 le- sions from DAYBREAK initiation to month 48 (Figure 174)[716]. In addition, 88.9%, 88.5% and 87.0%, respectively, had no GoE lesions at the month 48 scan.

FIGURE 174. NUMBER OF NEW/ENLARGED T2 LESIONS PER SCAN AT MONTHS 12, 24, 36 AND 48 OF THE DAYBREAK EXTENSION STUDY BY TREATMENT SUBGROUP OF THE MAIN TRIAL TO EVALUATE THE EFFICACY OF OZANIMOD IN PATIENTS WITH EMR



Note: New/expanded T2 lesions were analysed only in the subset of patients entering DAYBREAK from an active controlled phase 3 trial.

Abbreviations: CI: confidence interval; **MRI:** magnetic resonance imaging.

Source: Cree (2022)[716]

Finally, in addition to identifying and developing treatments for new MS targets, efforts are underway to improve the specificity and tolerability of available strategies. New drugs under investigation include ublituximab, a new anti-CD20 monoclonal antibody under review by the FDA, which has shown favourable results in patients with RMS in a placebo-controlled phase II trial. Between weeks 24 and 48, results showed 93% freedom from relapse, no GoE lesions (p=0.003) and 74% of patients with no evidence of disease activity[717].

Currently, there is a gap in the treatment of non-active progressive MS, and it is considered one of the most important unmet medical needs in the field. Efforts are therefore focusing on addressing the neurodegenerative pathology using high-throughput screening for drug discovery for these patients[718].

The pharmacological treatment of multiple sclerosis has made significant progress with the introduction of new disease-modifying therapies with improved efficacy and a better safety profile, as well as an expanding portfolio of agents with novel mechanisms of action that offer more options for MS patients.

Voge (2019)[702]; Kappos (2018)[707]; Cohen (2019)[712]

The highly effective therapeutic agents authorised in recent years for the treatment of multiple sclerosis have opened up new possibilities for patients with relapsing forms of the disease, reducing long-term relapses and neurological disability, thus improving their quality of life. The development of treatments directed at new targets, together with the improved specificity and tolerability of available strategies, holds promise for the future of multiple sclerosis treatment.

Amin and Hersh (2023)[718]; Silva (2020)[709]; Cree (2022)[716]; Kappos (2023)[705]

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic, degenerative, systemic, so-called autoimmune disease characterised by inflammation of the synovial membrane of the joints and surrounding tissues, causing pain, limited movement, swelling and stiffness[719]. It is a severely disabling disease due to the inflammatory activity it generates on the joints[720]. Problems with moving easily can reduce physical fitness and lead to loss of independence, incapacity for work, reduced well-being and mental health problems[721]. This leads to RA patients having a reduced quality of life compared to the general population[722].

Although RA itself is not a life-threatening disease, patients with RA are at increased risk of other diseases, such as diabetes, cardiovascular disease, cancer and certain infections[723]. Globally, RA is estimated to affect 17.6 million (95%CI: 15.8-20.3) people in 2020. According to data from seven countries, including Spain, the age-standardised mortality rate of RA was 0.47 (0.41-0.54) per 100,000 population, a decrease of 23.8% between 1990 and 2020[724]. In Spain, the estimated prevalence of RA was 0.82% (95%CI: 0.59-1.15) for 2016 and, extrapolating to the whole population, it is estimated that there are between 220,000 and 430,000 people over the age of 20 with RA[725].

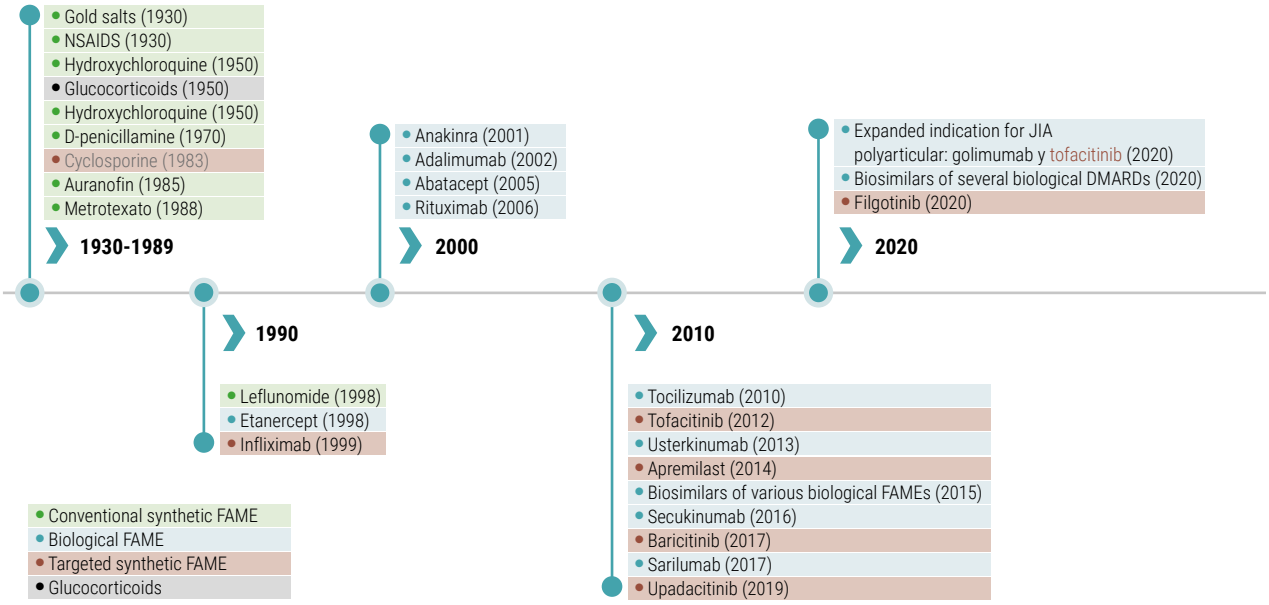
The treatment of RA has changed dramatically over the past 25 years. Traditionally, pharmacological treatment was limited to symptomatic drugs to reduce pain and inflammation, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and other anti-inflammatory drugs such as gold salts. Subsequently, disease-modifying antirheumatic drugs (DMARDs) were developed. DMARDs are slow-acting drugs with different mechanisms of action that are used in RA to reduce inflammation, relieve symptoms such as pain and prevent progression of structural damage. They are divided into two main groups: synthetic and biologics.

At the end of the 1990s, a significant shift occurred in the management of the disease, with the introduction of biological response modifier drugs, which target the disease's natural components. The use of biologic DMARDs is a key component of the immune system response that contributes to disease, while preserving immune function. Biologic DMARDs (bMARDs) include tumour necrosis factor α (TNF-α) inhibitors (infliximab, etanercept, adalimumab, golimumab, certolizumab), IL-1 inhibitors (anakinra), IL-6 inhibitors (tocilizumab and sarilumab), CD20 inhibitors (rituximab) and T-cell activation blockers (abatacept)[726].

Synthetic DMARDs, in turn, are classified into conventional and targeted synthetic DMARDs. Among the conventional synthetic DMARDs (cSMARDs), the most widely used is methotrexate, administered both as monotherapy and in combination with other agents, but there are also others such as leflunomide, sulfasalazine, minocycline, azathioprine and cyclosporine.

In recent years, new advances have been made in the treatment of RA with the introduction of Janus kinase inhibitors (also known as JAK inhibitors or iJAKs). These are orally administered, targeted syn- terapeutic DMARDs (dSMARDs) that induce inhibition of the activity of one or more of the kinase enzymes (JAK1, JAK2, JAK3, TYK2), achieving efficacy similar to that of biologic response mo- difficator drugs. Approved iJAKs for RA include tofacitinib, filgotinib, baricitinib and upadacitinib[727–729]. More recently, some indications have been expanded for the polyarticular form of juvenile idiopathic arthritis (JIA)[365] (Figure 175).

FIGURE 175. DEVELOPMENT OF RHEUMATOID ARTHRITIS TREATMENTS



Note: The chronology shows the leading rheumatoid arthritis medicines by class and year of first approval in the US and/or EU market.

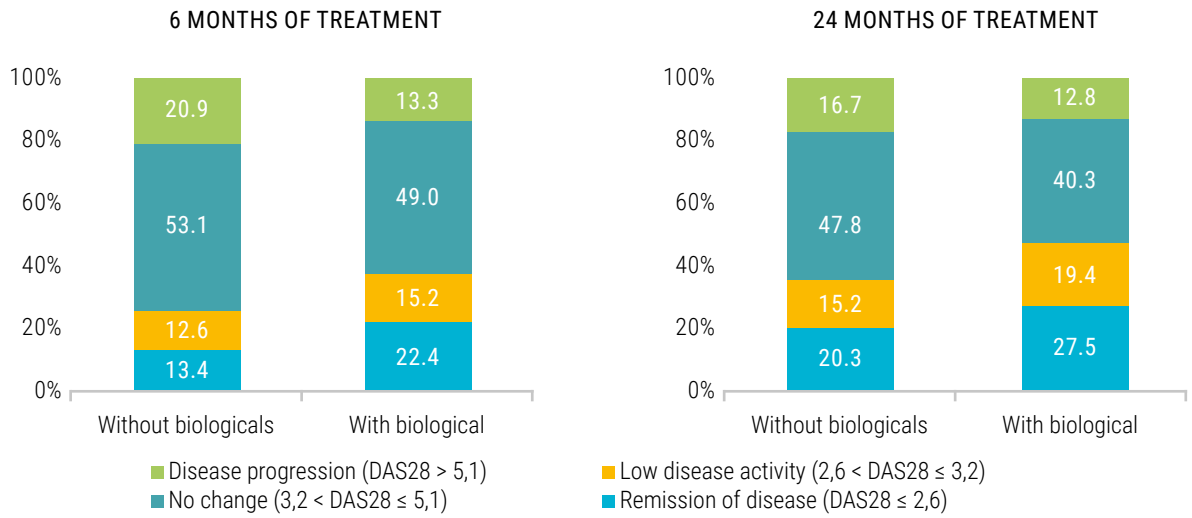
Abbreviations: **NSAIDs:** non-steroidal anti-inflammatory drugs; **DMARDs:** disease-modifying antirheumatic drugs; **JIA:** juvenile idiopathic arthritis; **NSAIDs:** non-steroidal anti-inflammatory drugs.

Source: adapted from (2020)[365], FDA (2022)[367], Burmester (2017)[727] and EMA (2020)[299]

In general, treatments aim to reduce inflammation, preferably by achieving complete remission or a low level of activity. Achieving remission and maintaining a low level of activity is clinically relevant, as it is associated with reduced risk of radiological progression, joint damage and disability[730]. In this sense, biological therapies have been a great advance in the management of the disease, proving to be effective in patients who do not respond to treatment with conventional DMARDs, reducing symptoms, delaying disease progression, and even reducing the risk of death. All of this is associated with a good safety profile and with potential benefits on patients' quality of life[731–733].

An example of the superiority of biologics in terms of treatment response and disease remission can be found in a British study comparing two cohorts of patients with moderate RA. According to this study, disease remission was statistically more frequent among patients treated with biologic DMARDs than among those treated with non-biologic modifiers. At 6 months follow-up, disease remission occurred in 22% of patients on biologics compared to 13% of patients in the control group, rising to 27.5% and 20%, respectively, after 24 months of treatment (Figure 176)[734]. The study also found a significant improvement in the degree of disability in patients treated with biologics.

FFIGURE 176. PERCENTAGE OF PATIENTS WITH MODERATE RHEUMATOID ARTHRITIS TREATED WITH AND WITHOUT BIOLOGICS, AFTER DIFFERENT MONTHS OF FOLLOW-UP, BY DISEASE STATUS, UNITED KINGDOM



Abbreviation: DAS28: Disease Activity Score for 28 joints.

Source: own elaboration based on Kotak (2015)[734]

A survey by the National Rheumatoid Arthritis Society in the UK analysed 612 responses from RA patients with an average age of 59 years, of whom 88% were women, 37.7% with a disease duration of 2-5 years and 27.9% with a disease duration of 5-10 years. According to the survey results, RA patients not treated with the new therapies (biologic and synthetic DMARDs) experience profound difficulties in daily life in a wide range of aspects, e.g. 70% reported the need to change working hours. In addition, multivariate analyses revealed that increased difficulties with daily physical activities and reduced emotional and physical well-being in the last week were significantly associated with pain, number of flares and ability to cope ($p<0.005$)[735].

The effectiveness of biologic DMARDs has been demonstrated in a German non-interventional, real data study involving a total of 824 adults with a confirmed diagnosis of RA without prior etanercept treatment. After 12 weeks of etanercept treatment, 24% (194/794) of RA patients achieved remission and 39% (313/794) of patients achieved low disease activity. This proportion increased steadily over time, with 37% (187/502) achieving remission by week 52 of treatment and the proportion of patients achieving low disease activity rising to 54% (273/502) (Figure 177). In addition, a clinically relevant reduction in pain was observed throughout the study. Fatigue and the mean Patient Health Questionnaire (PHQ-2) score, indicating depression, also decreased steadily throughout the study, with the most pronounced reductions observed during the first 12 weeks of etanercept treatment (Figure 177)[736].

FIGURE 177. PERCENTAGE OF RHEUMATOID ARTHRITIS PATIENTS RECEIVING ETANERCEPT ACHIEVING REMISSION AND LOW DISEASE ACTIVITY

Note: Remission and low disease activity were defined as DAS28<2.6 and DAS28≤3.2, respectively.

Source: Feist (2022)[736]

On the other hand, several studies have shown that the addition of biologics to treatment with conventional DMARDs such as methotrexate is more effective than methotrexate alone in RA. For example, adalimumab in combination with methotrexate achieves much higher response rates than those achieved with methotrexate alone (59% vs 24% in ACR20; 42% vs 10% in ACR50; 23% vs 5% in ACR70)[737]. According to the COMET study, 50% of patients treated with etanercept in combination with methotrexate achieved clinical remission, compared to 28% of those treated with the synthetic modifier alone[738]. Similarly, a meta-analysis of 158 clinical trials showed that the response rates of combination therapies of methotrexate with biologics such as abatacept, adalimumab, etanercept, infliximab, rituximab, or tocilizumab were higher than those of methotrexate alone (56%-67% vs. 41% in ACR50)[739].

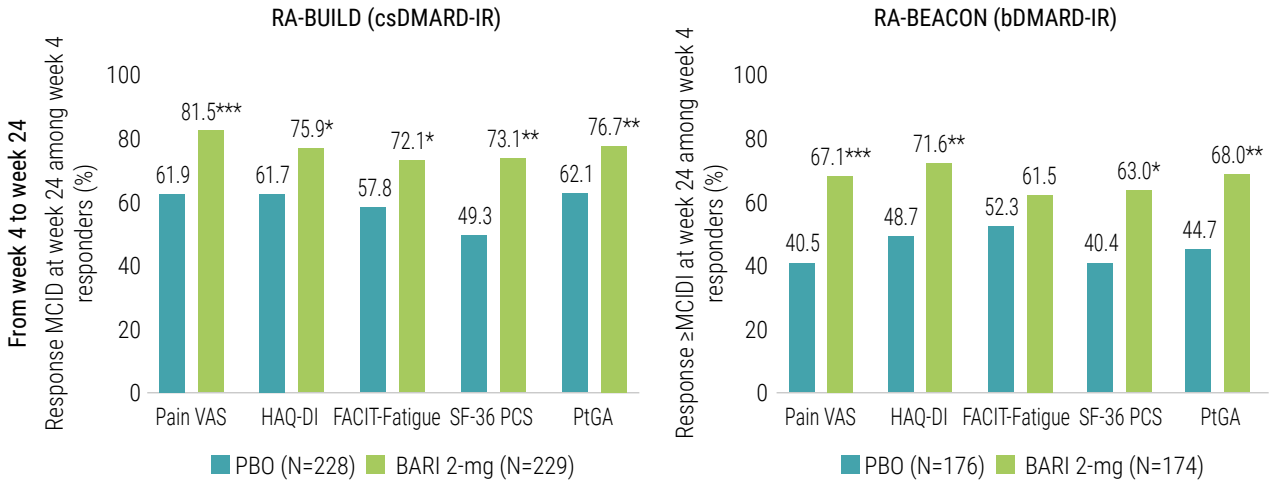
More recently, a meta-analysis has been published with data from 3,790 RA patients. According to the results, the addition of a biologic DMARD such as certolizumab, a TNF-α inhibitor, to conventional RA treatment was associated with an increased likelihood of achieving low overall disease activity. Specifically, patients treated with certolizumab are approximately 6.31 times more likely to experience the outcome of interest compared to patients who did not receive it (95%CI: 2.22-15.25)[740].

With respect to synthetic targeted DMARDs for the treatment of RA, iJAKs such as baricitinib and upadacitinib, and sarilumab, a monoclonal antibody targeting IL-6 receptors, stand out. These drugs have shown better results in controlling signs and symptoms and improving functional activity in patients with moderate-to-severe RA with inadequate response (or intolerance) to conventional synthetic DMARDs and/or with inadequate response (or intolerance) to biologic DMARDs (mainly anti-TNF)[741-743].

An example of the value provided by these new drugs can be seen in a study conducted on sarilumab, which demonstrated its efficacy in combination with methotrexate both in patients with no previous treatment and in patients with an inadequate response to other DMARDs, opening up new treatment possibilities for these patients[744]. Another study, conducted in Germany, has shown the effectiveness of sarilumab in patients with RA who have had an inadequate response (IR) to other DMARDs or to previous treatment with iJAKs (iJAK-RI group) and tocilizumab (tocilizumab-RI group), as well as those previously treated with any other biologic DMARDs (DMARDb group) and patients who had not received any biologic DMARDs or targeted synthetic DMARDs (DMARD naive group). During 6 months of sarilumab treatment, the clinical disease activity index improved in the iJAK-RI group [from 26.2 (14.18) to 12.8 (11.27)] and the tocilizumab-RI group [from (22,4 (14.60) to 11.2 (12.56)] to the same extent as in the FAMEb group [from 22.8 (12.69) to 10.7 (9.79)] and FAME naive patients [from 24.5 (13.32) to 9.9 (9.43)][745].

Baricitinib has also been shown to improve outcomes reported by RA patients who do not respond adequately to conventional synthetic and biologic DMARDs. The efficacy of the therapy has been tested in the RA-BUILD and RA-BEACON trials, which analysed RA patients who had inadequate response to conventional synthetic DMARDs and biologic DMARDs, respectively. According to the results of these trials, significantly more patients treated with ba- ricitinib maintained improvement in the minimal clinically important difference in various PROMs (responses in pain, physical function, fatigue, health-related quality of life and patient global assessment) at week 24 in those who responded to baricitinib treatment at week 4 compared to those who received placebo (Figure 178)[746]. Likewise, in the RA-BEACON trial, in the subgroup of patients with inadequate response to anti-TNF, baricitinib showed statistically significant improvements in ACR20 compared to placebo, indicating that this iJAK could be a valid option for this population of patients with high therapeutic need. In addition, for those who are not anti-TNF candidates, baricitinib could be considered as an oral alternative among the available treatments[747].

FIGURE 178. PROPORTION OF PATIENTS MAINTAINING IMPROVEMENTS IN PROMS GREATER OR EQUAL TO MCID AT WEEK 24 AMONG RESPONDERS AT WEEK 4 WITH BARICITINIB TREATMENT VERSUS PLACEBO IN PATIENTS WITH RA WHO ARE NON-RESPONDERS TO CONVENTIONAL SYNTHETIC DRUGS IN THE RA-BUILD STUDY (A) AND BIOLOGIC DRUGS FAMINES IN THE RA-BEACON STUDY (B)



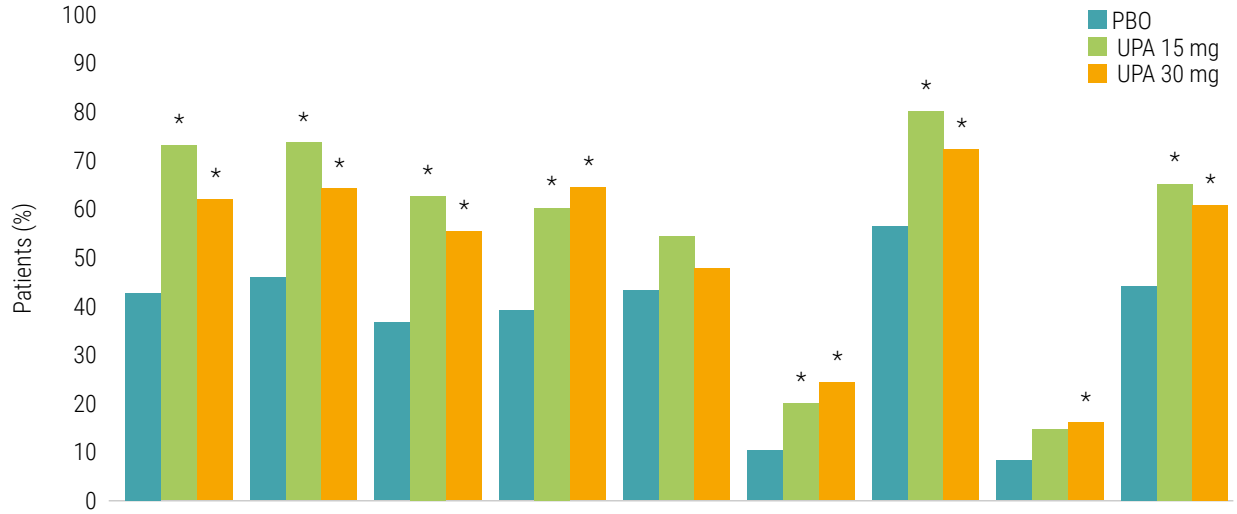
Notes: *p≤ 0,05, **p≤ 0,01, ***p≤ 0,001.

Abbreviations: MCID: minimal clinically important difference; **IR:** inadequate response; **csDMARD:** conventional synthetic disease-modifying anti-rheumatic drug; **bDMARD: biologic disease-modifying anti-rheumatic drug**; **DMARDsc:** conventional synthetic disease-modifying antirheumatic drugs; **DMARDsb:** biological disease-modifying antirheumatic drugs; **PBO:** placebo; **BARI:** baricitinib; Pain **VAS:** visual analogue pain scale; **HAQ-DI:** health assessment questionnaire - disability index; **FACIT-Fatigue:** functional assessment of chronic illness therapy-fatigue; **PBO:** placebo: Health Assessment Questionnaire Disability Index; **SF-36 PCS:** physical component of Short Form-36; **PtGA:** Patient Global Assessment of Disease Activity.

Source: Sholter (2022)[746]

For its part, upadacitinib has also demonstrated gains in health outcomes in patients unresponsive to biologic DMARDs. Upadacitinib has been shown to improve multiple aspects of quality of life, with more patients achieving clinically meaningful improvements compared to placebo. According to the results of SELECT-BEYOND, a randomised phase 3 trial in RA patients with inadequate responses to biologic DMARDs compared to placebo, statistically significant improvements were evident at week 12 with both upadacitinib 15 mg and 30 mg for patient global assessment of disease activity (PtGA), visual analogue pain scale, health assessment questionnaire - disability index (HAQ-DI), physical component (PCS) and morning stiffness (all p≤ 0.001) (Figure 179)[748].

FIGURE 179. PROPORTION OF PATIENTS WHO MAINTAIN IMPROVEMENTS IN HIGHER PROMS OR EQUAL TO DMCI AT WEEK 12 IN PATIENTS WITH RA UNRESPONSIVE TO BIOLOGIC FAME WHO RECEIVED UPADACITINIB VS. PLACEBO



	PtGA (n); NNT	Pain VAS (n);NNT	HAQ-DI (n); NNT	SF-36 PCS (n); NNT	SF-36 MCS (n); NNT	AM stiffness duration (n); NNT	AM stiffness severity (n); NNT	ISI (n); NNT	EQ-5D-5L (n) NNT
PBO	(71)	(76)	(61)	(65)	(72)	(17)	(95)	(12)	(73)
UPA 15 mg	(119); 3,3	(120); 3,6	(102); 3,9	(98) 4,8	(88); 9,4	(33); 9,9	(131); 4,2	(22); 15,1	(106); 4,7
UPA 30 mg	(101); 5,2	(103); 5,5	(89); 5,4	(104); 4,0	(77); 24,1	(40); 7,1	(119); 6,3	(24); 12,4	(97); 6,0

Note: * P < 0.05 for UPA vs PBO.

Abbreviations: AM: morning; BP, bodily pain; **EQ-5D-5L:** Euro Qol 5-Dimension 5-Level Questionnaire; **GH:** general health; HAQ-**DI:** Health Assessment Questionnaire Disability Index; **ISI:** Insomnia Severity Index; **MCID:** minimum clinically important difference; **MCS:** Mental Component Summary; **MH:** mental health; **NNT:** number needed to treat; **PBO:** placebo; **PCS:** Physical Component Summary; **PF:** physical functioning; **PRO:** patient-reported outcome; **PtGA:** Patient Global Assessment of Disease Activity; **RE:** role-emotional; **RP:** role-physical; **SF:** social functioning; **SF-36:** Short Form-36 Health Survey; **UPA:** upadacitinib; **VAS:** visual analog scale; **VT:** vitality.

Source: Strand (2019)[748]

Biological disease modifiers have been shown to be superior to conventional synthetics in terms of quality of life[749–751]. Both targeted synthetic DMARDs such as tofacitinib and other biologic DMARDs (b- DMARDs) under real-world conditions have reported improvements in quality of life in RA patients who had an inadequate response to conventional synthetic DMARDs[752]. Successful control of disease activity with these drugs improved the quality of life of RA patients from 0.77 to 0.83 after one year of follow-up, as measured by the EuroQuol 5D-3L (EQ5D)[753].

The gains in quality of life produced by biologic drugs have also been reproduced in real life in Spain. An example of this can be found in a study showing that treatment with certoli- zumab, after 12 weeks, improves patients' quality of life, following the SF-35 questionnaire, from 32 and 42 points at baseline in the physical and mental components to 38 and 50, respectively[754].

In addition, other studies have found that patients treated with biologics have fewer occupational problems than patients treated with conventional DMARDs[755,756]. For example, the combination of adalimumab and adalimumab has been shown to be more effective than conventional DMARDs. mab in combination with methotrexate decreased productivity during work time (average decrease of 18% and 21% with adalimumab at weekly doses of 7.5mg and 20mg, respectively) as well as the impact of the disease on work-related activities (15% reduction with adalimumab 7.5mg and 20% with the 20mg regimen)[757].

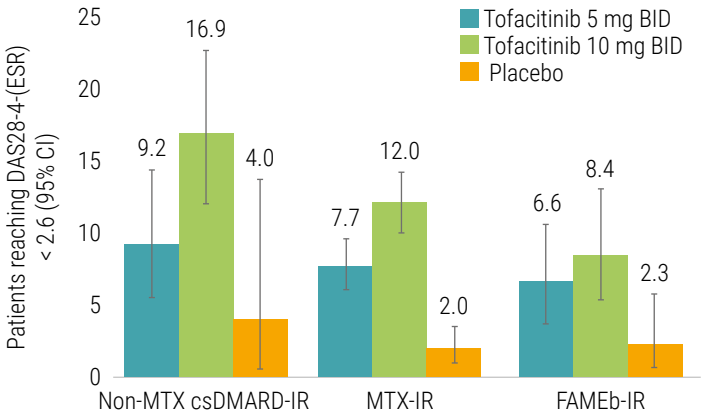
Another example of how the use of biologics improves patients' job performance is seen in a study of etanercept, where 71% of treated patients remained employed after 1 year of treatment, compared to 55% of the control group. In addition, they worked an average of 7.4 hours more per week than those treated with placebo[758].

Innovations in pharmacology should not only be measured by their ability to deliver health outcomes, but also by opening up treatment possibilities for patients who are intolerant to current treatments and, more recently, their extension to other indications such as the treatment of polyarticular juvenile idiopathic arthritis (JIA), a type of juvenile arthritis that causes inflammation in five or more joints in the first six months of the disease. In this respect, iJAKs present themselves as a particularly important treatment alternative for patients who do not respond adequately to biologic therapies and, in the case of tofacitinib and golimumab, also for those patients affected by juvenile forms of arthritis[365].

First, to assess the efficacy of tofacitinib in patients inadequately responding to biologic therapies, a pooled data analysis of phase II/III trials of patients receiving tofacitinib 5 or 10 mg twice daily or placebo has been conducted, where separate assessments were performed for three populations with previous inadequate response (IR) to: conventional synthetic DMARDs only without methotrexate (MTX) (no MTX csDMARD-IR; n = 537); MTX (MTX-IR; n = 3113); and other biologic DMARDsb (bDMARD-IR; n = 782). On the one hand, it has been shown that the proportions of patients achieving remission were numerically higher with tofacitinib 10 mg versus 5 mg. Regardless of treatment group, the remission rate as defined by DAS28- 4(ESR) was numerically higher in the FAMEsc-RI population without MTX than in the MTX-RI or FAMEb-RI populations, although the 95%CIs overlapped (Figure 180). In addition, in all three patient populations analysed, ACR20 response rates were significantly higher, ACR50 and ACR70 at month 3 were significantly higher with tofacitinib compared to placebo[759].

On the other hand, tofacitinib is the first oral JAK inhibitor evaluated in patients with JIA that has been shown to improve signs and symptoms of the disease in a rapid and sustained manner[760]. Its efficacy and safety have been tested in the second part of a randomised, double-blind, placebo-controlled Phase 3 trial evaluating 142 patients with polyarticular JIA who were randomly assigned to tofacitinib (n=72) or placebo (n=70). According to the results, the flare rate at week 44 was significantly lower with tofacitinib (21 [29%] of 72 patients) than with placebo (37 [53%] of 70 patients; hazard ratio 0.46, 95%CI 0.27-0.79, p=0.0031) (Figure 181).

FIGURE 180. PROPORTION OF PATIENTS ACHIEVING DAS28-4 (ESR)-DEFINED REMISSION AT MONTH 3 WITH TOFACITINIB VS. PLACEBO

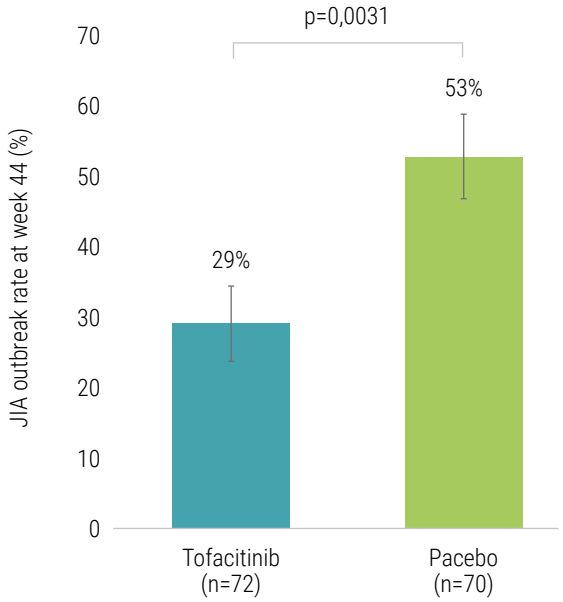


Note: DAS28-4(ESR): Disease activity score in 28 joints derived from 4 measures, erythrocyte sedimentation rate.

Abbreviations: BID: twice daily; **MTX:** methotrexate; **IR:** inadequate response; **cDMARDs:** conventional synthetic disease-modifying antirheumatic drugs; **bDMARDs:** biologic disease-modifying antirheumatic drugs.

Source: Tesser (2023)[759]

FIGURE 181. EFFICACY OF TOFACITINIB VS. PLACEBO IN PATIENTS WITH POLYARTICULAR JIA IN THE RATE OF JIA FLARES AT WEEK 44 (TOFACITINIB CRITERIA)



Abbreviation: JIA: juvenile idiopathic arthritis.

Source: Ruperto (2021)[760]

Similarly, the GO-VIVA trial examined for the first time the safety and efficacy of intravenously administered golimumab in 127 paediatric patients aged 2 to <8 years with persistent polyarticular JIA who had previously shown no improvement with methotrexate monotherapy. Based on the results, golimumab functions as an effective treatment option for polyarticular JIA with a good safety profile. Overall, 84%, 80%, 70% and 47% of patients treated with golimumab achieved JIA ACR 30, 50, 70 and 90, respectively, demonstrating clinically relevant improvement of disease signs and symptoms[761].

From another perspective, several studies have reported a decrease in mortality in RA patients, especially after 2000, and the possible relationship of this reduction in mortality to changes in the approach to RA towards early and intensive treatment with DMARDs, the introduction of biologic therapy and targeted treatment strategies has been raised[762,763]. A UK study, using the THIN electronic medical records database of over 10 million medical records, observed a significant improvement in the mortality rate in patients with RA compared to chronic patients without RA for the periods 1999-2006 and 2007-2014. The differences in mortality rates between patients with and without RA were 11.0 deaths per 1,000 patients (95%CI: 9.0 - 13.0) for the first period and 4.1 (95%CI: 2.6 - 5.6) in the second period[762].

A study in Australia involving 17,125 RA patients investigated temporal changes in standardised mortality rates (SMRs) for RA patients over the period 1980-2015. The SMR decreased to 1.59 (95%CI: 1.39-1.81) for the period 2011-2015, although it was noted that mortality is still 1.59 times higher than that of their community counterparts, indicating that it can still improve. Comorbidity is the main modifiable risk factor to further reduce mortality in RA patients[763].

Finally, it is worth mentioning that advances have been possible thanks to a better understanding of the molecular mechanisms of autoimmune diseases, allowing the development of more specific and effective drugs not only against RA, but also against other types of arthritis and other inflammatory diseases, such as inflammatory bowel disease, psoriasis or ankylosing spondylitis[764].

Currently, RA treatment is evolving towards a precision medicine approach with more precise therapies, either through improved delivery methods or individualised therapies that are increasingly targeted and effective, minimising side effects and maximising outcomes for each patient. This paradigm, similar to personalised therapeutic regimens in oncology, aims to establish a specific standard of care for each individual, offering optimal efficacy with minimal incidence of side effects. In the future, the use of nanoparticles and cell therapy hold great promise for developing precise therapeutic options, enabling the reduction of side effects by specifically targeting the affected areas[765].

Biological and targeted synthetic disease-modifying antirheumatic drugs such as JAK inhibitors have been an unprecedented therapeutic advance in the field of rheumatoid arthritis, achieving not only advances in disease remission, functional status and risk of death in patients, but also improvements in quality of life and increased effective treatment options in patients who did not respond adequately to standard treatments.

Yamaoka (2016)[729], Burmester (2018)[765], Genovese (2018)[741], Wu (2018)[742], Donahue (2008)[731]

In recent years, biologic therapies have demonstrated their effectiveness in the remission of rheumatoid arthritis in real clinical practice. In addition, the indication of JAK inhibitors has been extended to forms of juvenile arthritis, where they improve the signs and symptoms of the disease. Thanks to targeted biologic and synthetic therapies, these patients have been able to reduce the difficulties in their daily lives.

Nikiphorou (2021)[735]; Feist (2022)[736]; Sholter (2022)[746]; Ruperto (2021)[760]; McIntosh (2023)[761]

PSORIASIS

Psoriasis is an inflammatory skin disease with a variable and chronic clinical course, characterised by unpredictable relapses and remissions, and may be associated with arthritis in 30% of patients[766]. It can occur at any age, with two peaks of incidence between 20-30 years and 50-60 years, and 10-15% of new cases in children under 10 years of age[767]. Its causes include genetic and environmental factors such as stress or infections[768]. It presents various clinical forms, the most common being plaque psoriasis (90% of cases), characterised by reddish plaques covered with scales[769]. Often progressive, it affects areas such as the trunk, limbs and scalp, causing itching and significantly affecting quality of life in moderate to severe cases[770,771].

Globally, more than 60 million people suffer from psoriasis[767]. In Spain, it is estimated that there are around 900,000 adult patients with psoriasis, 90% of whom have plaque psoriasis and approximately 29% have moderate to severe forms[772].

The aim of treatment is to achieve sustained control of skin involvement, as well as long-term control of systemic inflammation, prevention of the onset and progression of systemic comorbidities and improvement of quality of life[773,774]. At the cutaneous level, the aim is to achieve long-term maintenance of complete or near-complete clearance of the skin, or otherwise minimal localised involvement[775].

The most widely accepted measure is the Psoriasis Area and Severity Index (PASI)[776]. The PASI scale measures the affected area and its severity (erythema, induration and scaling) in each body area. PASI 75 and 90 means the percentage of patients achieving an improvement (reduction) in the baseline PASI score ≥ 75% and ≥ 90%, respectively. A PASI100 means a complete clearing of lesions. Traditionally, the most commonly used indicator in clinical trials is PASI 75, which means a 75% reduction in the area affected by psoriasis, but nowadays the main goal of treatment is to obtain a PASI 90 or 100[776].

The Physician's Global Assessment (PGA) is another tool commonly used in clinical trials to assess the severity of psoriasis comprehensively from the physician's perspective. The PGA scale ranges from 0 to 5, where 0 indicates clear skin (no disease) and higher values represent increasing levels of severity, with 1 or 2 indicating very mild or mild disease, and 4 or 5 indicating severe disease. Physicians use the PGA to globally assess the severity of psoriatic lesions based on erythema, induration, and scaling of the skin. In clinical trials, a significant therapeutic response is considered achieved when patients achieve a PGA of 0 or 1, indicating complete or nearly complete clearing of the skin[776].

Another aim is to avoid, as far as possible, the side effects of treatment and to improve quality of life. From the patients' point of view, these include the elimination of symptoms, no disruption of their daily life, the convenience of the treatment and an improvement in their emotional situation[776,777].

The treatment of psoriasis has evolved considerably in recent decades. This evolution in therapeutic approaches is an outstanding example of success in translational research, where a better understanding of the pathogenesis of the disease has driven the development of targeted therapies with increasing precision[778].

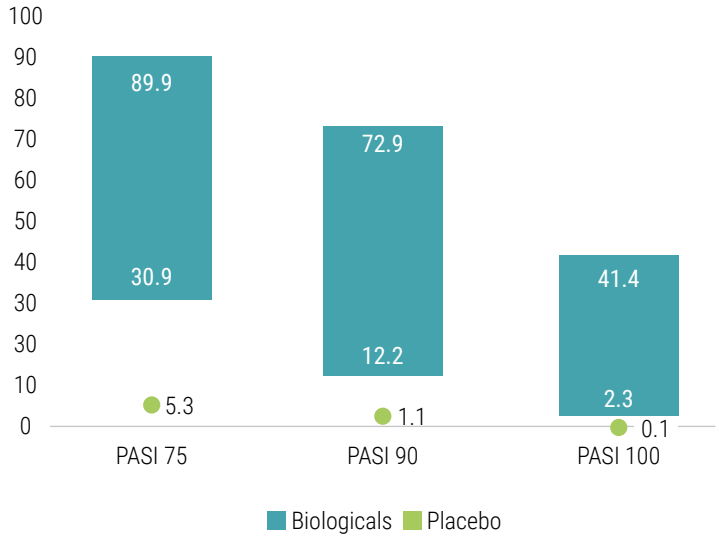
Determining the severity of psoriasis, which includes factors such as the extent of the disease, the location of lesions, the degree of inflammation and the impact on quality of life, is crucial in deciding the therapeutic approach. In the second half of the 20th century, significant advances were made in the treatment of psoriasis. This included the introduction of conventional systemic therapies such as methotrexate and cyclosporine, as well as topical treatments and phototherapy. In addition, oral therapies such as fumaric acid esters were developed[778].

Currently, the treatment of mild or limited psoriasis is predominantly done with topical therapies due to their safety and good tolerance. Topical glucocorticoids and vitamin D derivatives, or their combination, are preferred[779]. However, in cases where psoriasis cannot be controlled with topical treatments, affects areas of functional compromise or is associated with psoriatic arthritis, conventional systemic therapies may be necessary. These therapies are sometimes combined with phototherapy, which includes ultraviolet A, ultraviolet B or narrowband ultraviolet B radiation[780].

Since the 2000s, the introduction of biologic therapies, such as monoclonal antibodies and receptor fusion proteins, has revolutionised the treatment of moderate to severe psoriasis. These biologics target specific components of the immune system involved in the pathogenesis of the disease. The first biologics, developed between 2000 and 2005, such as infliximab, etanercept and adalimumab, inhibit tumour necrosis factor-alpha (TNF-α), a key cytokine in immune-mediated disease[778].

Subsequently, certolizumab pegol was introduced. In 2009, the first interleukin (IL) 12/23 inhibitor, ustekinumab, was launched. The realisation that psoriasis is an IL-23 and IL-17 mediated disease led to the development of more advanced IL-17 (secukinumab, ixekizumab, brodalumab) and IL-23 (guselkumab, tildrakizumab, risankizumab) inhibitors. In addition, deucravacitinib, a selective tyrosine kinase 2 (TYK2) inhibitor, has recently been licensed for use[778].

FIGURE 182. 16-WEEK EFFICACY OF THE BIOLOGIC THERAPIES IN PATIENTS WITH MODERATE TO SEVERE PSORIASIS, % OF PATIENTS ACHIEVING SPECIFIC DEGREES OF CLEARENCE

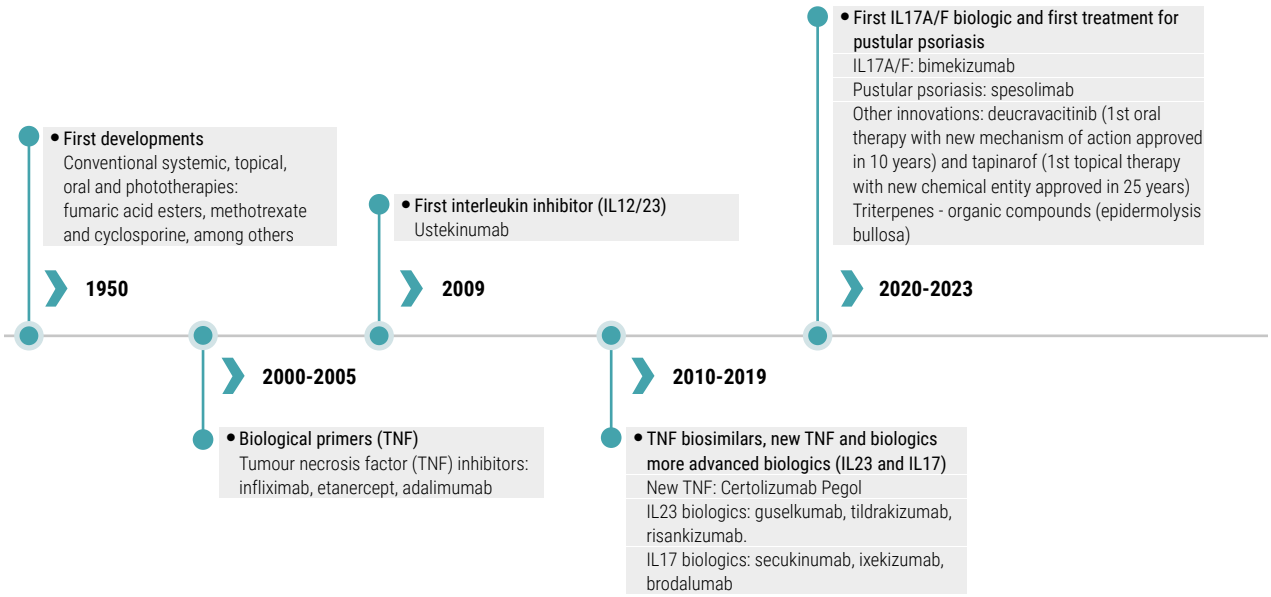


Fuente: own elaboration based on Armstrong (2015)[781]

The effectiveness of biologics, which are generally used as second-line therapy[780], has been demonstrated in several clinical trials. The range of patients achieving a PASI75 in up to 16 weeks has been demonstrated in several clinical trials. The range of patients achieving near complete clearance (PASI90) with these drugs varies from 31% to 90%. Similarly, the range of patients achieving near complete clearance (PASI90) with these drugs ranges from 12% to 73%. Finally, the proportion of patients achieving complete clearance (PASI100) after using these therapies ranges from 2% to 41% (Figure 182)[781].

Between 2020 and 2023, the EMA and FDA have approved four new substances for the treatment of psoriasis. These include **bimekizumab** (EMA: 2021; FDA: 2023), the first IL17A/F biologic to treat plaque psoriasis; **spesolimab** (EMA and FDA: 2022), the first treatment for pustular psoriasis; **deucravacitinib** (EMA: 2023; FDA: 2022), the first oral therapy with a new mechanism of action approved in a decade; and tapinarof (FDA: 2022), the first topical therapy with a new chemical compound approved in 25 years (Figure 183).

FIGURE 183. EVOLUTION OF PSORIASIS TREATMENTS



Source: Reid (2020)[778], EMA (2020[361], 2021[362], 2022[363], 2023[364]) and FDA (2020[365], 2021[366], 2022[367], 2023[404])

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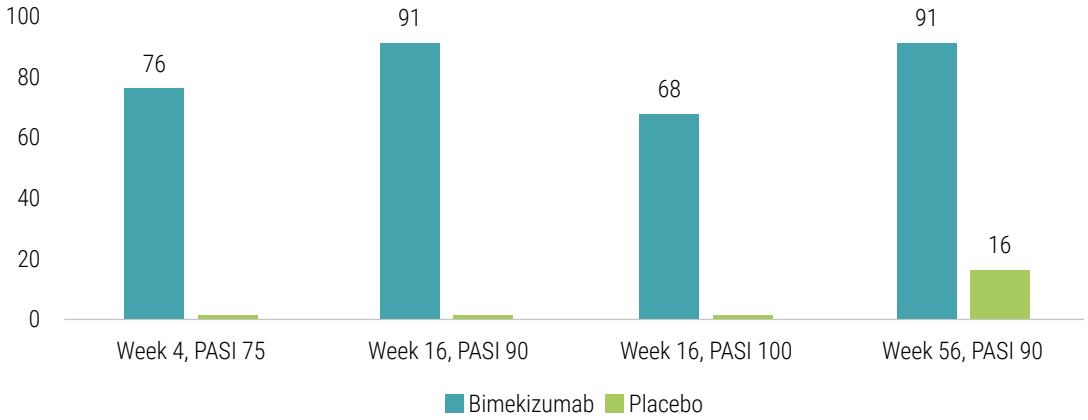
Bimekizumab is an IgG1 monoclonal antibody that selectively inhibits both IL-17A and IL-17F, two key cytokines in mediating inflammatory processes[782]. It is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic treatment. In its pivotal study versus placebo (BE READY), bimekizumab was shown to provide a high degree of clearance in a rapid and sustained manner. At week 4, after one dose of bimekizumab, 76% (n=265) of treated patients achieved a lesion clearance grade ≥75% (PASI 75), in contrast to only one patient in the placebo group (1%). At week 16, 91% (n=317) of bimekizumab-treated patients achieved near complete clearance (PASI 90), compared to only one patient (1%) in the placebo group (p<0.0001). In addition, 68% (n=238) of bimekizumab-treated patients achieved complete clearance (PASI 100), compared to only one patient (1%) in the placebo group (p<0.0001). Of the bimekizumab-treated patients who achieved a PASI 90 at week 16 and who underwent re-randomisation (re-assigned to bimekizumab and placebo groups), the proportion of patients who achieved a PASI 90 at week 56 was significantly higher in the bimekizumab-treated group (91%) compared to the placebo group (16%)(Figure 184)[783].

FIGURE 184. EFFICACY OF BIMEKIZUMAB IN THE TREATMENT OF PATIENTS WITH MODERATE TO SEVERE PSORIASIS, WEEKS 4, 16 AND 56, % OF PATIENTS ACHIEVING SPECIFIC DEGREES OF CLEARENCE



Note: Patients in the placebo group at week 56 received bimekizumab until week 16.

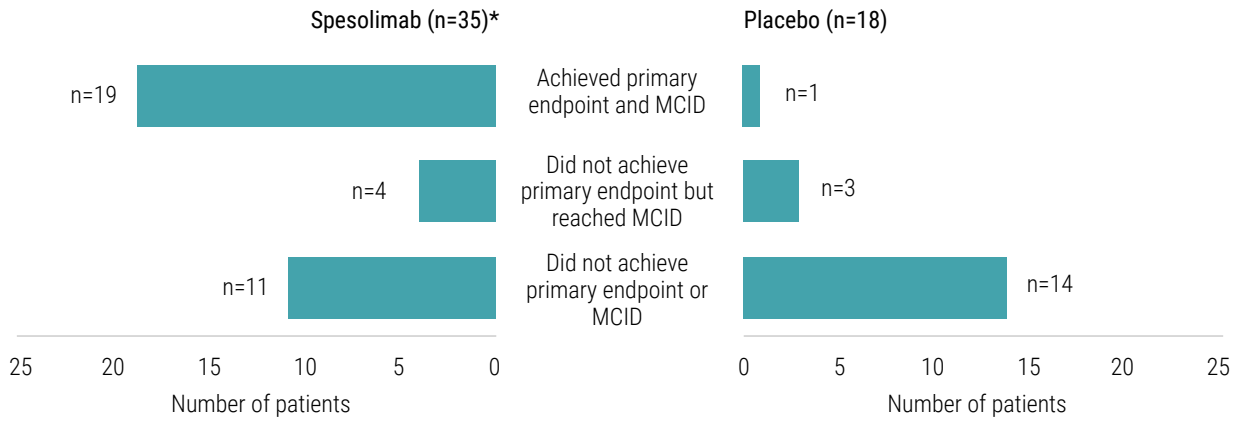
Source: Gordon (2021)[783]

In this same clinical trial, bimekizumab demonstrated not only remarkable efficacy in clearing psoriasis lesions, but also a significant improvement in patients' HRQoL. At week 16, a significantly higher proportion of patients treated with bimekizumab reported that psoriasis did not affect their HRQoL, with 76% of patients achieving a DLQI score of 0-1, compared to only 6% of patients receiving placebo (p<0.0001)[783].

Espesolimab is a drug that modulates the immune system. It is used in adults to treat flare-ups of generalised pustular psoriasis, an inflammatory skin condition characterised by the appearance of pustules (pus-filled lesions) over large areas of the dermis.

A pivotal study involving 53 adults with moderate to severe flares of generalised pustular psoriasis demonstrated the superiority of spesolimab over placebo in improving disease symptoms. After one week, 54% (19 out of 35) of patients receiving a single dose of spesolimab had no visible pustules, compared to 6% (1 out of 18) of patients receiving placebo. These results were assessed using the GPPGA pustulation subscore (a measure of pustule severity) (Figure 185)[784].

FIGURE 185. NUMBER OF PATIENTS WITH MODERATE TO SEVERE GENERALISED PUSTULAR PSORIASIS WHO ACHIEVED MCIDS IN GPPGA PUSTULATION SUBSCORE (≥2 POINTS), WEEK 1, ACCORDING TO PUSTULE VISIBILITY



Note: MCID = minimally clinically important difference.

Source: Elewski (2023)[784]

Deucravacitinib marks a milestone as the first oral therapy with an innovative mechanism of action approved in a decade to treat adults with moderate to severe plaque psoriasis who are candidates for systemic therapy. In one of the pivotal studies involving patients with this condition, deucravacitinib was compared with placebo. The results revealed a marked improvement in patients' symptoms after 16 weeks of treatment. 58.4% of patients treated with deucra- vacitinib achieved a PASI75, compared to 12.7% of those receiving placebo (P<0.0001)[785].

Tapinarof, represents the first FDA-approved topical therapy with a new chemical compound in the last 25 years[iii] . Its efficacy has been demonstrated in two large 12-week Phase III trials, known as PSOARING 1 and 2. These trials revealed that between 35.4% and 40.2% of patients using 1% tapinarof cream achieved the primary endpoint (consisting of a Physician Global Assessment of 0 or 1 and a decrease of ≥2-5 points at week 12), compared to 6.0%-6.3% for the group using vehicle cream (similar to placebo used in pill or injection trials), respectively[786].

Several studies have corroborated the translation of lesion clearance into improved quality of life for patients. Thus, according to one study, patients with psoriasis who maintain complete clearance (PASI100) have better scores on the DLQI and PSS quality of life indices in the short and long term and greater improvements in the long term, compared to patients with PASI90-99 and PASI75-89. In these groups, 91%, 75% and 43% reported a DLQI = 0/1 (no effect on HRQoL), and 83%, 49% and 21% reported a PSS = 0 (no symptoms) in the long term, respectively (all $p < 0.05$)[787]. In another case, of patients with complete skin clearance (sPGA of 0), 61.4-91.1% reported a DLQI of 0, indicating that psoriasis has no detectable impact on quality of life, compared to 45.7-48.3% who were almost clear. Patients who were completely clear felt that psoriasis had less impact on their leisure activities and daily life[788].

Biological therapies introduced in the 2000s allowed between 4 and 7 out of 10 patients with moderate to severe psoriasis achieve complete or near-complete clearing of their skin lesions.

Armstrong (2015)[781], Reid (2020)[778]

iii *Not approved by the EMA at the time of writing.*

In recent years, the therapeutic arsenal available for moderate to severe psoriasis has expanded, improving the degree of clearance achieved, its speed and its persistence over time. This has significantly improved the quality of life of patients. In addition, a treatment for pustular psoriasis was approved for the first time.

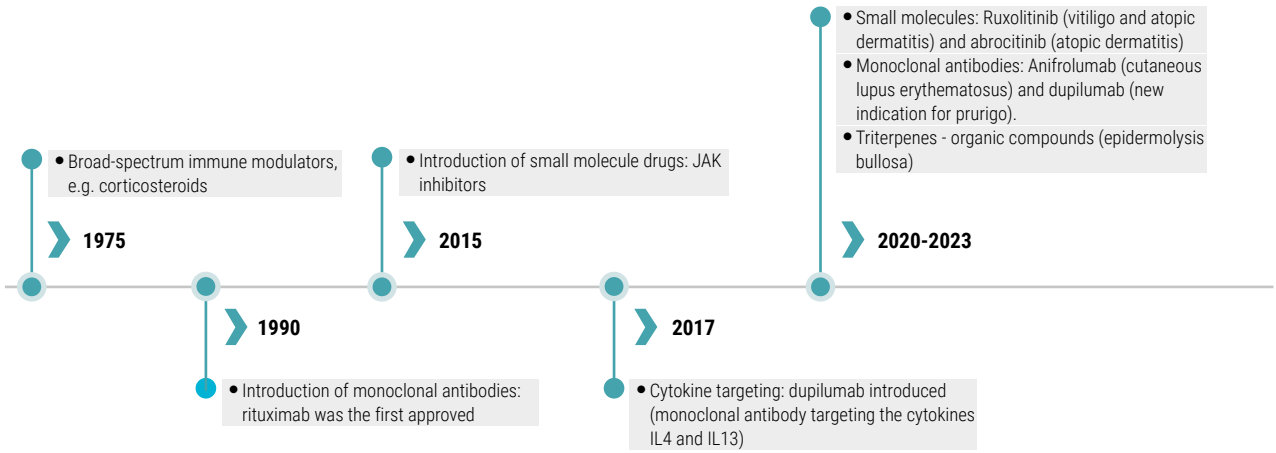
Gordon (2021)[783], Elewski (2023) [784]

OTHER DERMATOLOGICAL IMMUNE-MEDIATED DISEASES

Autoimmune diseases are disorders in which the immune system, which defends the body against infection and damage, mistakenly begins to attack the body's own cells, tissues or organs[789]. They affect approximately 5% of the population and are more common among women. Dermatological autoimmune diseases are those that specifically affect the skin and its structures. These conditions can present themselves in various forms, such as rashes, blisters, lesions and pigmentation changes. Some of the dermatological autoimmune diseases that will be discussed in this section include vitiligo, atopic dermatitis, cutaneous lupus erythematosus and nodular prurigo[iv]. These diseases can have a significant impact on patients' quality of life and require appropriate clinical management to control symptoms and prevent complications[789].

The treatment of autoimmune skin diseases depends on the specific condition. The traditional arsenal of treatments, based on broad-spectrum immunomodulators, has evolved with the introduction of agents with high specificity, arising from monoclonal and molecular biotechnology and highly targeted small molecule synthesis. However, its management often remains a challenge due to its complex pathogenesis and diverse range of clinical manifestations[790].

FIGURE 186. EVOLUTION OF THE MAIN TREATMENTS FOR IMMUNOMEDIATED DERMATOLOGICAL DISEASES



Source: own elaboration based on McInnes (2021)[791] and Alaibac (2023)[790]

iv *Other diseases such as pemphigoid, dermatitis herpetiformis, scleroderma/morphea, vasculitis, among others, were not addressed. This is because there are no pharmacological treatments available, or because of their multiple ramifications and subtypes, which would make them difficult to explain, or because of the level of published evidence on existing treatments.*

Vitiligo

Vitiligo is an acquired skin disorder caused by a loss of pigmentation. It is characterised by well-demarcated depigmented patches resulting from a functional loss or decrease in the number of melanocytes in the mucosa, epidermis and other tissues. Vitiligo can occur in people of any age or gender and affects 0.5%-2% of the world's population. The prevalence of vitiligo is estimated to be 0.76%-1.11% in the United States, 1.6% in Europe and about 2.0% in Spain[792,793].

Although vitiligo is not life-threatening, it can be stigmatising due to the colour difference between the lesion and normal skin, which causes psychological distress, increases the risk of psychiatric disorders and social stress, and affects the quality of life of patients, especially in childhood and adolescence. In addition, vitiligo poses a substantial societal burden, including direct costs for vitiligo health care services and indirect costs due to absentism[792].

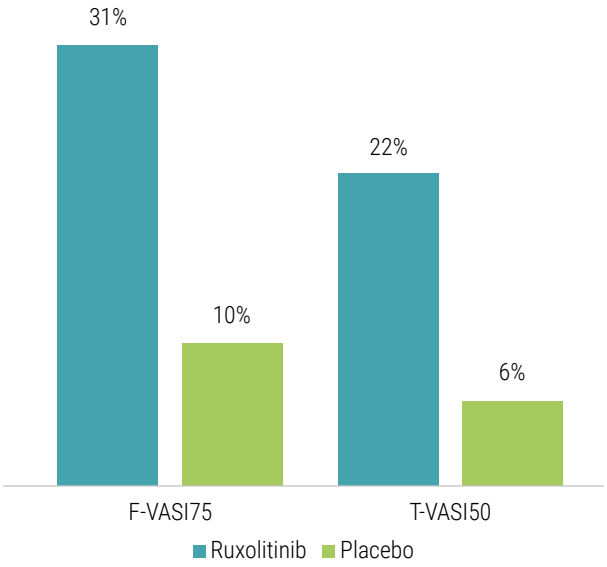
In general terms, treatments include the use of topical steroids and calcineurin inhibitors (tacrolimus and pimecrolimus), which are most appropriate in the treatment of limited disease, usually when up to 10% of the body surface area (BSA) is affected. Second-line treatments involve phototherapy (with NB-UVB and PUVA) and the use of systemic steroids. In more advanced stages, last-line treatment options such as surgical grafting techniques and depigmenting treatments are considered[792].

Combination therapy with topical tacrolimus has been shown to be effective in the treatment of vitiligo, especially in lesions on bony prominences. Several studies indicate that this combination achieves significant repigmentation compared to individual therapies (at least 75% repigmentation in 50% of patients with tacrolimus + EL vs. 19% in those treated with EL alone), with outstanding results in body areas usually resistant to UV radiation (lesion reduction in 42% of patients with tacrolimus + NB-UVB, vs. 29% of patients with NB-UVB alone). In addition, tacrolimus demonstrates efficacy on facial lesions, although its effectiveness may vary according to location.

Significant progress has been made recently, with the approval of ruxolitinib by the FDA (in 2022) and the EMA (in 2023) to treat non-segmental vitiligo. The drug works by inhibiting JAK 1 and 2 enzymes, which are involved in interferon-gamma (IFNgamma) activity. In vitiligo, IFN-gamma plays a role in the activity of immune system cells that attack melanocytes. By blocking JAK1 and JAK2, ruxolitinib reduces the immune system's ability to attack melanocytes, allowing pigment production to continue.

In studies comparing ruxolitinib with placebo, two main aspects were assessed to measure improvement in facial and body repigmentation. One was the standard facial vitiligo score (F-VASI75), which indicates an improvement of at least 75% in facial pigmentation, while the other (T-VASI50) assesses an improvement of at least 50% in body pigmentation. The results showed that patients treated with ruxolitinib were significantly more likely to achieve an F-VASI75 (RR 3.38, 95% CI 2.0-5.72, $p<0.00001$, $I2 = 14\%$) and a T-VASI50 (RR 2.96, 95%CI 1.96 to 4.57; $p < 0.00001$; $I2 = 34\%$) compared to those receiving placebo. Overall, approximately 31% of ruxolitinib-treated patients experienced at least 75% improvement in facial pigmentation after 6 months, in contrast to about 10% of those receiving placebo. In addition, at least 22% of ruxolitinib-treated patients showed a 50% improvement in total body pigmentation, compared to 6% of those receiving placebo (Figure 187)[794].

FIGURE 187. EFFECTIVENESS OF RUXOLITINIB IN THE TREATMENT OF PATIENTS WITH NON-PIGMENTAL VITILIGO, 661 PATIENTS, 6 MONTHS, % OF PATIENTS WHO ACHIEVED IMPROVEMENTS



Note: F-FASI75: standard facial vitiligo score, measuring at least 75% improvement in facial pigmentation. T-VASI50: standard body vitiligo score, measuring an improvement of at least 50%.

Source: Ehsan (2024)[794]

Atopic dermatitis

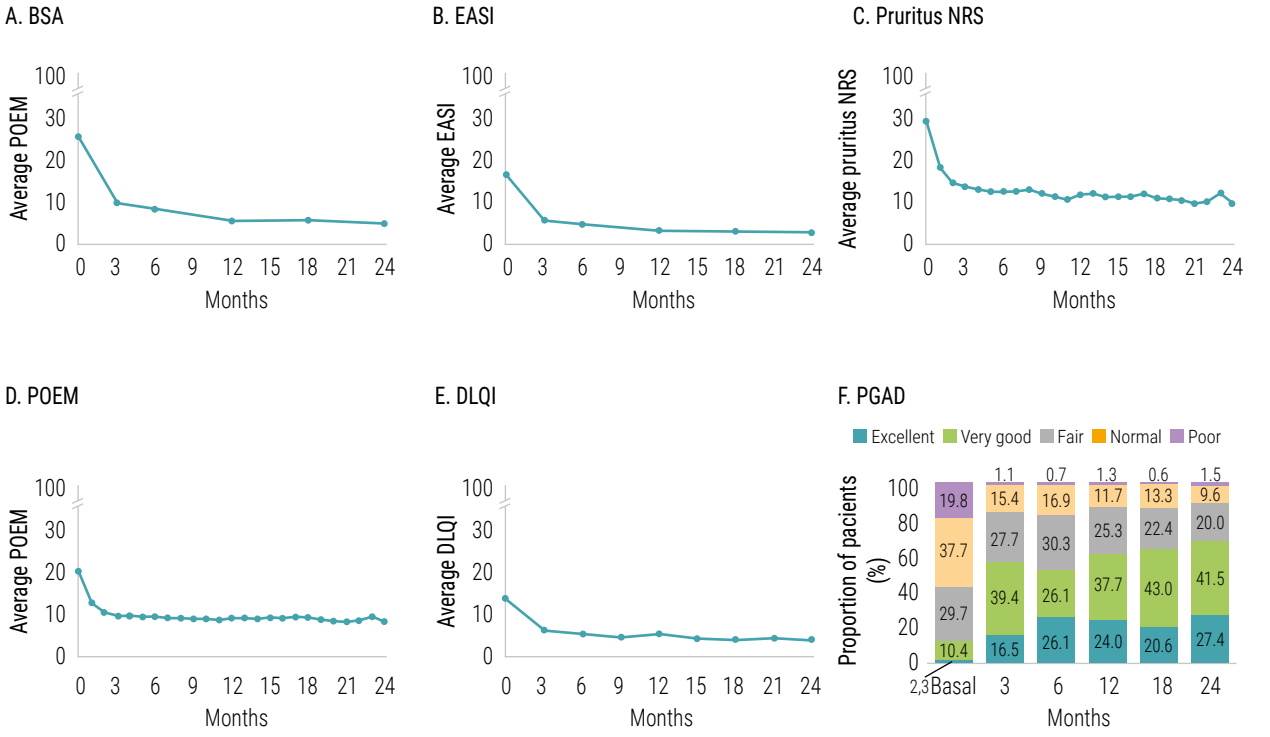
Atopic dermatitis (AD), also known as eczema, is a chronic disease that causes inflammation, redness and irritation of the skin. It usually begins in childhood but can affect people of any age. Symptoms include intense itching, redness, swelling, cracking and flaking. Although the exact cause is unknown, genes, the immune system and environment are thought to play a role[795]. It is one of the most common chronic inflammatory skin conditions, affecting approximately 15-20% of children and 1-3% of adults[796].

Although atopic dermatitis has no definitive cure, it is manageable with appropriate treatments. There are several therapies that can contribute to the control of the symptoms associated with atopic dermatitis, including topical steroid creams, systemic immunosuppressants (oral corticosteroids or cyclosporine for short-term treatment), targeted biologic drugs (dupilumab, tralokinumab) and JAKi (upadacitinib, baricitinib, abrocitinib)[797].

For the last 15-20 years, topical corticosteroids and calcineurin inhibitors were still considered the mainstay of topical treatments in the management of mild forms of atopic dermatitis. However, despite their undisputed efficacy, these drugs, as well as conventional systemic immunosuppressants, are not indicated for long-term continuous use due to their safety profile. There is consensus on the need to use systemic treatment in all patients with moderate-severe AD (patients with extensive eczema and dryness, intense itching leading to incessant scratching and severe limitation of sleep and daily activity) in whom lesions and/or itching are not controlled with topical treatment, whether or not associated with narrowband UV phototherapy (UVB-BE)[798]

The monoclonal antibody dupilumab, which targets the cytokines IL4 and IL13 and was launched in 2017, has been shown to offer a range of long-term benefits to patients with atopic dermatitis in real-world clinical practice. In a registry study involving more than 600 patients and with a median follow-up of 18 months, rapid and sustained improvements in atopic dermatitis signs, symptoms and quality of life were observed with dupilumab treatment, as illustrated in (Figure 188)[799].

FIGURE 188. IMPROVEMENT IN ATOPIC DERMATITIS SIGNS, SYMPTOMS, QUALITY OF LIFE, AND PATIENTS' PERSPECTIVE OF DISEASE FROM BASELINE.



Abbreviations: **BSA:** body surface area, **DLQI:** dermatological quality of life index, **EASI:** eczema area and severity index, **NRS:** numerical rating scale, **POEM:** patient-oriented measure of eczema, **PGAD:** patient global assessment of disease.

Source: Simpson (2024)[799]

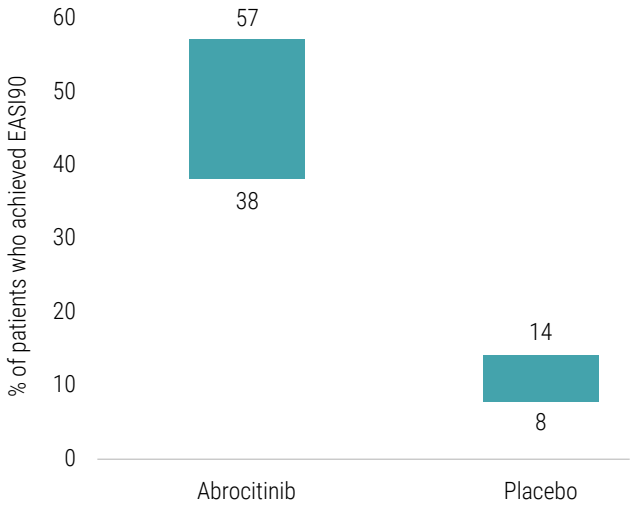
Between 2020 and 2023, two new drugs have been approved for atopic dermatitis, namely ruxolitinib (by the FDA in 2021) and abrocitinib (by the EMA in 2021 and by the FDA in 2022).

Ruxolitinib is a JAK inhibitor indicated in the US for the short-term, non-continuous topical treatment of mild to moderate atopic dermatitis in non-immunocompromised patients aged 12 years and older whose disease is not adequately controlled with prescription topical therapies or when such therapies are not advisable. With this drug, 62-67% of patients achieved complete or near-complete skin clearance, as measured by the Investigator's Global Assessment Index (IGA 0/1), after two months of treatment, compared to 22-24% of placebo patients[800].

Abrocitinib, used to treat moderate to severe atopic dermatitis in adults, is administered to patients for whom topical treatment is not feasible or when treatment results have been insufficient. This medicine blocks the action of enzymes known as Janus kinases, which play an important role in the inflammatory process associated with atopic dermatitis. By blocking these enzymes, abrocitinib helps to reduce itching and inflammation of the skin. In pivotal, observational studies in routine clinical practice, 38-57% of patients treated with abrocitinib had lesion-free or nearly lesion-free skin, as measured by the Eczema Area and Severity Index (EASI90), compared to 8%-14% in the placebo group. In other words, abrocitinib increased patients' likelihood of achieving complete or near-complete clearance of lesions by 3.3 times compared to placebo (Figure 189)[801,802].

Several studies have also corroborated the translation of lesion clearing to improved quality of life in patients with AD. For example, according to a real-life study, the proportion of patients reporting POEM 0-2 and DLQI 0/1 was highest among those with no or minimal itching (73% POEM 0-2; 72% DLQI 0/1) and fair or almost fair skin (46% POEM 0-2; 45% DLQI 0/1)[803].

FIGURA 189. EFFICACY OF ABROCITINIB IN THE TREATMENT OF PATIENTS WITH ATOPIC DERMATITIS, % OF PATIENTS WHO ACHIEVED COMPLETE OR NEARLY COMPLETE SKIN CLEARANCE



EASI90: Eczema Area and Severity Index, which measures an improvement of at least 90% in the degree of skin clearing.

Source: own elaboration based on Zheng (2023)[801] and Kamphuis (2024)[802]

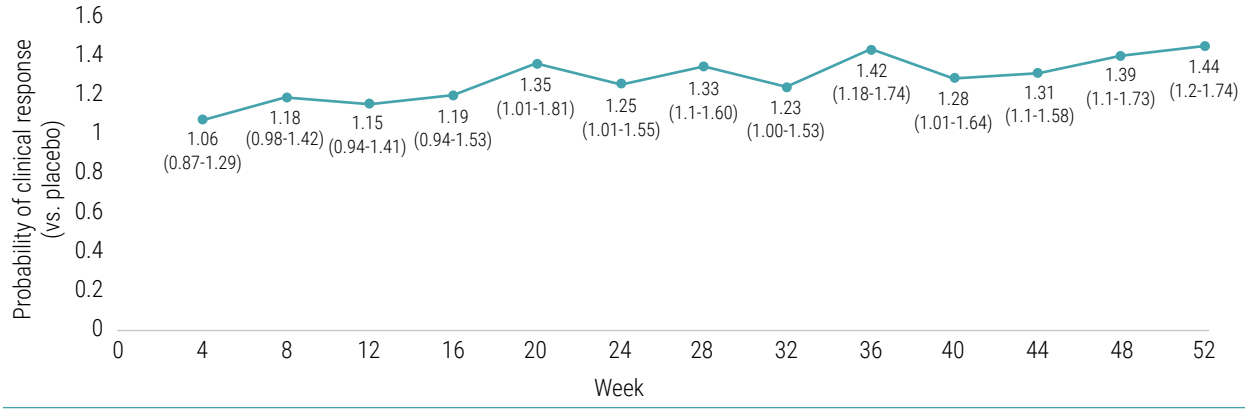
Cutaneous lupus erythematosus

Cutaneous lupus erythematosus (CLE) is a diverse group of autoimmune connective tissue disorders located in the skin that may be associated with systemic lupus erythematosus (SLE) to varying degrees. It is classified into different types, which are acute, subacute, intermittent, or chronic. SCLE has a prevalence of 73 cases per 100,000 people[804]. As with SLE, there is a marked female predominance and it particularly affects women aged 20-50 years. However, all age groups and both sexes can be affected. Up to 75% of SLE patients develop cutaneous signs, and up to 50% of SLE patients develop renal manifestations[804,805].

The treatment of lupus erythematosus includes local therapy (topical steroids, intravenous steroids, intravenous steroids), (antimalarials, usually hydroxychloroquine; immune modulators such as methotrexate, mycophenolate, dapsone, cyclosporine; systemic corticosteroids; belimumab; and anifrolumab, a type I interferon receptor subunit 1 blocker)[804].

Lupus can be an ongoing source of discomfort, however, with proper treatment and frequent clinical follow-up, it is estimated that 80-90 percent of people with lupus will have a normal life expectancy[806]. An example of treatment that produces benefits for patients with CLE (with or without SLE) is evidenced by the use of belimumab, a drug approved by the EMA in 2011, and for which its use has been found to be associated with a robust clinical response of 44%, with a 49% lower risk of relapse during one year of treatment compared to those not using this drug (OR: 0.51 [95% CI, 0.31-0.84]; P<0.001, I2=0%)[807,808]. Clinical response was first observed after 20 weeks of starting treatment with a sustained clinical response thereafter peaking at one year (Figure 190)[808].

FIGURE 190. EFFICACY OF BELIMUMAB IN THE TREATMENT OF PATIENTS WITH CUTANEOUS LUPUS ERYTHEMATOSUS, PROBABILITY OF CLINICAL RESPONSE VS. PLACEBO



Source: Kneeland (2022)[808]

In addition, a new drug has recently been approved as adjuvant treatment in adults with SLE, anifrolumab, which has been shown to reduce disease activity by 47%-48% compared to 30%-32% in placebo patients[809].

Nodular prurigo

Nodular prurigo (NP) is a chronic inflammatory and pruritic skin disease characterised by numerous symmetrically distributed hyperkeratotic nodules, most commonly on the outer surfaces of the extremities and trunk. NP is a relatively rare condition, with an estimated prevalence of 72 per 100,000 individuals, with the majority being between 51 and 65 years of age[810]. NP was first characterised in the early 20th century. The condition is associated with increased rates of mental health, endocrine, cardiovascular and renal disorders, as well as HIV and malignancy[810].

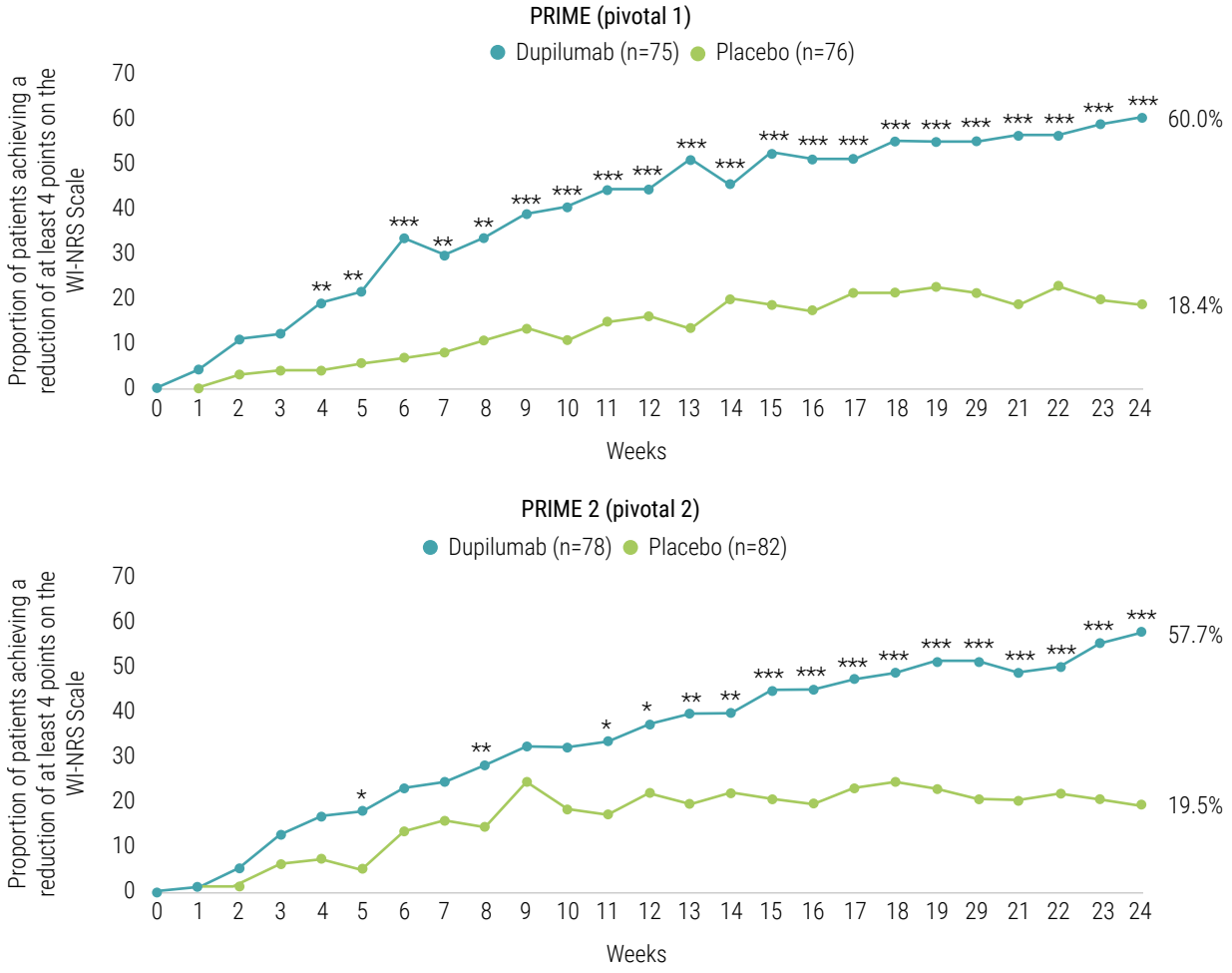
Treatments for prurigo nodularis are aimed at stopping skin itching and include topical corticosteroids, tacrolimus ointment 0.1%, emollients, antihistamines, phototherapy, systemic immunosuppressive treatments (oral corticosteroids or cyclosporine), and biologic drugs (nemolizumab, dupilumab)[811].

The benefits of the various treatments for this condition are unpredictable. Corticosteroids and calcineurin inhibitors have not been effective in moderate to severe cases, although they may provide relief for some symptoms. Immunosuppressants can be used as systemic therapies, but do not address the pathophysiological mechanisms of the disease. Ultraviolet phototherapy may be beneficial in older patients taking multiple medications, although there is no established standard treatment[812].

The US FDA approval of nemolizumab in 2019 has shown promising data by targeting IL-31 and its receptor IL-31RA. In patients with a disease severity scale score of 7-8 out of 10, a reduction of more than 50% has been observed after 4 weeks of treatment, compared to 20% in untreated patients. Improvements in quality of sleep and quality of life have also been reported, as well as a decrease in the number of lesions[812].

In 2022, both the FDA and the EMA approved dupilumab for moderate to severe nodular prurigo in adults. The drug can be used either alone or in combination with topical corticosteroids. Dupilumab is a monoclonal antibody designed to block IL-4 and IL-13 receptors. After six months of treatment, 58% to 60% of patients showed significant improvements in their symptoms, as measured by a reduction of at least 4 points on the Most Intense Itch Rating Scale (WI-NRS), compared to 18% to 19% of patients receiving placebo (Figure 191)[813].

FIGURE 191. EFFICACY OF DUPILUMAB IN THE TREATMENT OF PATIENTS WITH PRURIGO NODULARIS, % OF PATIENTS ACHIEVING SIGNIFICANT IMPROVEMENT IN SYMPTOMS



Source: Yosipovitch (2023)[813]

Traditionally, treatments for dermatological immune-mediated diseases were based on broad-spectrum immunomodulators, with limitations in efficacy and safety. The introduction of other agents, such as monoclonal antibodies and small molecules, has shown significant clinical improvements.

Alaibac (2023)[790], Simpson (2024)[799], Li (2024)[792]

The drugs approved in recent years offer greater specificity and efficacy than those approved in the past. They are associated with improvements in patients' quality of life by reducing the burden of disease and minimising the side effects associated with less specific and more invasive treatments, such as systemic corticosteroids.

Yosipovitch (2023)[813], Zheng (2023)[801], Ehsan (2024)[794], Kamphuis (2024)[802]

INFLAMMATORY BOWEL DISEASES

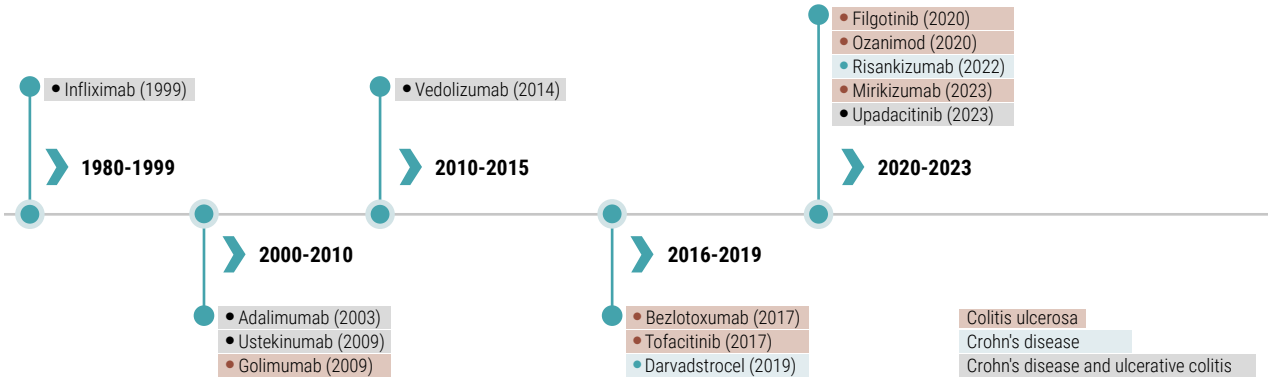
Inflammatory bowel diseases (IBD) are a series of pathologies characterised by inflammation and lesions throughout the gastro-intestinal tract, mainly affecting the intestine[814,815]. In addition to these lesions, IBD can lead to extraintestinal complications, such as musculoskeletal complications (in approximately 20-30% of patients)[816], cutaneous (approximately 10-20%)[817], ocular (10%)[817] and thromboembolic complications which, although with a lower incidence (1.2%-6.1%)[817], are the major cause of IBD mortality[816] . IBD is also associated with a higher incidence of hepatobiliary diseases (10-50% of patients), although these may be caused by other factors unrelated to the disease, such as the use of certain medications, nutritional disorders or the use of parenteral nutrition[818]. Studies also show that IBD patients are more likely to develop colorectal cancer than the general population[819,820]. IBD mainly encompasses two similar but distinct diseases, ulcerative colitis and Crohn's disease.

The global prevalence of IBD has increased in recent years, from 3.3 million cases in 1990 to 4.9 million in 2019, and it is estimated that there are currently 40,998 deaths from this cause[821]. In Spain, a recent population-based study puts the incidence of IBD at 16 cases per 100,000 inhabitants, higher than previous studies and other European countries[822]. The upward trend has also been demonstrated in a study which concluded that both the prevalence and incidence of IBD has increased in recent years, and is expected to continue to do so in the coming years[823].

Although IBD has not been associated with an elevated risk of death, its disease burden has increased worldwide. Both ulcerative colitis and Crohn's disease, due to their symptomatology, chronicity and the fact that both diseases often occur during the most productive time of life, affect all areas of the patient's life: studies, work, social and family relationships[824].

While there is still no curative treatment for IBD, the different treatments available are focused on reducing disease activity, minimising relapses, improving quality of life and avoiding surgery[825]. Specific treatment depends on the type, severity and location of lesions, and has evolved over the past decades (Figure 192)[826].

FIGURA 192. EVOLUTION OF APPROVED TREATMENTS IN EUROPE FOR INFLAMMATORY BOWEL DISEASES, 1980-2024



Source: Own elaboration based on EMA (2024)[826]

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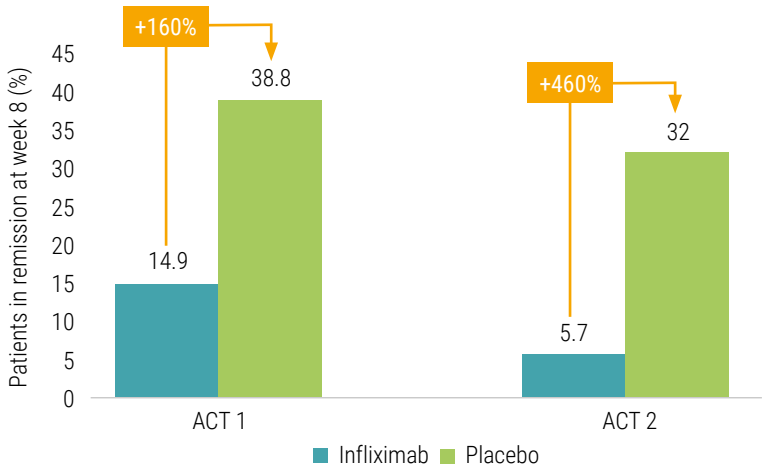
For **ulcerative colitis,** the first successful treatments emerged in the second half of the 20th century with the development of mesalazine and corticosteroids[827]. In recent years, different treatments have been developed for patients who do not respond to first-line therapies or who are in advanced stages of the disease, such as the monoclonal antibodies infliximab, adalimumab, ustekinumab, golimumab, vedolizumab, bezlotoxumab and mirikizumab, JAK pathway inhibitors such as tofacitinib or filgotinib and, more recently, a sphingosine 1-phosphate receptor modulator (ozanimod).

Thus, infliximab was the first anti-TNF monoclonal antibody approved (in 1999) for ulcerative colitis. In the pivotal trial, it demonstrated a 160% improvement in the percentage of patients in remission at week 8 versus placebo. In paediatric patients, infliximab improved outcomes by 461%, achieving clinical remission in 32% of patients versus 5.7% in the placebo group (Figure 193)[828].

FIGURE 193. PERCENTAGE OF ADULT AND PAEDIATRIC PATIENTS IN CLINICAL REMISSION IN THE TREATMENT OF ULCERATIVE COLITIS WITH INFLIXIMAB



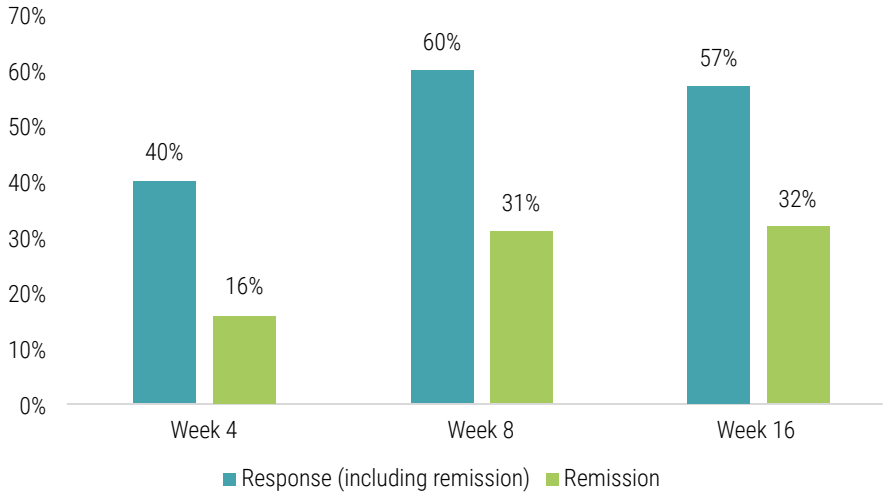
Source: adapted from Rutgeerts (2005)[828]

In the Spanish context, a study with the biologic golimumab in 124 patients with moderate to severe ulcerative colitis showed that 65% of patients achieved clinical response in the short term, while in the long term, 57.7% of patients maintained sustained clinical benefit after a median follow-up of 12 months[829].

In addition to improvements in the reduction of severe flare-ups and disease-related hospitalisations, a key aspect of ulcerative colitis treatment is the improvement of patients' quality of life, especially in cases where the disease manifests in its most severe forms. In this regard, a systematic review of the monoclonal antibodies infliximab, adalimumab, golimumab, vedolizumab and the JAK inhibitor tofacitinib shows that these treatments improve health-related quality of life by at least 16 points in patients with moderate to severe disease, using the inflammatory bowel disease questionnaire or IBDQ[830].

Filgotinib was approved by the EMA in 2020 for refractory patients with moderately to severely active ulcerative colitis. The pivotal trial of the therapy, conducted in 40 countries, showed that after 58 weeks of treatment, 37% of patients treated with filgotinib had clinical remission compared to 11% in the placebo group[831]. The real-life effectiveness in Spain of another JAK inhibitor, tofacitinib, has been evaluated in a study conducted in 82 centres with patients refractory to biologic therapy. At week 8 of treatment, approximately one third of patients achieved disease remission, and about two thirds responded to treatment. Positive results were also obtained at 4 weeks, confirming the rapidity of treatment response (Figure 194)[832].

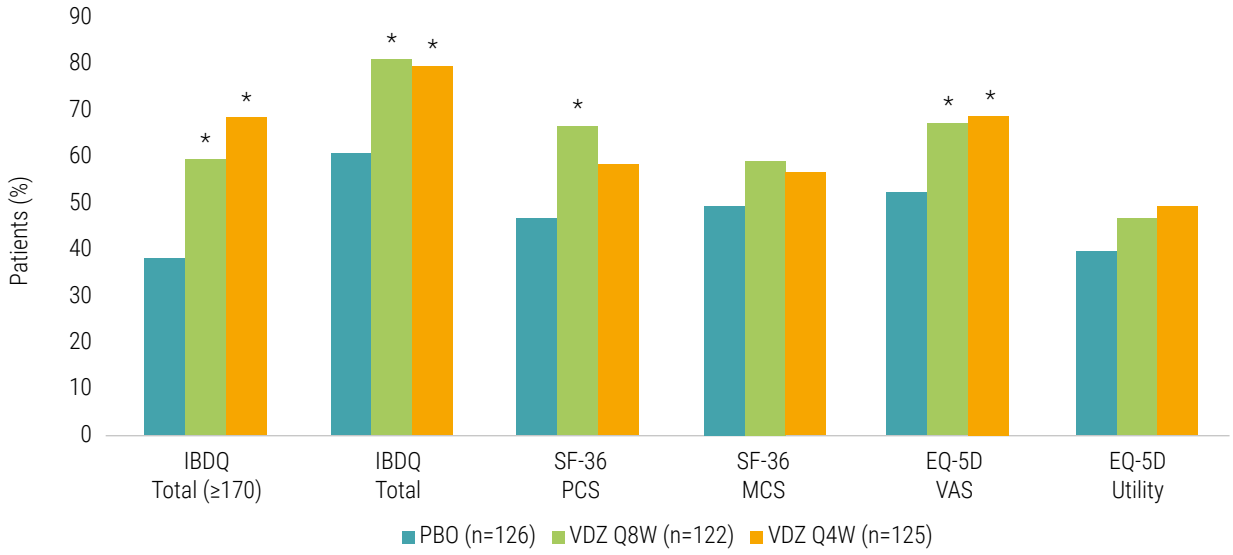
FIGURE 194. SHORT-TERM EFFECTIVENESS OF TOFACITINIB IN PATIENTS WITH ULCERATIVE COLITIS, SPAIN



Source: Chaparro (2021)[832]

An example of improvement of ulcerative colitis treatment in terms of quality of life is found in a study assessing variation in patient-perceived quality of life on two generic quality of life questionnaires (SF-36 and EQ-5D) and one specific to IBD (IBDQ). This study shows that treatment with vedolizumab is associated with a higher proportion of patients achieving high scores on the IBDQ, either in 4-weekly or 8-weekly regimens. Also, more patients reached the minimum thresholds of clinically important difference on the IBDQ. Using generic quality-of-life questionnaires, vedolizumab treatment on both regimens resulted in statistically significant differences on the EQ-5D VAS scale and the SF-36 physical scale (only in the every-8-week treatment) (Figure 195)[833].

FIGURE 195. QUALITY OF LIFE OUTCOMES ACCORDING TO DIFFERENT QUESTIONNAIRES IN THE TREATMENT OF ULCERATIVE COLITIS WITH VEDOLIZUMAB

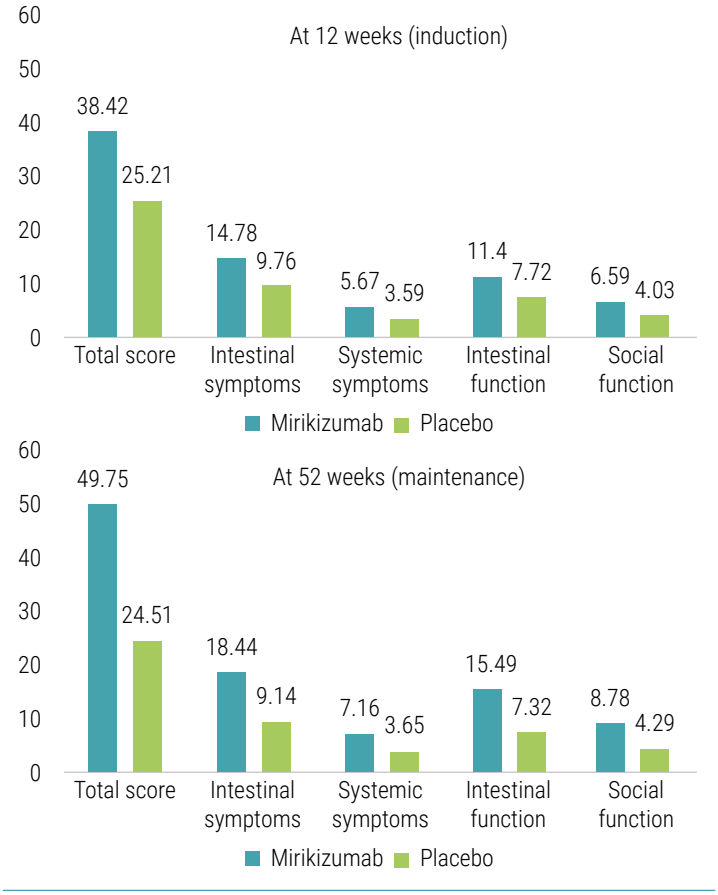


Abbreviations: **EQ -5D:** EuroQol 5 dimensions; **IBDQ:** Inflammatory Bowel Disease Questionnaire; **MCS:** mental component summary; **PBO:** placebo; **PCS:** physical component summary; **SF -36:** 36-item short form health survey; **VAS:** visual analogue scale; **VDZ Q4W:** vedolizumab every 4 weeks; **VDZ Q8W:** v edolizumab every 8 weeks.

*: statistically significant

Source: Feagan (2017)[833]

FIGURE 196. QUALITY OF LIFE OUTCOMES (IBDQ) OF PATIENTS WITH MODERATE-SEVERE ULCERATIVE COLITIS, AT 12 AND 52 WEEKS OF TREATMENT WITH MIRIKIZUMAB AND PLACEBO



Source: Sands (2023)[834]

Another example is a study that evaluated the efficacy of mirikizumab on patients' quality of life at 12 and 52 weeks of treatment. The IBDQ (Inflammatory Bowel Disease Questionnaire) total score improved significantly ($p<0.001$) in the mirikizumab group compared to placebo in both the induction and follow-up periods, showing a significant improvement in all IBDQ scores compared to placebo (Figure 196)[834].

Traditional treatment of **Crohn's disease**, based on aminosalicylates such as mesalazine, corticosteroids and conventional immunosuppressive drugs, does not provide an adequate long-term response[835], leading to the introduction of biologics.

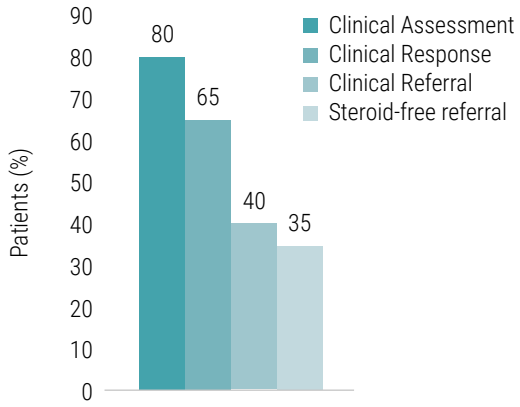
The first biologic drug approved for Crohn's disease was infliximab, an anti-TNF monoclonal antibody, whose use in several studies reported disease remission, increased healing of the intestinal mucosa and improved clinical status of patients with fistulas[836,837].

Although the first monoclonal antibodies were a breakthrough in the treatment of Crohn's disease, some patients experienced intolerance or lack of response, so these patients often go through different treatments, in search of the one that brings the greatest improvement in health. In this regard, a Spanish study assessed the effect of adalimumab over one year in patients intolerant or unresponsive to infliximab. The study showed that 85% of patients achieved a clinical response and 42% achieved remission by week 4. In addition, the use of this drug did not lead to serious adverse or infectious effects[838].

In another study, conducted in Spain, treatment with ustekinumab in Crohn's disease in patients highly refractory to previous treatments revealed clinical remission in 90% of patients with a Harvey-Bradshaw index score of less than 4 (n=88). In the remaining study patients (n=217) 58% of patients achieved clinical remission[839]. Real-world studies have shown that this treatment is not only effective and safe in the short term, but also in the long term, with a probability of maintaining clinical remission of 84%, 74% and 66% at 6, 12 and 18 months, respectively[840].

Another monoclonal antibody launched on the market in the last decade for the treatment of Crohn's disease has been vedolizumab which, because it is directed at a different therapeutic target to other monoclonal antibodies, opened up a new avenue of treatment for patients with no response to available biologics. In this regard, a study of 149 patients with intolerance or non-response to biologics showed that after 14 weeks of follow-up, 80% of patients had demonstrated clinical response as assessed by the physician, while 65% of patients demonstrated response based on the Crohn's disease index score. Similarly, 40% achieved clinical remission while 35% achieved steroid-free remission (Figure 197)[841].

FIGURE 197. EFFICACY IN THE TREATMENT OF CROHN'S DISEASE AT 14 WEEKS WITH VEDOLIZUMAB



Source: adapted from De Vos (2018)[841]

Similarly, a systematic review and meta-analysis conducted to test the real-world effectiveness of vedolizumab in Crohn's disease showed that 30% of patients achieved clinical remission after 12 months. Also, the percentage of patients achieving clinical remission free of corticosteroids was 32% and 42% at 6 and 12 months, respectively[842].

On the other hand, anal fistulas are common manifestations of Crohn's disease that are treated with surgical and/or pharmacological therapy. Until the approval of darvadstrocel in 2019, pharmacological treatment included only antibiotics (metronidazole and/or ciprofloxacin), immunosuppressants (azathioprine or mercaptopurine) and/or anti-TNF. However, these allogeneic expanded stem cells extracted from adipose tissue allow better results to be achieved. According to the latest follow-up report available from Valtermed (June 2022), after six months of treatment, closure of all fistulas was achieved in 69% of treated patients and 96% were free of abscesses larger than 2 cm[843].

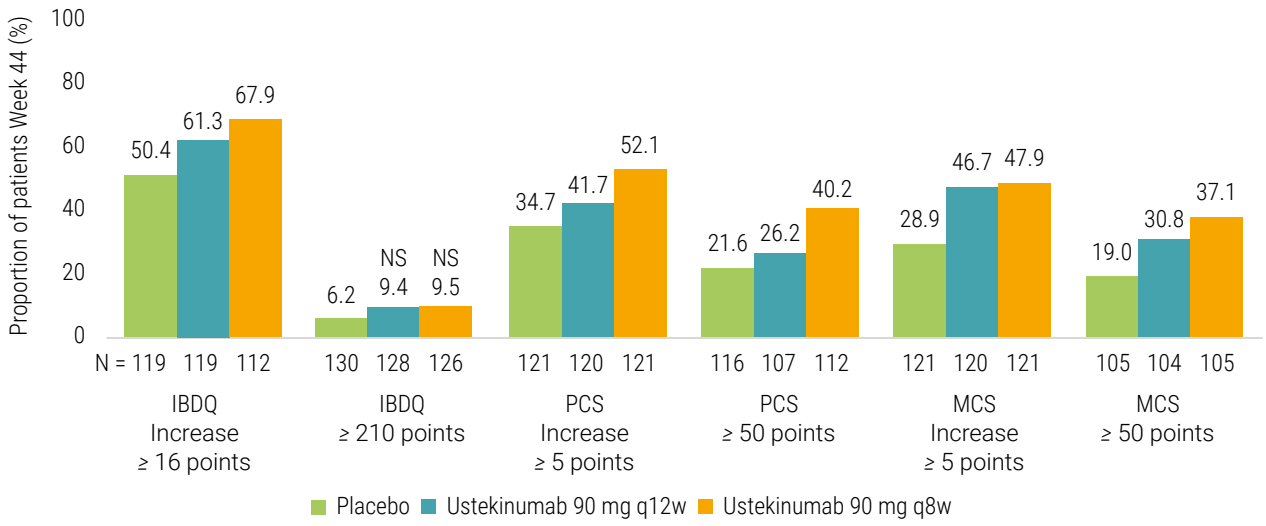
The EMA also approved risankizumab, a monoclonal antibody designed to bind to and block the activity of interleukin-23 (IL-23). A study of 542 patients who responded to treatment looked at the efficacy of maintenance therapy administered subcutaneously every 8 weeks. After one year, about 52% of those receiving risankizumab were in remission and 47% had an endoscopic response, compared to 40% and 22%, respectively, of those receiving placebo[844].

In 2023, the EMA approved upadacitinib for Crohn's disease. The efficacy of this JAK was assessed at week 52 by classifying patients as responders (clinical response at week 52). 16) and double responders (clinical and endoscopic response at week 12 and 16, respectively), with a higher proportion of patients achieving clinical remission (73% and 52%, respectively), as well as an endoscopic response of 50% (69% and 45%, respectively) and a CDAI<150 (69% and 55%, respectively), compared to the control group[845].

In terms of quality of life, biologics have also made progress in Crohn's disease. Treatment with adalimumab has reported improvements in quality of life in several studies[846,847]. One study, conducted in Spain, reported improvements in HRQoL in patients with stable disease control. In this study, following the IBDQ, normalisation of HRQoL levels was observed in 46% of patients before treatment, increasing to 68% after 6 months of control and stabilising in 78% during the follow-up period (36 months)[846].

Similarly, a study of the pivotal UNITY-1 and UNITIY-2 trials has shown that ustekinumab treatment improved patients' quality of life, using the IBDQ and SF-36 health-related quality of life measurement tools at 44-week follow-up (Figure 198). According to the IBDQ, 67.9% of patients who received ustekinumab in the 8-week regimen had a significant clinical improvement over placebo (50.4%). On the SF-36 physical and mental component scores, the two ustekinumab groups (infusion every 8 and 12 weeks) had significantly higher proportions of patients with clinically significant improvement (>5 increase from baseline) than the placebo arm[848].

FIGURE 198. HEALTH OUTCOMES BY IBDQ AND SF-36 AT WEEK 44 WITH USTEKINUMAB IN CROHN'S DISEASE

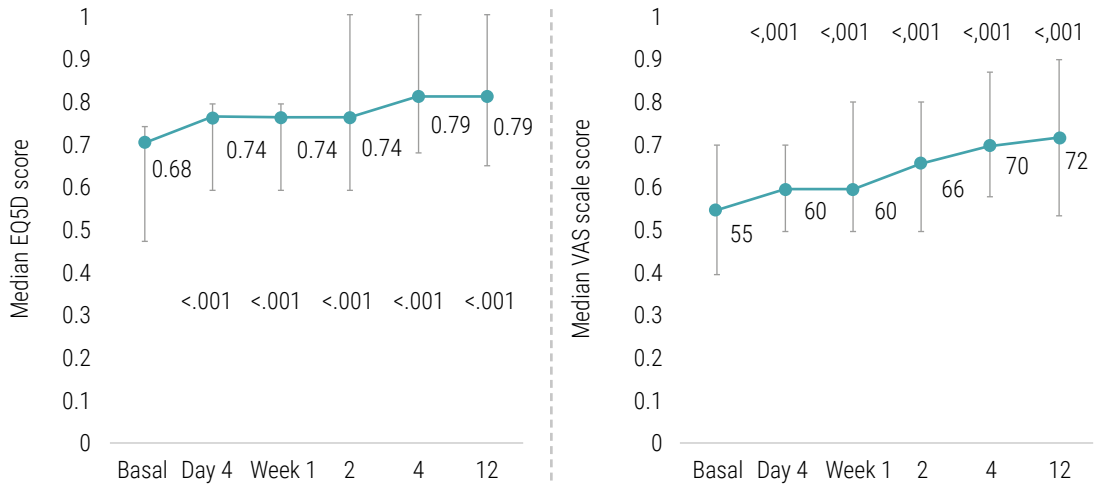


Abbreviations: **IBDQ:** Inflammatory Bowel Disease Questionnaire; **MCS:** mental component summary score; **NS:** not statistically significant; **PCS:** physical component summary score; q8w: every 8 weeks; **q12w:** every 12 weeks; **SF-36:** 36-item short form health survey

Source: Sands (2018)[848]

Biologics allow IBD patients to lead a life that is in many cases normal. This has been evidenced in studies such as that of Thomas et al. (2022), where 65% of patients with clinically active disease treated with tofacitinib reported improved productivity at six months follow-up[849] . Some studies show how the improvement in quality of life derived from the use of biologics is transferred to generic quality of life questionnaires, such as the Euroqol-5D. An example is found in a study evaluating the impact on quality of life of adalimumab therapy in adult patients with moderate-severe CD in Spain[850], in an open-label, single-arm, prospective, multicentre clinical trial with 86 patients. Clinical disease activity was reduced from a median of 9.0 to 6.0 points at day 4 and all QoL scores improved significantly and inflammatory biomarkers decreased significantly from day 4 (p<0.0001), with improvements carried over to EQ-5D (Figure 199).

FIGURE 199. CHANGE IN EQ-5D INDEX SCORE (A) AND EQ-5D EVA SCORE (B) IN PATIENTS WITH CROHN'S DISEASE TREATED WITH ADALIMUMAB



Source: Marín-Jiménez (2022)[850]

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The treatment of inflammatory bowel diseases has evolved positively. The first treatments based on corticosteroid regimens to control exacerbations, to the advent of biologic drugs and advanced therapies that have allowed patients to live a "normal" life in many cases

Vermeire (2004)[835], De Vos (2018)[841], Paschos (2018)[830], Marín-Jiménez (2022)[850], Sands (2023)[834], Chaparro (2021)[832], Thomas (2022)[849]

MIGRAINE

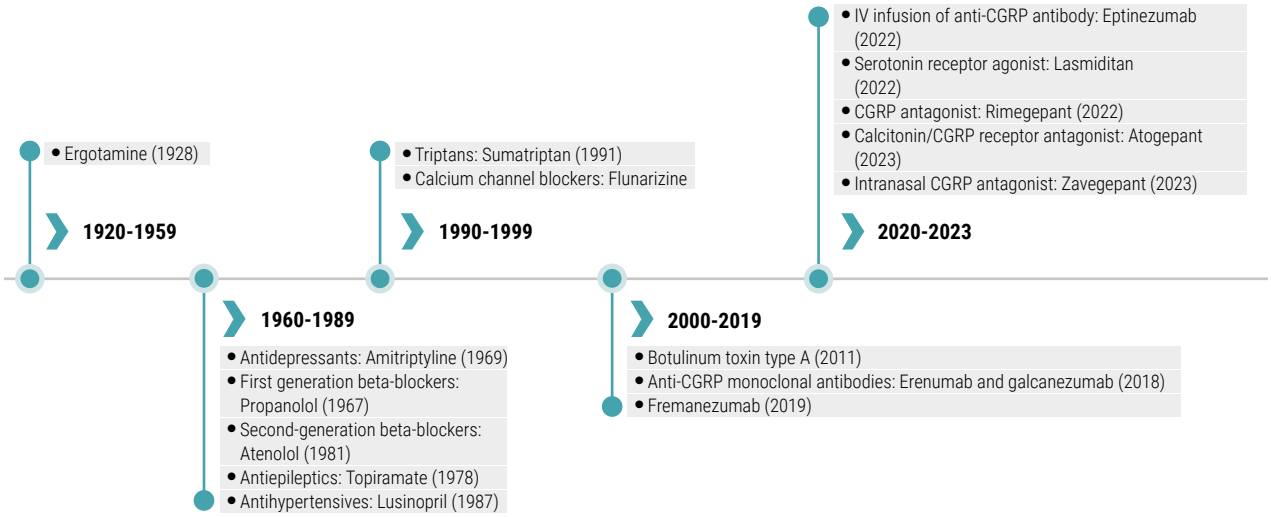
Migraine is the third most common disease in the world and the second most common cause of disability[851], with a global prevalence estimated at 1.1 billion [95%CI: 0.98-1.3] cases in 2019[852] . Migraine affects around 14% of the European population, mainly women (approximately 80% of cases) in middle age (20-50 years). In Spain, migraine affects more than 5 million people, of whom 1.5 million suffer from chronic migraine, i.e. they experience headaches for more than 15 days per month[853].

Acute episodes of migraine, as well as its associated comorbidities (depression, respiratory disorders and cardiovascular risks, among others), significantly affect the physical, psychosocial and mental well-being of the patient[854–856]. Chronic migraine also has significant implications in the workplace. Results from a study conducted in France, Germany, Italy, Spain and the UK showed that these patients reported higher levels of absenteeism (14.4% vs. 9.5%) and general work impairment (38.7% vs. 23.3%) than patients without migraine[857]. Migraine is the leading cause of lost days due to disability in the world among those under 50 years of age[858]. In addition to time lost from paid work, migraine causes substantial socio-economic losses in unpaid work activities due to its high prevalence among women[137].

The therapeutic approach of migraine is based on symptomatic treatment of migraine attacks and their prevention. The main objectives of symptomatic treatment are the rapid and consistent recovery of symptoms such as pain without recurrences, as well as the patient's functional status, minimising the need for repeated doses or rescue medication and achieving optimal self-care while avoiding the use of healthcare resources, all with the least possible adverse events (AE).

Greater understanding of the pathophysiology of the disease has led to the development of more specific and effective therapies for migraine. The main therapeutic advance in this pathology came with the appearance of 5-HT1B/1D receptor agonists, commonly known as "triptans", which were the first specific drugs for the symptomatic treatment of migraine, and which have a higher level of efficacy and a better safety profile than the ergot drugs[859]. In subsequent years, botulinum toxin A was approved as a treatment option for patients with episodic migraine (EM) or chronic migraine (CM) who are refractory to treatment and cannot be controlled with standard treatments. Generally, the preventive therapeutic arsenal is similar for EM and CM, including beta-blockers (metoprolol, propranolol), antiepileptics (topiramate, valproic acid), calcium antagonists (flunarizine), antidepressants (amitriptyline, venlafaxine) and antihypertensives (candesartan, lisinopril). Further progress has been made with the development of personalised medicine, with monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) receptor, including parenteral monoclonal antibodies (erenumab, galcanezumab, fremanezumab, eptinezumab)[860,861]. More recently, a more selective drug has been approved, which unlike the triptans, only stimulates one of the serotonin receptors, 5-HT1F, and new anti-CGRP therapies known as "gepan-tes" including two oral drugs (rimegepant and atogepant), and the first inhaled option (zavegepant) (Figure 200).

FIGURE 200. EVOLUTION OF MIGRAINE TREATMENTS



Note: The chronology shows the leading migraine medicines by class and year of first approval in the US and/or EU market.
Abbreviations: **CGRP:** calcitonin gene-related peptide receptor; **IV:** intravenous.

Surce: own elaboration adapted from Mínguez-Olaondo (2024)[862]; Medical News Today (2022)[863]; FDA (2020-2023)[365–367,404]

Several clinical trials have shown that botulinum toxin A therapy can improve migraine duration and the number of total and severe attacks per month[859,864–867]. For example, according to data from the PREEMPT trial, which involved 1,400 patients in the United States, the use of botulinum toxin A (onabotulinumtoxin A, ONA) resulted in 49% of patients treated in a first cycle (24 weeks) seeing a reduction of more than 50% in the frequency of painful days, with an additional 11% in a second cycle[866]. A long-term follow-up of the safety and efficacy of this therapy (REPOSE study) showed that treatment with ONA improved the health status of patients, reducing the frequency of headache days (from 20.6 to 7.4 days) at the end of the study. Furthermore, this treatment significantly improved both the median scores on the EQ-5D quality of life questionnaire and the migraine-specific quality of life questionnaire (MSQ)[868]. Subsequently, a multicentre observational study was conducted in a population of 725 patients living in Spain. At one-year follow-up, 79.3% of chronic migraine patients treated with ONA demonstrated a 50% reduction in the number of headaches[869].

More recently, a study was published that investigated the effects of a 3-month treatment session with ONA in patients with chronic migraine. After treatment, the intensity of neck pain and migraines decreased by almost half ($p< 0.001$). The median number of headache days per month decreased from 20 to 6 days ($p< 0.000$). Furthermore, the quality of life level, which was severely affected with a score of 68 points before treatment as measured by the Headache Impact Test, HIT-6, decreased to a substantial effect with 58 points after treatment ($p< 0.001$)[870].

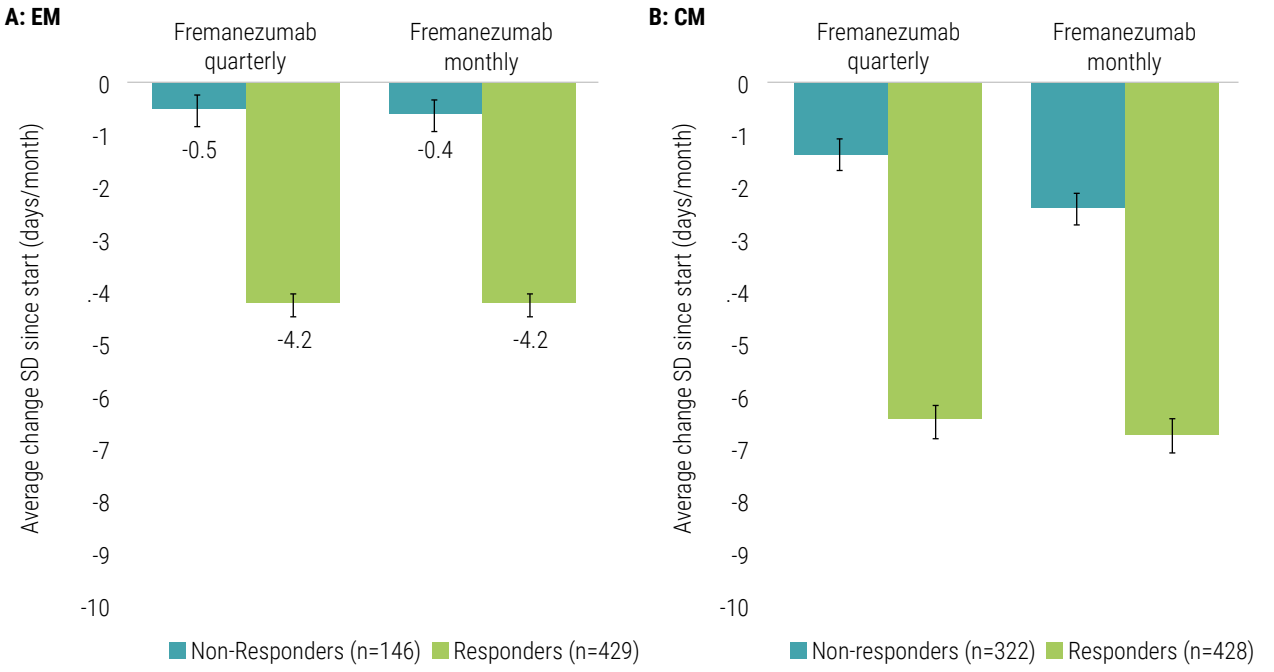
Anti-CGRP monoclonal antibodies (erenumab[871], galcanezumab[872] and fremanezumab[873]) act as inhibitors of the CGRP receptor, significantly reducing both episodic and chronic migraine episodes in patients with migraine at least 4 days per month[874]. These approvals opened up a range of possibilities for patients, providing practitioners with more options for the treatment of the disease, especially in patients whose previous therapies have not produced sustained results over time or had adherence problems[733].

Migraine prophylaxis often requires long-term treatment, which can affect adherence due to the need for multiple daily doses and low tolerability of classical treatments such as beta-blockers, antidepressants and antiepileptics. Anti-CGRP monoclonal antibodies, administered monthly or quarterly, promise to improve adherence due to their lower frequency of administration and better tolerability. An example of the efficacy of this therapeutic group is galcanezumab reported in a study of 3 clinical trials (EVOL- VE-1, EVOLVE-2 and REGAIN). The study, conducted on 1,773 patients from different countries (including Spain), shows that more than 40% of patients treated with

the drug obtained a response over 3 months with a follow-up of more than 50%[875]. A total of 89.3% of participants reported benefit from galcanezumab treatment. Treatment with galcanezumab resulted in a decrease in frequency (80.0%), severity (85.7%) and use of acute medication for migraine attacks (71.4%)[876].

Fremanezumab has been shown to be effective in patients with MoE or CM who received this monoclonal antibody quarterly or monthly during the 12-week randomised, double-blind, placebo-controlled HALO EM and HALO CM trials. In a subsequent analysis, 857 participants from the HALO trials who were identified as responders (ME: 429 [73.8%]; CM: 428 [56.7%]) were selected to analyse the clinical benefit in this cohort relative to the general population with the condition. Over 12 weeks of treatment, mean monthly migraine days (MDD) in responders to EM therapy decreased by 5.4 days with quarterly fremanezumab and 5.5 days with monthly fremanezumab (58.5% and 60.2% reductions, respectively), which were greater than those observed in the general EM population (quarterly: -3.4 days, 37.0% reduction; monthly: -3.7 days, 41.6% reduction). Among responders to CM treatment, MDD decreased by 8.7 days with quarterly fremanezumab and 9.1 days with monthly fremanezumab during the study period (53.7% and 57.0% reductions, respectively). These reductions were also greater than those in the general CM population (quarterly: -4.9 days, 30.2% reduction; monthly: -5.0 days, 31.3% reduction) (Figure 201)[877]. In addition, greater reductions in mean number of days of acute headache medication use, greater reductions in headache-related disability scores and superior improvements in HRQoL were observed among patients responding to therapy with both episodic and chronic migraine compared to general populations[877].

FIGURE 201. MEAN CHANGE SINCE BASELINE IN AVERAGE MONTHLY MIGRAINE DAYS BETWEEN RESPONDERS AND NON-RESPONDERS TO FREMANEZUMAB TREATMENT IN PATIENTS WITH EPISODIC MIGRAINE (A) AND CHRONIC MIGRAINE (B)



Abbreviations: EM: episodic migraine; **SD:** standard deviation; **CM:** chronic migraine.

Source: Silberstein (2021)[877]

Preventive treatment is indicated for patients who suffer three or more migraine attacks per month, as it is the chronic nature of the headache that most reduces quality of life. In this context, preventive therapy aims to reduce the frequency and severity of attacks, improving self-perceived quality of life and the degree of disability[878–880]. Anti-CGRP monoclonal antibodies specifically target the pathophysiology of migraine and are effective and safe treatment options, particularly for patients who have contraindications or have not previously responded to other therapies[881]. Preventive treatment of migraine with anti-CGRP monoclonal antibodies has been shown to have a positive effect on patients' HRQoL[882].

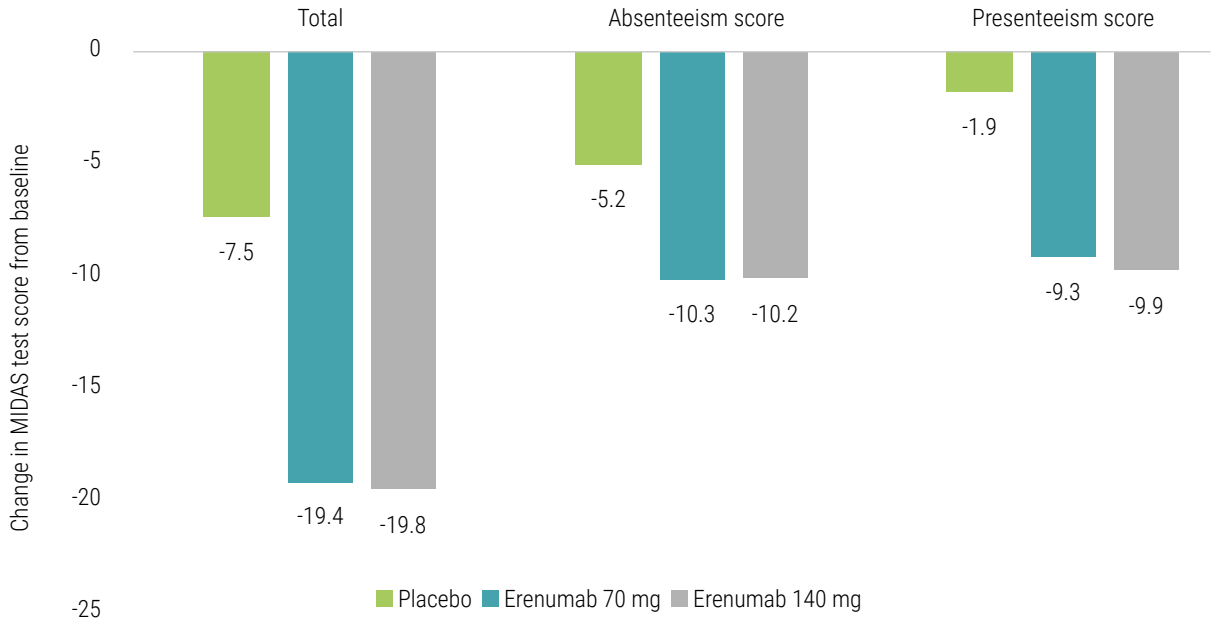
Several studies have demonstrated the benefits of pharmacological therapy, both preventive and acute treatment of attacks, on the health and quality of life of patients[883–889]. One of them, based on data from 9 developed countries, including Spain, showed that migraine-specific medication reduces the duration of both chronic and episodic headache by more than 60%[855].

Another example, from a study conducted in Portugal, is that six months of preventive pharmacological treatment of episodic migraine without aura not only reduced the frequency of migraine attacks to less than one third, but also substantially improved the patients' quality of life. After treatment, significant improvements were observed in patients' physical role, bodily pain, vitality, social function, mental health and overall health[890]. On the other hand, according to a study conducted in Spain, the use of rizatriptan during migraine attacks has been shown to improve patients' self-perceived quality of life after only 3 months of treatment, relieving symptoms, improving physical role and reducing pain, as well as enhancing patients' social function[889].

More recently, a significant deterioration in headache impact and generic HRQoL of migraine patients has been demonstrated after discontinuation of anti-CGRP monoclonal antibody therapy. HRQoL was assessed at the time of the last injection of these therapies (V1), eight weeks later (V2) and sixteen weeks later (V3). The observed deterioration is above the minimum clinically important differences established for each of the questionnaires and can therefore be considered clinically significant. The study cohort consisted of n= 61 patients (n= 29 treated with erenumab and n= 32 with galcanezumab or fremanezumab). The HIT-6 total score was 59.69±6.90 in V1 and increased by 3.69±6.21 in V3 ($p<0.001$), indicating a greater impact of headache on patients' lives. The mean total EQ-D5-L5 score decreased from 0.85±0.17 in V1 to -0.07±0.18 in V3 ($p= 0.013$). The SF-12 mental and physical component scores significantly worsened during treatment discontinuation, namely the PCS-12 total score decreased by -4.04± 7.90 from V1 to V3 ($p= 0.013$) and the MCS-12 score by - 2.73±9.04 ($p= 0.003$)[882].

In relation to the quality of life benefits of anti-CGRP monoclonal antibodies, one study showed that erenumab treatment resulted in improvements over baseline using the Migraine Disability Assessment Scale (MIDAS), a tool designed to measure the impact of migraine on a person's daily life. It consists of five questions that quantify the number of days in the past three months when migraine has affected three main areas: work or school, household chores, and social or recreational activities. Following this scale, erenumab-treated patients had a decrease in disability score of 19.4 on the 70mg regimen and 19.8 on 140mg versus a 7.5 point decrease on placebo at 3-month follow-up. Similarly, erenumab had better scores on measures of absenteeism and presenteeism (Figure 202)[891]. Notably, results from a recently published study simulating the incremental benefits of erenumab versus standard treatment show that prescribing erenumab to the indicated population in Germany could lead to a reduction of 166 million migraine days per year[137].

FIGURE 202. IMPACT OF ERENUMAB MIGRAINE TREATMENT ON PATIENT QUALITY OF LIFE (MIDAS SCALE)



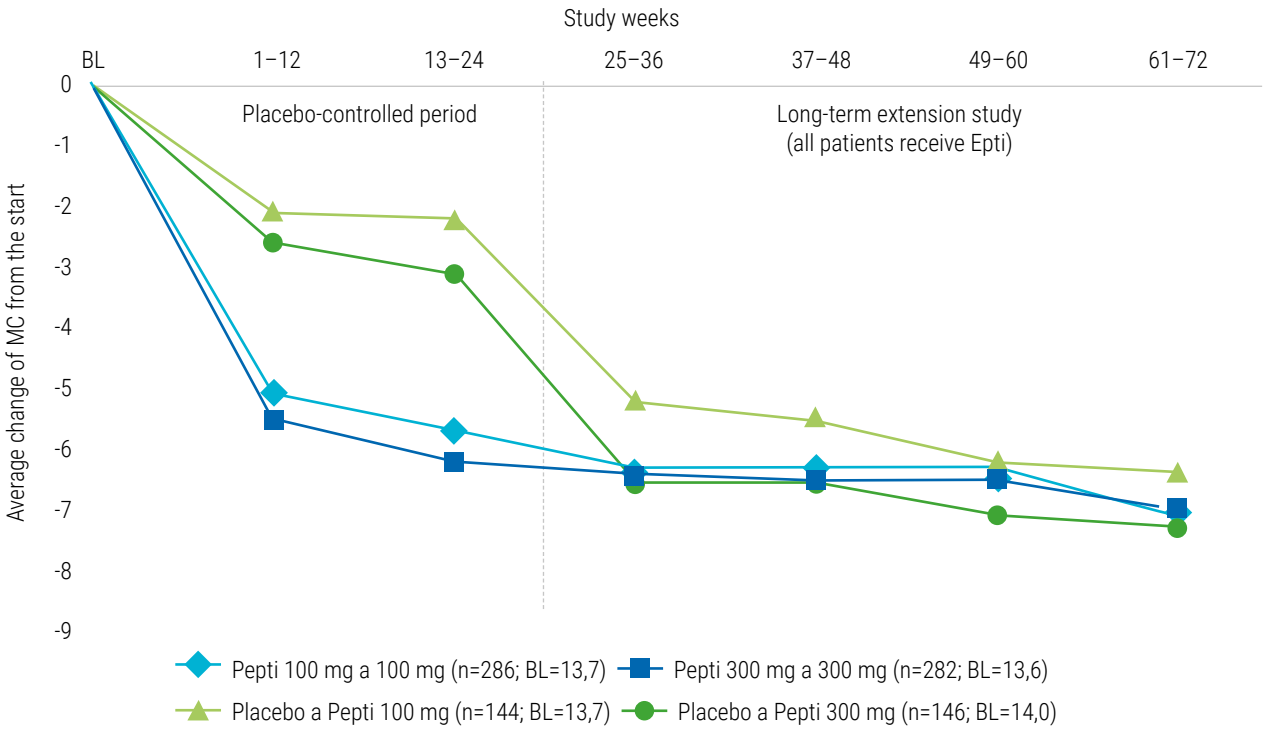
Source: adapted from Lipton (2019)[891]

In addition to improving quality of life, it is important to achieve improvements in other aspects such as improving adherence, which allows patients to better control their treatment. In this regard, a single pill combining sumatriptan and naproxen sodium in monotherapy was marketed by the FDA in 2008. After 1 year, 83% of patients treated with this pill were satisfied or very satisfied with its efficacy, a substantial improvement in the degree of satisfaction with the treatment, as only 35% were satisfied or very satisfied with the efficacy of their previous treatment[892].

In recent years, innovative medicines have been approved for the treatment of migraine that have also led to a significant improvement in terms of quality of life and a decrease in the average number of migraine days per month. Firstly, the approval of eptinezumab in 2022 in Europe for the preventive treatment of migraine in adults[893], being the first anti-CGRP monoclonal antibody administered by intravenous infusion at a dose of 100 mg every 3 months[894].

Eptinezumab demonstrated efficacy in adults with migraine and previous preventive treatment failures in the placebo-controlled phase of the DELIVER clinical trial and its long-term efficacy in this population has been tested in a long-term extension study. For patients randomised to placebo during the placebo-controlled period, who only initiated eptinezumab treatment in the long-term extension, the first dose of eptinezumab produced on average a pronounced decrease in MMD relative to baseline (weeks 25-28: -5.8 [0.50] MMD, placebo/100 mg; -7.2 [0.50] MMD, placebo/300 mg), similar to that observed with first eptinezumab treatment in the placebo-controlled period. In all groups, mean MMD reductions were maintained until the final assessment (Figure 203). In addition, reductions in headache severity and acute medication use were observed, as well as improvements reported by patients receiving eptinezumab in most bothersome symptoms, disease status, quality of life and work productivity[895].

FIGURE 203. CHANGE FROM BASELINE IN MIGRAINE DAYS PER MONTH FOR PATIENTS RECEIVING EPTINEZUMAB IN THE PLACEBO-CONTROLLED PHASE AND IN THE LONG-TERM EXTENSION STUDY



Abrevations: BL: baseline; **LC:** least squares; **Epti:** eptinezumab.

Source: Ashina (2023)[895]

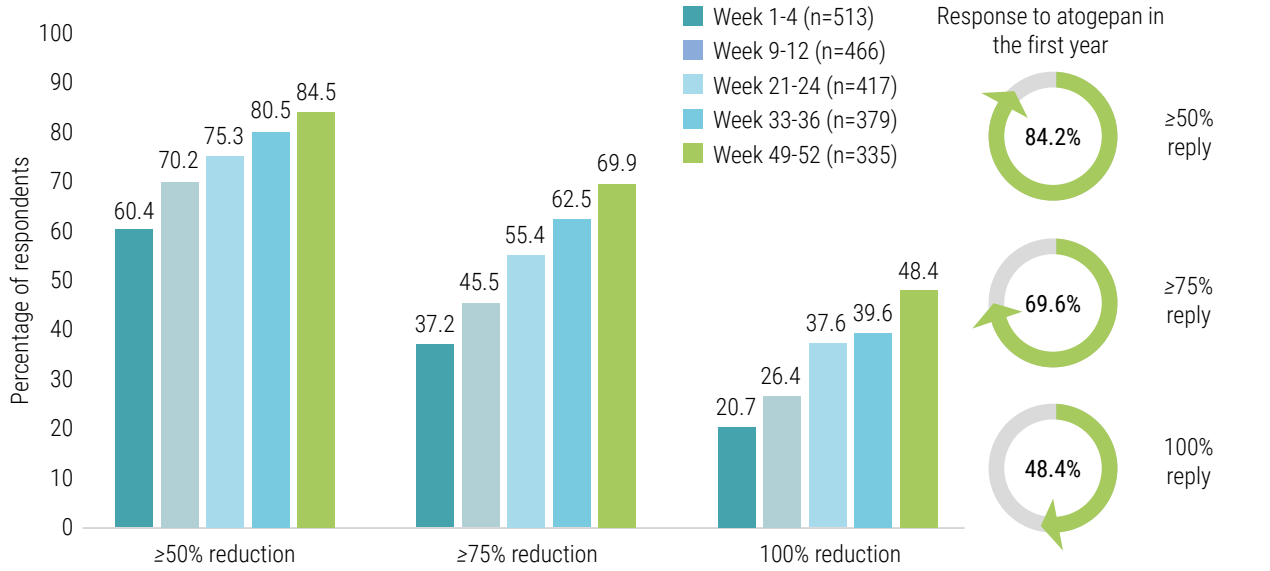
On the other hand, the approval of lasmiditan, a drug from the "ditanes" group with high selectivity for the serotonergic 5-HT1F receptor, with a low affinity for other serotonergic receptors, which has been associated with a low or no vasoconstrictor effect, which is mediated by the activation of 5-HT1B receptors, is noteworthy, so the cardiovascular safety profile of these new treatments is favourable[896] . Furthermore, the global effect estimate showed that lasmiditan was significantly superior to placebo in terms of no pain (RR 1.71, 95%CI 1.55-1.87), pain relief (RR 1.40, 95%CI 1.33-1.47), global impression (much/much better) (RR 1.55, 95%CI 1.44-1.67) and no or mild disability (RR 1.15, 95%CI 1.10-1.20) at 2 hours[897].

Finally, there are new drugs known as gepants, of which two have received EMA approval: rimegepant in 2022 as the only gepant with dual action as acute and pre- ventive treatment of ME with and without aura (visual or other unusual sensory experiences) in adults[898] and atogepant in 2023 as the first and only oral antagonist for the preventive treatment of migraine that has demonstrated efficacy in the prophylaxis of ME and CM[899]. The remaining gepants include FDA-only approved drugs: ubrogepant (2019) and zavegepant (2022)[862].

Rimegepant therapy has been evaluated in a study that pooled 3,827 patients from four randomised clinical trials, and the primary endpoints were freedom from pain, most bothersome symptom, and pain relief at 2 hours after dosing. It was observed that 75 mg rimegepant led to significant freedom from pain ($p < 0.001$), pain relief ($p < 0.001$) and freedom from the most bothersome symptom ($p < 0.001$) at 2 hours after dosing compared to placebo. In addition, there was no statistically significant increase in adverse events compared to placebo[900].

Regarding atogepant, a recent 52-week, multicentre, randomised, open-label, multicentre trial in adults (18-80 years) with migraine where efficacy assessments included change from baseline in mean monthly migraine days and the proportion of participants with reductions from baseline of ≥50%, ≥75% and 100% in MMD. At weeks 49-52, 84.2% (282/335), 69.9% (234/335) and 48.4% (162/335) of atogepant-treated participants reported a reduction of ≥50%, ≥75% and 100% in MMD. ≥50%, ≥75% and 100% of the MMD, respectively (Figure 204)[901].

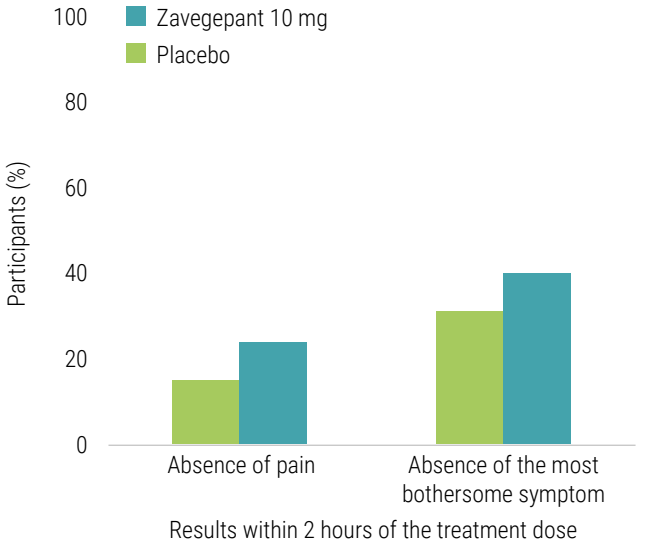
FIGURE 204. PROPORTION OF RESPONDERS WITH ≥50%, ≥75% AND 100% REDUCTION IN MONTHLY MIGRAINE DAYS IN ATOGEPANT-TREATED MIGRAINE PATIENTS



Source: Ashina (2023)[901]

For its part, zavegepant achieves rapid and sustained relief of pain and other troublesome symptoms, according to a recent meta-analysis[902]. Its efficacy has been evaluated in a study in which, between 27 October 2020 and 20 August 2021, 1,405 participants were selected (703 were assigned to zavegepant and 702 to placebo), and 1,269 were included in the efficacy analysis set (623 in the zavegepant group and 646 in the placebo group). According to the results, after 2h of the treatment dose, more participants in the zavegepant group than in the placebo group were free of pain (147 [24%] of 623 participants vs 96 [15%] of 646 participants, risk difference 8-8 percentage points, 95%CI 4-5-13-1; p<0-0001) and free of their most bothersome symptom (247 [40%] vs 201 [31%], risk difference 8-7 percentage points, 3-4-13-9; p=0-0012) (Figure 205)[903].

FIGURE 205. ZAVEGEPANT VERSUS PLACEBO FOR THE ABSENCE OF PAIN AND THE ABSENCE OF THE MOST BOTHERSOME SYMPTOM 2H AFTER THE TREATMENT DOSE WITH



Source: Lipton (2023)[903]

Finally, it should be noted that these innovative therapies aim not only to improve the effectiveness of migraine treatment, but also to provide a variety of management options and timelines, with a primary focus on improving tolerability for patients. These new therapies could represent a significant approach to migraine [904].

Greater understanding of the pathophysiology of migraine has led to the development of more specific and effective drug treatments that have reduced the duration of migraine attacks and lengthened the period between attacks. The range of available drug therapy, both preventive and acute treatment of attacks, has led to significant improvements in patients' health and quality of life, even offering options for those with chronic forms that have not responded or are intolerant to certain therapies.

Santos-Lasaosa (2019)[733], Urits (2019)[874], Blumenfeld (2011)[855], Láinez (2005)[889] , Láinez (2007)[859], Bordini (2005)[890] , Raggi (2015)[884]

In recent years, new preventive therapies for migraine have been approved, with the first oral option that has been shown to reduce the number and frequency of attacks and improve quality of life. New acute treatments have also been introduced for immediate and long-lasting relief of pain and other symptoms that can accompany migraines, including a dual-action therapy for acute and preventive migraine treatment.

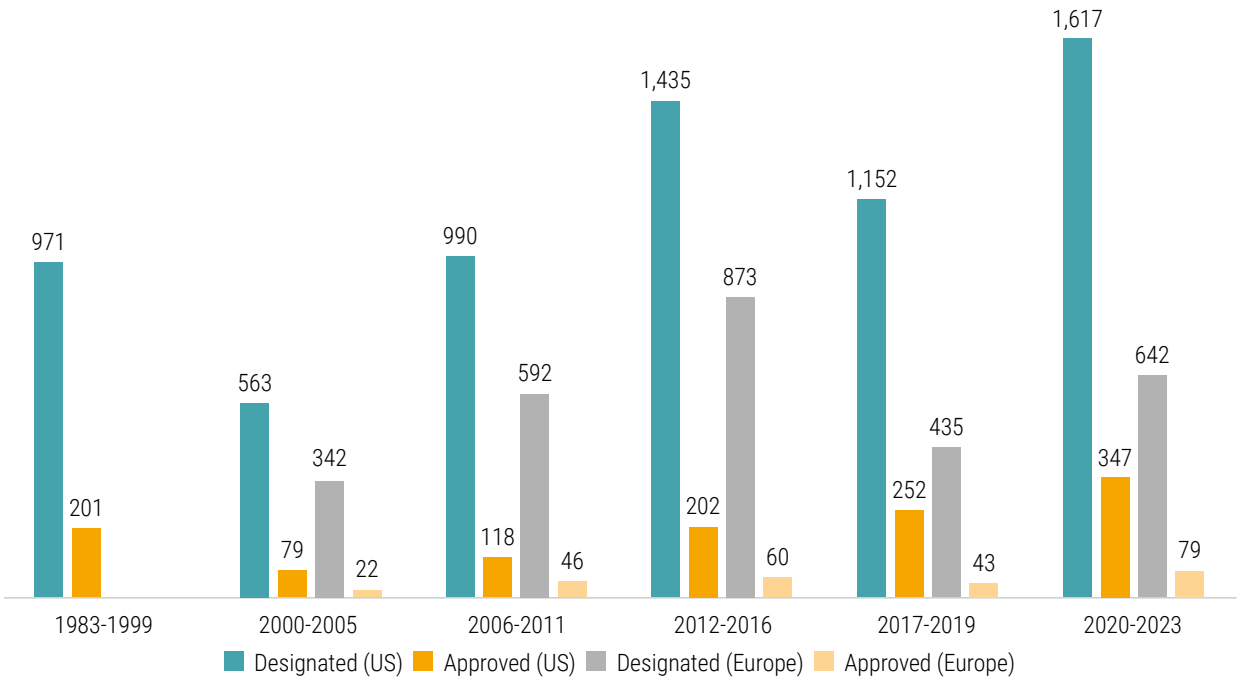
Mínguez-Olaondo (2024)[862]; Ashina (2023)[901] ; Ashina (2023)[895] ; Gao (2020)[900]

RARE DISEASES

Rare diseases (RDs) are characterised as chronic and degenerative life-threatening conditions with a low prevalence (less than 5 per 10,000 people in the EU)[905]. Moreover, they often lack specific treatment. Overall, it is estimated that there are between 5,000 and 8,000 different RDs, of which only 5% have treatment available[906], and which together affect approximately 36 million people in the European Union[907].

Orphan drug designation is a preliminary recognition granted by regulatory authorities, such as the EMA or the FDA, to treatments for rare diseases in order to incentivise their development through benefits such as fee waivers and scientific support. Approval, on the other hand, is the final process in which the drug has successfully passed the necessary clinical trials and has been shown to be safe and effective, allowing it to be marketed and used clinically in patients. In general, European and American regulations establish two-stage procedures, first establishing the orphan designation (so that the company can obtain funding and regulatory support to carry out research and development of medicines) and then, at the time of marketing authorisation, the regulatory agencies must verify that the criteria are met to allow it to be marketed as an orphan drug and to benefit from the market exclusivity periods established by the regulation (10 years in general in the EU, or 12 if they are for paediatric use)[908]. Since the adoption of specific legislation for RDs (Orphan Drug Act 1983 in the USA and EC Resolution 141/2000 on orphan drugs in the EU) until 2023, 6,728 orphan drugs (ODs) have been designated in the United States, of which a total of 1,119 have been approved. In Europe, 2,883 drugs have been designated as orphan drugs, of which 250 had received marketing authorization (Figure 206).

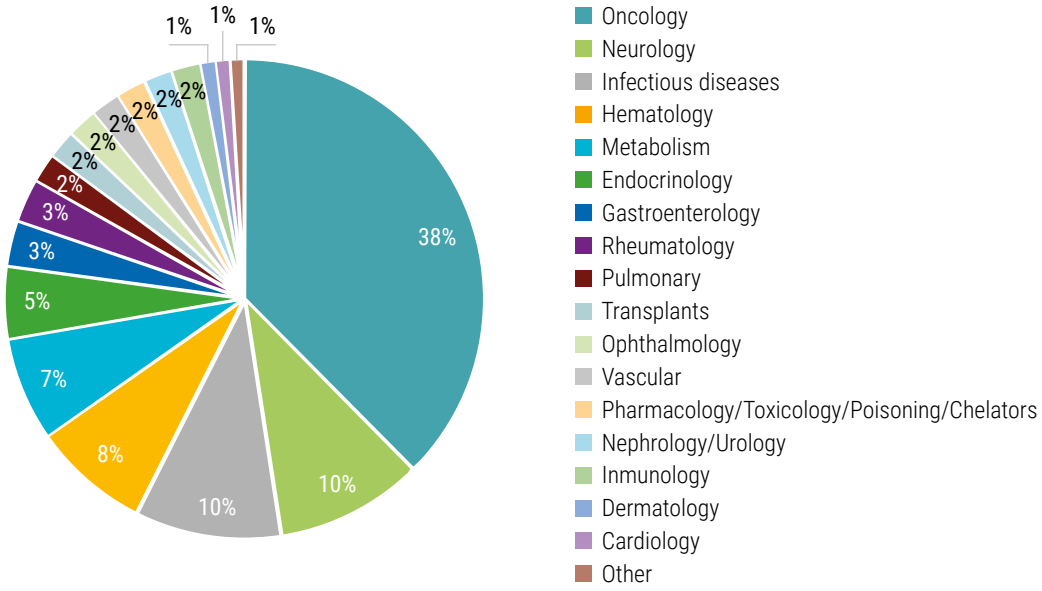
FIGURE 206. ORPHAN DRUG DESIGNATIONS AND APPROVALS. EUROPE AND THE UNITED STATES, 1983-2023



Source: own elaboration based on FDA (2024)[909]; EMA (2019-2023)[361–364,405] and EMA (2024)[910]

In recent years, it has been reported that cancer remains the dominant therapeutic area for orphan drugs (ODs) (Figure 207), so in this section we will make a differentiated analysis for oncological and non-oncological rare diseases[911].

FIGURE 207. FDAH APPROVALS OF ODs (PERIOD 1983-2022), BY THERAPEUTIC AREA



Note: Other includes orthopaedics, obstetrics and gynaecology, ENT and nutrition.

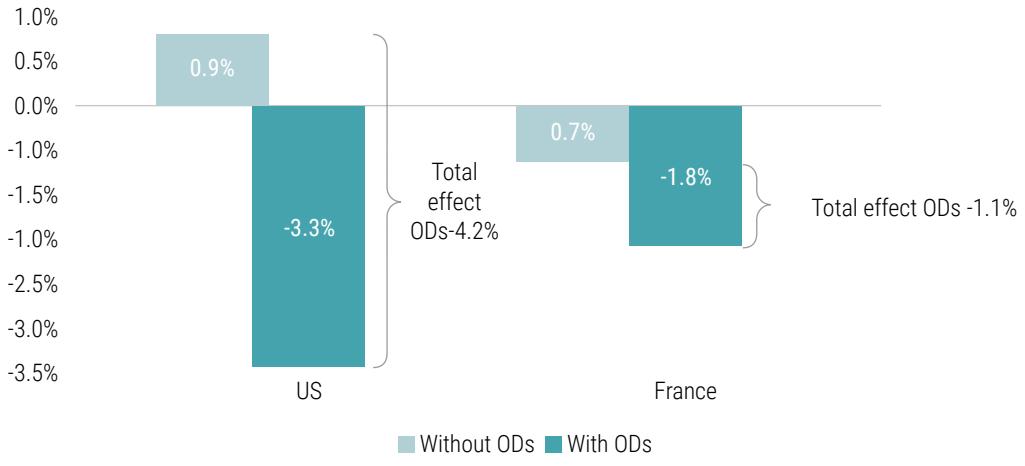
Source: adapted from Fermaglich (2023)[911]

Pharmaceutical innovations have made unprecedented advances in the field of RDs by introducing therapeutic options for severe conditions that were previously untreatable. This has led to reduced symptomatology and improved quality of life for patients, and in some cases substantial improvements in survival have also been achieved[912]. The impact on health outcomes and quality of life achieved by ODs has been studied by several authors, both in aggregate for all available ODs and individually for specific diseases.

Studies that have examined the aggregate effect of the introduction of ODs have focused on assessing how these drugs impact on mortality and quality of life in the population. For example, regarding the impact on mortality, Lichtenberg (2001) carried out an analysis whose objective was to estimate the impact of the introduction of ODs in the United States, in the period between 1983 (Orphan Drug Act) and 1999, on mortality in people with RDs, concluding that each ODs introduced prevented a total of 499 deaths (211 of them in the first year), and that the 216 ODs launched in this period prevented a total of 108,000 deaths[913].

Years later, this same author analysed the potential effect that the therapeutic arsenal of ODs approved in the United States and France has had on premature mortality, concluding that such an effect exists from the third year after the drug's approval and that it is greater in the American country than in Europe[914]. Their analysis shows that the ODs have allowed premature mortality to fall at a faster rate than it would have done had they not existed. Thus, in the absence of new ODs, premature mortality would have fallen at a rate of 0.6% per year in France between 2000 and 2007, but thanks to them it finally fell at a higher rate (1.8% per year on average). In the absence of ODs, premature mortality would have increased at a rate of 0.9% per year in the US, but thanks to these factors it eventually fell by 3.3% per year. Thus, the total effect of the ODs on the growth rate of premature mortality was -4.2% in the US and -1.1% in France (Figure 208)[914].

FIGURE 208. EFFECT OF APPROVED ODs ON THE ANNUAL GROWTH RATE OF PREMATURE MORTALITY, UNITED STATES AND FRANCE (%)



Note: Premature mortality approximated by Potential Years of Life Lost before age 65. Period 2000-2007 for France and 1999-2006 for the USA.

Source: Own elaboration based on Lichtenberg (2013)[914]

Chambers et al. (2017) compared the quality of life benefits of the introduction of specialty drugs, which are indicated for diseases with low prevalence, with those of traditional medicines, which are usually indicated for diseases that affect a larger number of people[915]. The authors concluded that, despite its indication for a lower prevalence population, the quality of life gains after the first year of drug introduction were 3 to 6 times greater in patients using the special drugs launched in the period 1999-2011.

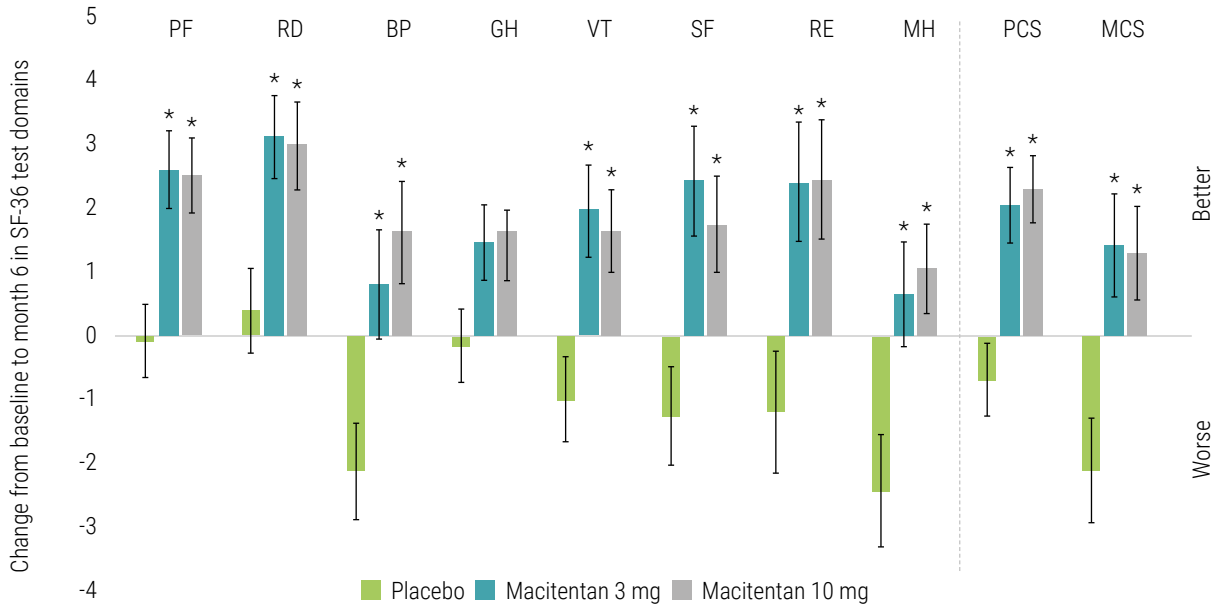
The evolution of treatments for RDs comprises different therapeutic modalities that differ in their ability to target the molecular mechanisms of disease, encompassing a variety of biological targets and mechanisms of action. Among these, chemical molecules have been approved over the past decades, along with a variety of biological therapies including enzyme replacement therapies, oligonucleotide- and antibody-based therapies and, more recently, advanced therapies[916].

Chemical molecules

Among the most innovative chemical molecules for RDs, defibrotide, which was approved in 2013 in Europe for severe hepatic veno-occlusive disease, stands out. This drug has been shown to improve complete response (23.5% of those treated in the trial vs 9.4% in the historical control) and survival rate (38.2% vs 25% of the historical control) of patients[917].

In the case of pulmonary arterial hypertension (PAH), therapy with the chemical molecule macitentan, approved in 2013, has been shown not only to reduce patients' disease-associated morbidity and mortality, but also to improve their quality of life. Using the SF-36 questionnaire, treatment with macitentan 10 mg significantly improved seven of the eight domains compared to placebo. Significant improvements were also shown in seven of eight individual domains of the SF-36 and in the physical and mental component scores after treatment with macitentan 3 mg compared to placebo (Figure 209)[918].

FIGURE 209. QUALITY OF LIFE MEASUREMENTS USING THE SF-36 QUESTIONNAIRE WITH PLACEBO, MACITENTAN 3 MG, OR MACITENTAN 10 MG IN THE TREATMENT OF PAH

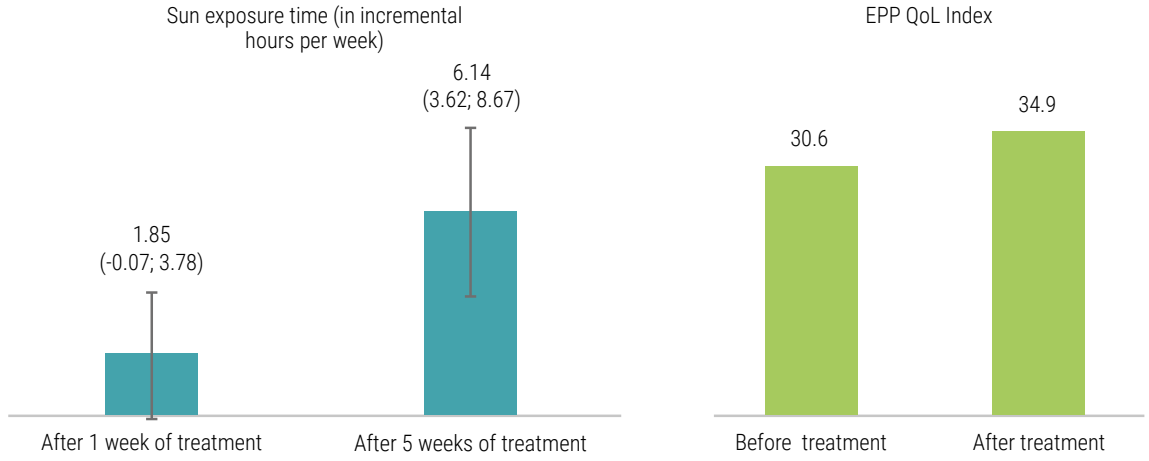


Note: **BP:** bodily pain; **GH:** general health; **MCS:** mental component summary; **MH:** mental health; **PCS:** physical component summary; **PF:** physical functioning; **RE:** role-emotional; **RP:** role-physical; **SF:** social functioning; **VT:** vitality.

Source: Mehta (2017)[918]

Later in 2014, afamelanotide was approved for patients with light sensitivity caused by erythropoietic photoporphyria (EPP). These patients can experience significant deterioration in their quality of life, as brief exposure to the sun can cause extremely painful skin lesions. This innovative treatment allows these patients an increase in the time they can be exposed to sunlight, and consequently, an improvement in their quality of life. This has been demonstrated in a study of 117 people in the Netherlands, where, after the use of afamelanotide, an increase of 6.1 hours per week was observed in the time these patients were able to stay under sunlight exposure (95%CI; 3.62 to 8.67; p<0.01), in addition to a 14% increase in the quality of life index (95%CI; 4.53% to 23.50%) (Figure 210)[919].

FIGURE 210. IMPACT OF AFAMELANOTIDE USE IN PATIENTS WITH EPP ON SUN EXPOSURE TIME AND QUALITY OF LIFE AFTER 5 WEEKS, NETHERLANDS

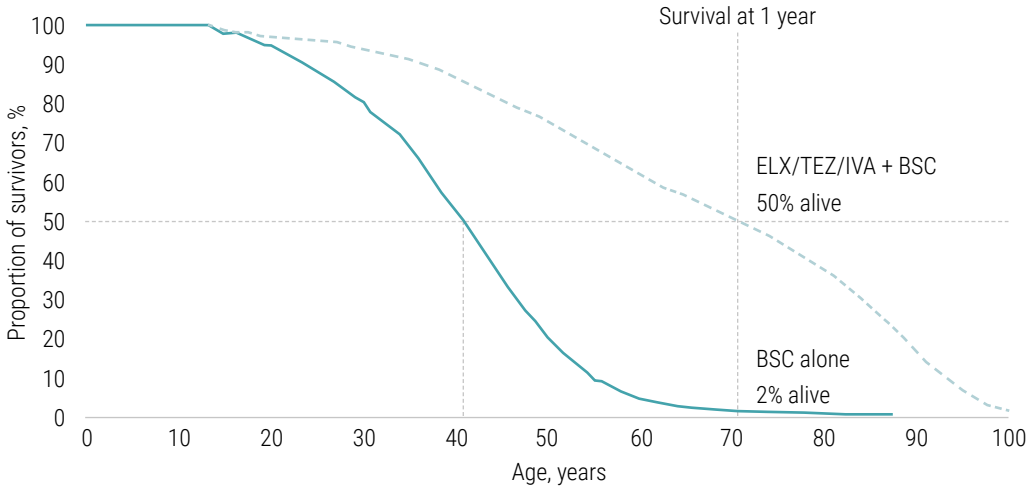


Note: **EPP:** Erythropoietic photoporphyria. **EPP QoL:** Quality of Life Questionnaire for erythropoietic photoporphyria disease.

Source: own elaboration based on Wensink (2020)[919]

On the other hand, in the treatment of cystic fibrosis, the combination therapy of the chemical molecules elexacaftor/tezacaftor/ivacaftor, approved in 2019, is the first combination therapy for this disease. This innovative treatment has been shown, together with supportive treatment (airway clearance, bronchodilators, mucolytics, antibiotics and nutritional management) to increase the median survival of cystic fibrosis patients by 29.7 years (70.4 years vs. 40.8), relative to supportive treatment (Figure 211), representing a step change in clinical practice[920].

FIGURE 211. IMPACT OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR THERAPY ON CYSTIC FIBROSIS TREATMENT



Nota: **ELX/TEZ/IVA:** elexacaftor/tezacaftor/ivacaftor; **BSC:** best supportive care (airway clearance, bronchodilators, mucolytics, antibiotics and nutritional management).

Source: Adapted from Rubin (2022)[920]

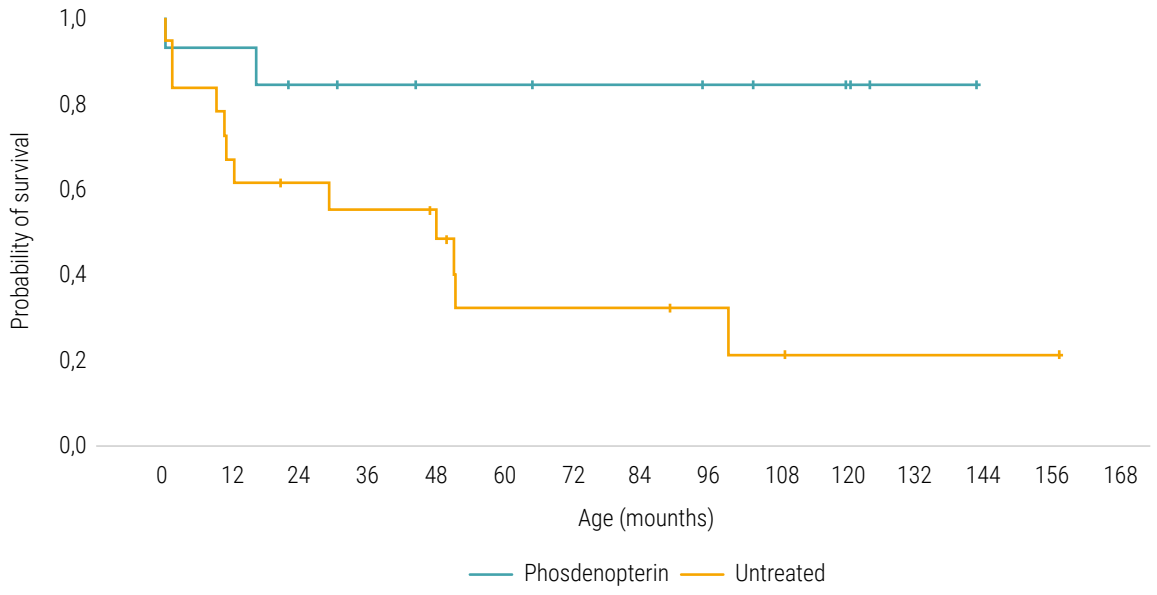
In recent years, other molecules have been approved with the potential to significantly benefit patients with RDs for whom no other therapies exist. For example, risdiplam was approved in 2020, becoming the first oral treatment for patients with certain types of spinal muscular atrophy (SMA)[921]. The FIREFISH study is an ongoing, multicentre, open-label study that recruited infants aged 1-7 months with a confirmed genetic diagnosis of SMA from 14 hospitals in ten countries in Europe, North and South America and Asia. According to preliminary results, treatment with risdiplam for 24 months resulted in continuous improvements in motor function and achievement of developmental motor milestones[922].

Also of note is the approval in 2021 of tagraxofusp, a molecule designed specifically for plasmacytoid blast dendritic cell neoplasia (BPDCN) that has demonstrated long-term benefits. Tagraxofusp monotherapy in previously untreated patients has demonstrated overall response rates of 75% and has achieved complete responses or residual skin abnormality not indicative of active disease in 57% of patients, with a median time to remission of 39 (95%CI 14-131) days[923].

Other innovative drugs approved during 2021 include fosdenopterin to improve survival of a specific genetic disorder (combined molybdoflavoprotein enzyme deficiency, or MoCD Type A); avacopan for the treatment of adults with granulomatosis with polyangiitis or severe active microscopic polyangiitis, a rare type of inflammation of the blood vessels; vosoritide for the treatment of achondroplasia, a disease that prevents bone growth and causes dwarfism; and finally, selumetinib for the treatment of paediatric patients aged 2 years and older with neurofibromatosis type 1, as described below.

Improved survival with fosdenopterin in MoCD Type A was demonstrated in a cohort of 13 treated patients from two clinical studies and one retrospective observational study compared to an observational cohort of 18 untreated patients. The median survival time at 3 years was 32 months for patients treated with fosdenopterin compared to 24 months for untreated patients. At 3 years, the probability of survival was 84% (95%CI: 49% - 96%) for treated patients and 55% (30% -74%) for untreated patients (Figure 212)[924].

FIGURE 212. KAPLAN-MEIER SURVIVAL CURVES OF THE GROUPS TREATED WITH FOSDENOPTERIN VERSUS THOSE UNTREATED FOR MOCD TYPE A



Source: Farrell (2021)[924]

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On the other hand, clinical trials conducted with avacopan for anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis demonstrated that the treatment was able to achieve remission and improve renal function in patients with ANCA-associated vasculitis without increasing the risk of adverse events during treatment, while reducing the toxic effects associated with corticosteroid use[925] . In addition, patients with ANCA-associated vasculitis who received avacopan reported statistically and clinically significant improvements in health-related quality of life at 26 and 52 weeks and in EQ-5D and SF-6D health utility scores at 52 weeks[926].

Regarding vosoritide, the results of the pivotal clinical trial showed that the adjusted mean difference in annualised growth velocity between patients in the vosoritide group and those in the placebo group was 1.57 cm/year in favour of vosoritide (95%CI: 1.22-1.93; p<0.0001)[927]. In addition, an expert panel has assessed that the earlier long-term treatment is initiated, the more likely vosoritide is to have a positive effect on the lifetime incidence of the most clinically important complications of achondroplasia due to its high impact on comorbidity, mortality and/or quality of life (symptomatic spinal stenosis, kyphosis, obstructive sleep apnoea and foramen magnum stenosis)[928].

The efficacy of selumetinib has been tested in a phase 2 clinical trial. After one year of treatment, there was an average reduction of 2 points in child-reported tumour pain intensity scores, which is considered a clinically meaningful improvement. In addition, clinically significant improvements were observed in pain interference with daily functioning, as reported by both children (38%) and parents (50%), as well as in HR-QoL (48% and 58%, respectively). Improvements in functional outcomes were also recorded, with 56% of patients showing improvements in strength and 38% in range of motion[929].

Most recently, the 2022 approval of lonafarnib stands out, as it has become the first treatment for children with progeroid syndromes, an ultra-rare genetic disease that causes premature ageing and death. Clinical trials have shown that lonafarnib prolongs the lives of patients affected by Hutchinson-Gilford progeria syndrome, a devastating disease that accelerates many features of ageing and causes premature death from cardiovascular sequelae[930].

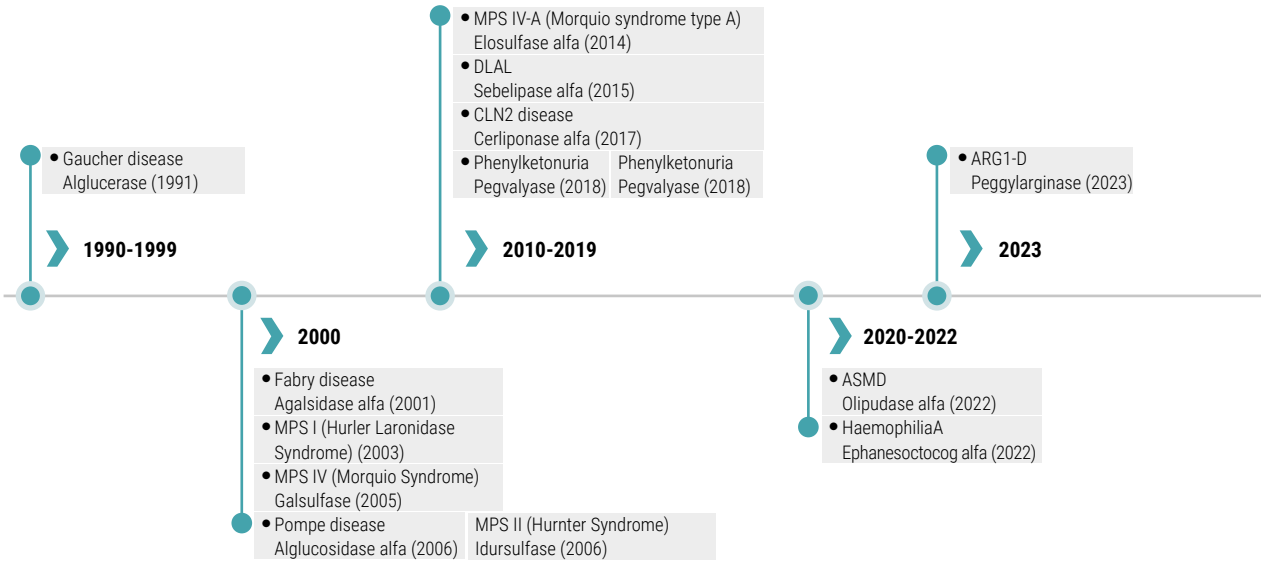
Another example of oncohaematological innovation is momelotinib, approved in 2023 as the first treatment for myelofibrosis (MF), a type of haematological cancer affecting the bone marrow, in patients with anaemia. The need for red blood cell transfusions is an adverse risk factor for both overall survival and leukaemic transformation and there is a lack of therapeutic options to address it. This unmet medical need can be addressed with this innovative molecule that may also have overall survival benefits for MF patients in first and second line treatment[931]. According to the results of SIMPLIFY-2, a randomised phase 3 study to evaluate the efficacy of momelotinib versus best available therapy in anaemic or thrombocytopenic subjects with MF, it has been shown that, over the entire treatment period, 40% (42/104) of patients treated with momelotinib versus 27% (14/52) of the best available therapy cohort did not require red blood cell transfusions[931].

Biological therapies

Enzyme replacement therapies

Another strategy for the treatment of RDs is enzyme replacement therapy (ERT) or protein replacement therapy. The evolution of this type of therapy has addressed unmet medical needs in a number of rare diseases for which there were no previous treatments (Figure 213).

FIGURE 213. EVOLUTION OF ENZYME REPLACEMENT THERAPIES FOR RDs



Abbreviations: **ARG1-D:** Arginase 1 deficiency; **ASMD:** Acid sphingomyelinase deficiency; **CLN2:** Batten disease (neuronal ceroid lipofuscinosis type 2); **DLAL:** Lysosomal acid lipase deficiency; **MPS I:** Mucopolysaccharidosis type I (Hurler syndrome); **MPS II:** Mucopolysaccharidosis type II (Hunter syndrome); **MPS IV:** Mucopolysaccharidosis type II (Hunter syndrome); **MPS IV-A:** Mucopolysaccharidosis type IV-A (Morquio Syndrome type A); **PKU:** Phenylketonuria

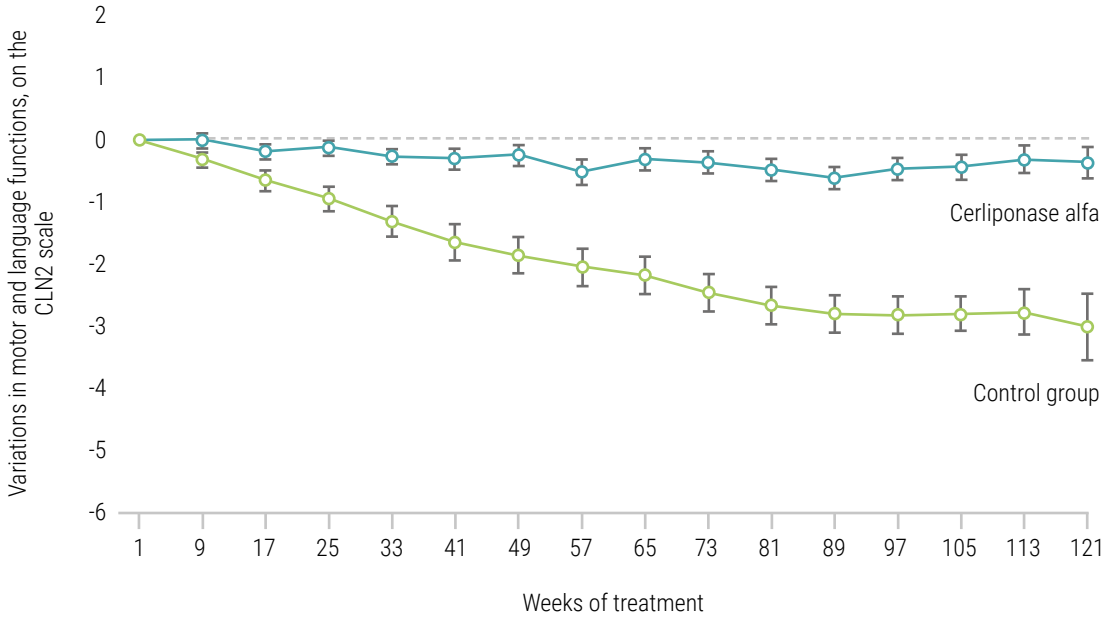
Source: own elaboration adapted from Safary (2018)[932]; FDA (2023)[933] and EMA (2019-2023)[361–364,405]

One of the most prominent examples of this therapeutic modality is in Pompe disease, where treatment with alglucosidase alfa, approved in 2006, has shown significant improvements over the historical record of patients for whom no treatment was available. Pompe disease is a rare infantile metabolic disease that causes respiratory and feeding problems, respiratory tract infections and generalised muscle weakness, which together lead to premature mortality in these patients. Alglucosidase alfa therapy has been shown to increase life expectancy by 13.4 years (13.8 versus 0.4) as well as an improvement in QALYs by 6.8 years (7.0 versus 0.2). In addition, 65% of children are reported to be alive 5 years after receiving TSE, with no deaths observed thereafter[934].

Later, sebelipase alfa, approved in 2015, became the first treatment for lysosomal acid lipase deficiency (DLAL). This drug resulted in a reduction of multiple liver (70% better alanine aminotransferase normalisation rates versus placebo) and lipid abnormalities (56% and 78% better results in triglyceride and cholesterol levels, respectively, versus placebo) associated with this potentially lethal condition in children and adults[935].

Also noteworthy is the approval in 2017 of cerliponase alfa, a TSE for CLN2 disease. This is a rare disease that causes progressive neurological deterioration in children, including seizures, personality disorders, dementia and loss of the ability to walk, speak and communicate. In a study of 24 children aged 3 to 16 years, the effect of intraventricular infusion of cerliponase alfa every 2 weeks for 96 weeks was evaluated, concluding that the rates of motor and language function impairment were significantly lower in patients on this treatment than in the control group (-0.2 vs. -1.9 at week 49; -0.5 vs. -2.8 at week 97) (Figure 214)[936].

FIGURE 214. IMPACT OF CERLIPONASE ALFA TREATMENT ON MOTOR AND MOTOR-LANGUAGE SCORES AMONG CHILDREN AGED 3-16 YEARS WITH CLN2. GERMANY, ENGLAND, UNITED STATES AND ITALY, VARIATIONS ON THE CLN2 SCALE



Abbreviation: CLN2: Ceroid Neuronal Lipofuscinosis type 2.

Source: Schulz (2018)[936]

Another example of health improvements from TSE is in phenylketonuria (PKU), a disease caused by phenylalanine hydroxylase deficiency, which can result in high concentrations of phenylalanine in the blood, causing impaired brain function and development. The approval of pegvalyase in 2018 was undoubtedly a significant milestone in addressing unmet medical needs in the treatment of PKU. The efficacy of this treatment has been demonstrated in a study of 261 adult patients. Compared to the initial treatment period, after periods of 1 and 2 years, pegvalyase treatment demonstrated a 54% to 75% reduction in blood phenylalanine levels (1,232 µmol/L at baseline versus 564.5 and 311.4 after 1 and 2 years, respectively)[937]. This reduction is clinically relevant because levels above 360 µmol/L phenylalanine can cause neurological and cognitive impairment; therefore, lowering these levels improves the prognosis and quality of life of PKU patients[938].

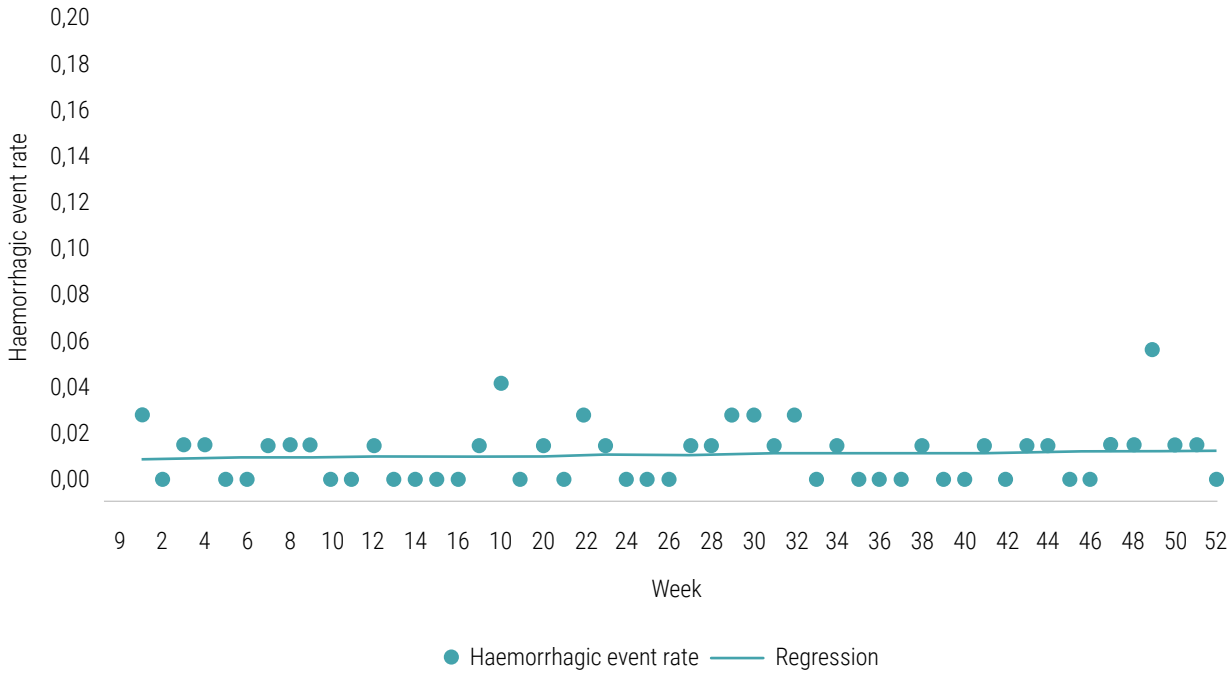
Also in 2018, velmanase alfa was approved for the treatment of patients with non-neutrophilic manifestations of mild to moderate alpha-mannosidosis (AM). Results from a multicentre, open-label Phase 2 study demonstrated significant improvements in children under 6 years of age with AM treated with this in- novating TSE, reflected in decreases in serum oligosaccharide concentrations, along with improvements in hearing, immune profile and quality of life, suggesting a beneficial effect of early treatment[939].

More recently, in 2022, olipudase alfa was approved, which has become the first and only SCT for the treatment of patients with acid sphingomyelinase deficiency (ASMD), a genetic disease historically known as Niemann-Pick disease types A, A/B and B. The results of a survey aimed at understanding the real impact of ASMD on patients and caregivers, as well as assessing how olipudase alfa SCT influences the quality of life of paediatric patients and their caregivers, revealed that the therapy was associated with improvements in all non-neurological manifestations observed by patients and family members. These included tiredness and fatigue, abdominal pain, organ enlargement, vomiting and nausea, bone pain, bruising, chronic headaches, infections over a 6-month period, and shortness of breath. For example, abdominal pain at the start of the study was

present in 7/10 participants and was reduced after treatment, being reported by only 2/10 participants. In addition, after receiving olipudase alfa, 8/10 participants noted no enlargement and 2/10 noted somewhat enlarged organs[940].

Also noteworthy is the approval in 2022 in the United States of efanesoctocog alfa, the first long-acting recombinant factor VIII replacement therapy for severe haemophilia A. This therapy is effective in preventing and controlling bleeding episodes in previously treated children with severe haemophilia A, as shown by the results of a phase 3 study. The weekly bleeding rate throughout the study remained consistently low (Figure 215). Efanesoctocog alfa showed high haemostatic efficacy, resolving 95% of bleeds in children under 12 years of age, with a rating of excellent or good for almost all first injections evaluated (97%)[941].

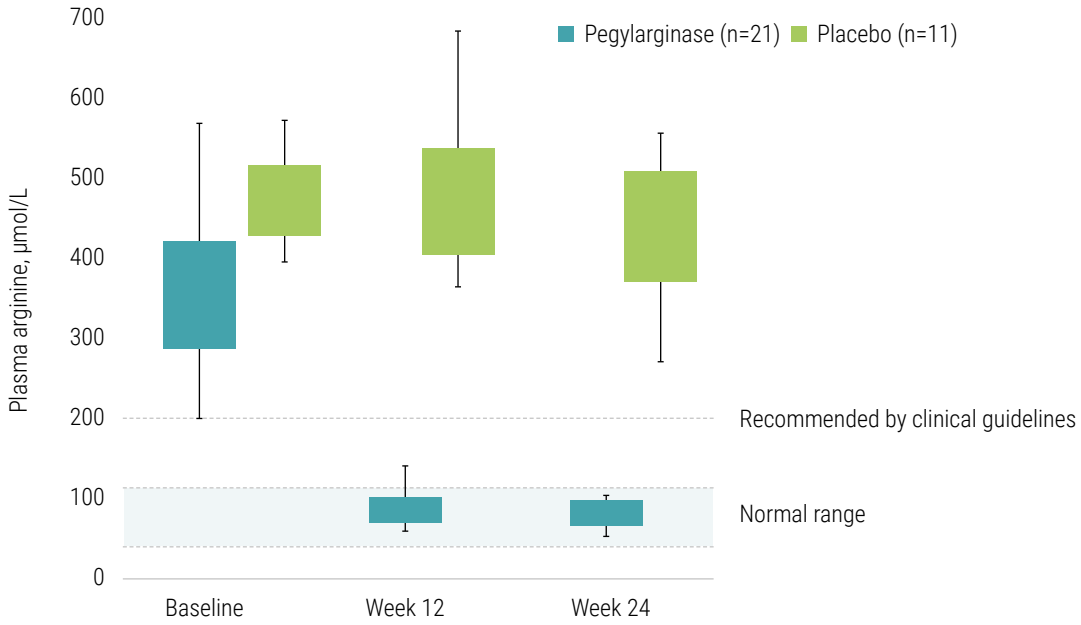
FIGURE 215. RATE OF BLEEDING EVENTS AMONG PATIENTS WITH SEVERE HAEMOPHILIA A TREATED WITH EFANESOCTOCOG ALFA THERAPY



Source: Malec (2023)[941]

Finally, it is worth mentioning the recent approval of pegzilarginase in 2023, a new replacement therapy based on recombinant human arginase 1 enzyme for the treatment of arginase 1 deficiency (ARG1-D). The treatment was effective in reducing long-term plasma arginine (pArg) levels in ARG1-D patients. Elevated pArg levels result in persistent hyperargininaemia, which is the main driver of developmental delay, intellectual disability and spasticity in these patients[942]. According to the results of a randomised, double-blind, phase 3 clinical trial involving 32 patients (pegzilarginase, n= 21; placebo, n= 11), pegzilarginase treatment reduced the geometric mean pArg from 354.0 µmol/L to 86.4 µmol/L at week 24 versus 464.7 to 426.6 µmol/L with placebo (95%CI: -67.1%), -83,5%; p < 0,0001). In other words, the therapy achieved a 76.7% reduction and, in addition, normalised levels in 90.5% of patients (compared to 0% with placebo) (Figure 216)[943].

FIGURE 216. EFFECT OF PEGZILARGINASE ON PLASMA ARGININE LEVELS IN PATIENTS WITH ARG1-D



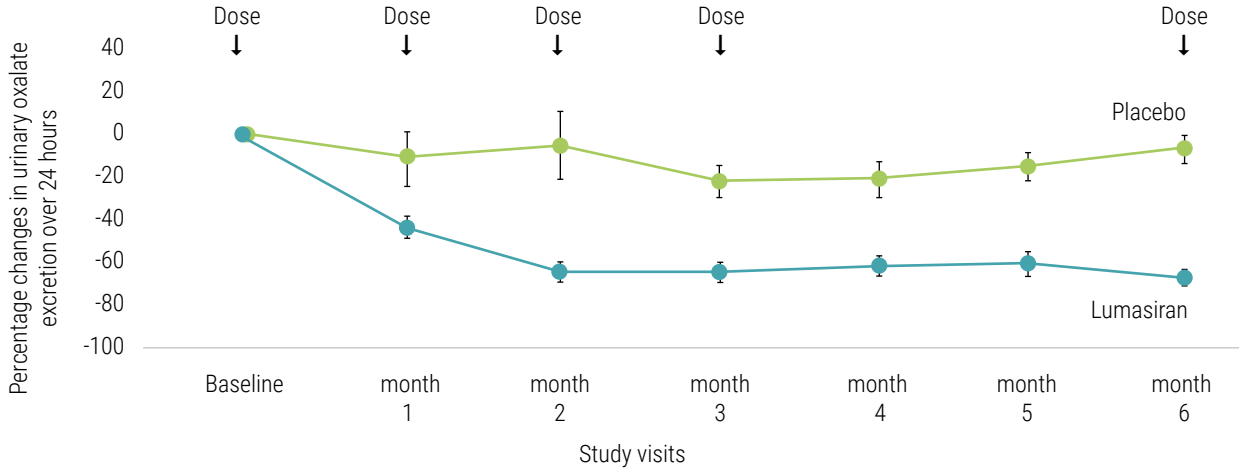
Source: Russo (2024)[943]

Oligonucleotide-based therapies

On the other hand, biologic therapies for rare diseases include **oligonucleotide-based therapies**. This therapeutic modality includes the first drug indicated for spinal muscular atrophy (SMA) (nusinersen), approved in 2016, which has been shown to improve both overall survival and motor function in patients participating in clinical trials, reducing the risk of death or permanent mechanical ventilation by 47% compared to the placebo group[944]. Recently, data have been published showing that treatment with nusinersen halted disease progression and produced real functional improvements in SMA patients. Clinically significant improvements were observed at the 30-month visit, such as a change in score of 3 points or more on the Hammersmith Extended Functional Motor Scale (HFMSE) in 76% of patients, 4 points or more on the Children's Hospital of Philadelphia Test for Neuromuscular Disorders (CHOP-INTEND) in 80% of patients and 2 points or more on the Revised Upper Limb Module (RULM) in 43.5% of patients. In addition, the Patient Global Impression of Improvement Scale (PGI-I) also showed positive results, with 75% of patients reporting improvement at the 14-month follow-up visit and 85% at 30 months, with none reporting worsening at the 30-month visit[945].

More recently, in 2020, lumasiran, the first liver-targeted RNA interference for the treatment of primary hyperoxaluria type 1 (PH1), a disease in which excess oxalate produced in the liver is a primary determinant of progression to end-stage renal failure and damage to other organs, was approved. The efficacy of the therapy has been demonstrated in a double-blind phase 3 trial where patients received lumasiran or placebo for 6 months (with doses administered at baseline and at months 1, 2, 3 and 6)[946]. According to the results, the mean reduction in the percentage change in 24-hour urinary oxalate excretion from baseline to month 6 was -53.5 percentage points for the group receiving lumasiran compared to placebo (95%CI -62.3 to -44.8, p<0.001). The mean percentage change from baseline was -65.4% in the lumasiran group and -11.8% in the placebo group (Figure 217).

FIGURE 217. PERCENTAGE CHANGES IN 24-HOUR URINARY OXALATE EXCRETION IN THE GROUP RECEIVING LUMASIRAN OR PLACEBO FOR 6 MONTHS FOR THE TREATMENT OF HYPEROXALURIA PRIMARY TYPE 1 (PH1)



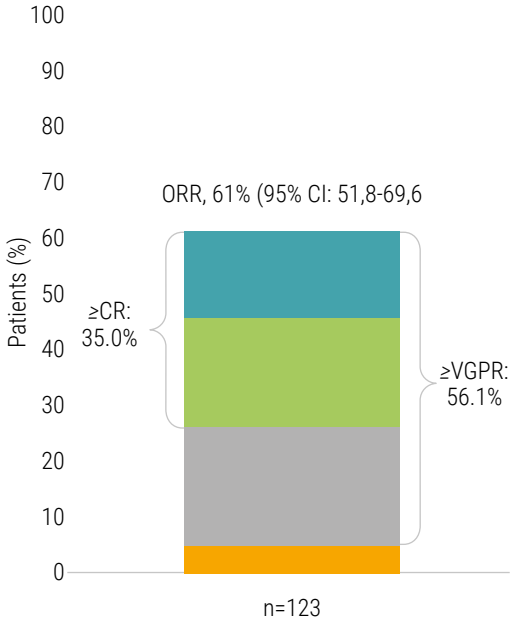
Source: Garrelfs (2021)[946]

Antibody-based therapies

Antibody therapies have also been a major therapeutic innovation for patients with RDs. For example, the antibody eculizumab, approved in 2007, offers better health outcomes than the usual practice seen in paroxysmal nocturnal haemoglobinuria (PNH), a rare disease that causes red blood cells to disintegrate[947]. The median survival of PNH from diagnosis is 14.6 years, with thrombosis and renal failure accounting for 60% of all deaths. Eculizumab has been shown to improve the quality of life of patients with PNH, achieving 2.4 QALYs longer than standard treatment, as well as an increase in life expectancy of 1.1 years[948].

Recent advances in antibody-based therapies have had a major impact on multiple myeloma (MM). Daratumumab has been a revolution in the treatment of MM and has been approved in many countries for use as monotherapy in relapsed/refractory MM (RRMM), and in combination with standard treatment regimens in RRMM and early-diagnosed MM not amenable to transplantation. The PERSEUS study reported that adding daratumumab to standard treatment resulted in a nearly 60% decrease in the risk of cancer progression or death (hazard ratio of 0.42)[949]. Furthermore, with respect to elranatamab, the first humanised bispecific antibody that targets both BCMA on myeloma cells and CD3 on T-cells (anti BCMA-CD3), the ongoing phase 2 MagnetisMM-3 trial evaluated the efficacy of this innovative therapy in MMR patients without prior BCMA treatment. A complete response or better (≥CR) was achieved in 35.0% of patients, and at least a very good partial response (≥V GPR) in 56.1% (Figure 218)[950].

FIGURE 218. RESPONSE RATE IN 123 PATIENTS WITH MULTIPLE MYELOMA TREATED WITH ELRANATAMAB



Abrevations: CR: complete response; **PR:** partial response; **MR:** minimum response; **sCR:** strict complete response; **VGPR:** very good partial response.

Source: Lesokhin (2023)[950]

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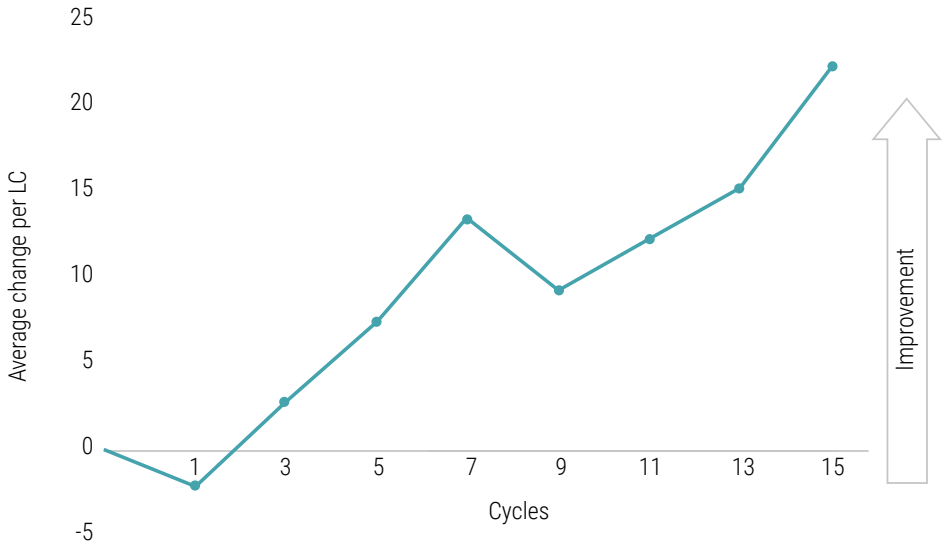
Talquetamab is the first bispecific T-cell redirecting antibody targeting GPRC5D and CD3 receptors. Patients with advanced-stage, heavily pre-treated MM generally experience poorer HRQoL and limited treatment options, reducing prospects for improvement. The impact on patient-reported outcomes on HRQoL, symptoms and functioning of this innovative therapy has been collected from the cohorts of the phase 2 MonumenTAL-1 study[951]. It assessed 122 patients treated with weekly doses of talquetamab who had received ≥3 prior lines of drugs from all three therapeutic classes (≥1 proteosome inhibitor/≥1 immunomodulatory drug, and ≥1 anti-CD38 monoclonal antibody). With treatment, the proportion of patients with significant improvement was high, for example, in cycle 9 for the cohort receiving 0.4 mg/kg of therapy, 42% experienced improvement in global health status, 34% in physical functioning, 40% in role functioning, 86% in pain symptoms, and 78% in fatigue symptoms (Figure 219)[951].

FIGURE 219. LEAST SQUARES MEAN CHANGE IN GLOBAL HEALTH STATUS OF EORTC QLQ-C30 IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS EXPOSED TO TRIPLE CLASS TREATED WITH TALQUETEMAB 0.4 MG/KG



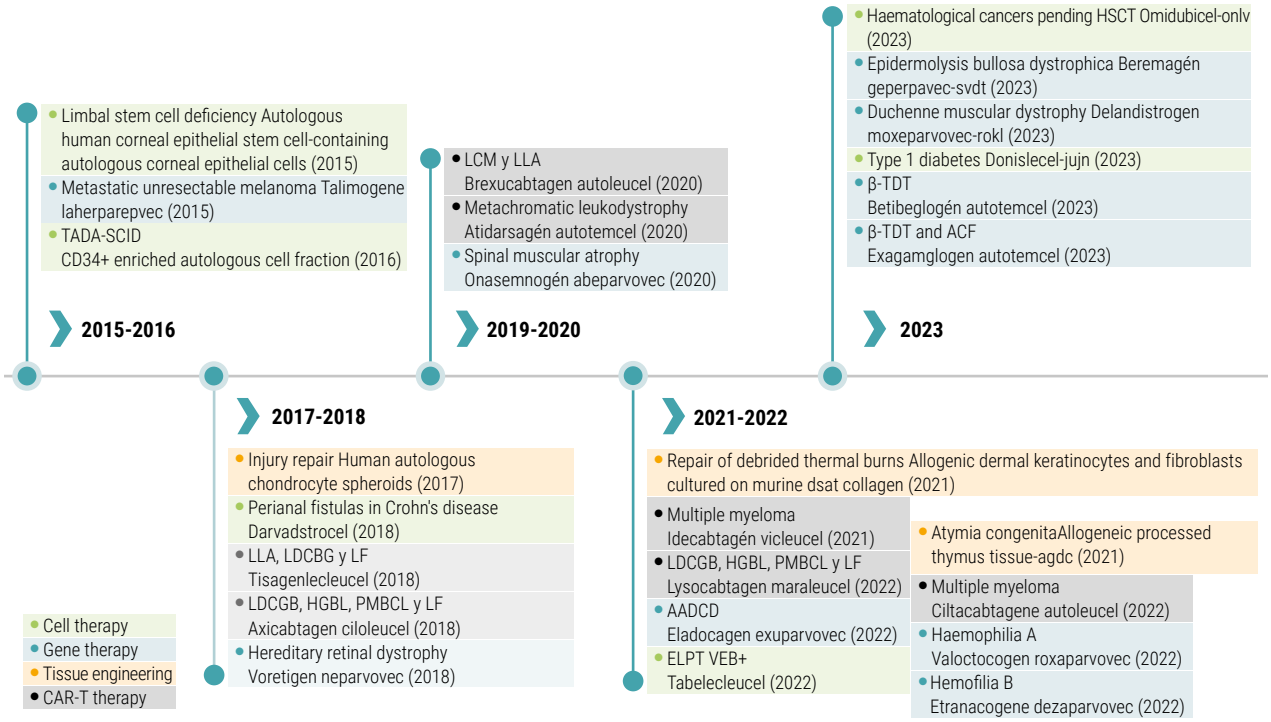
Abbreviations: LC: least squares; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Core 30-item questionnaire.

Source: van de Donk (2023)[951]

Advanced therapies

Advanced therapies for the treatment of RDs are expanding and are currently one of the most innovative therapeutic approaches for the treatment of this group of diseases. Advanced therapies include gene therapies, cell therapies and tissue engineering-based therapies and their combinations, such as chimeric antigen receptor T-cell therapies (CAR-T) that combine gene and cell therapy. All advanced therapies approved to date by the EMA had previously received orphan drug designation and are aimed at treating RDs or other serious, low-prevalence diseases, many of which are oncological in nature (Figure 220).

FIGURE 220. EVOLUTION OF ADVANCED THERAPIES



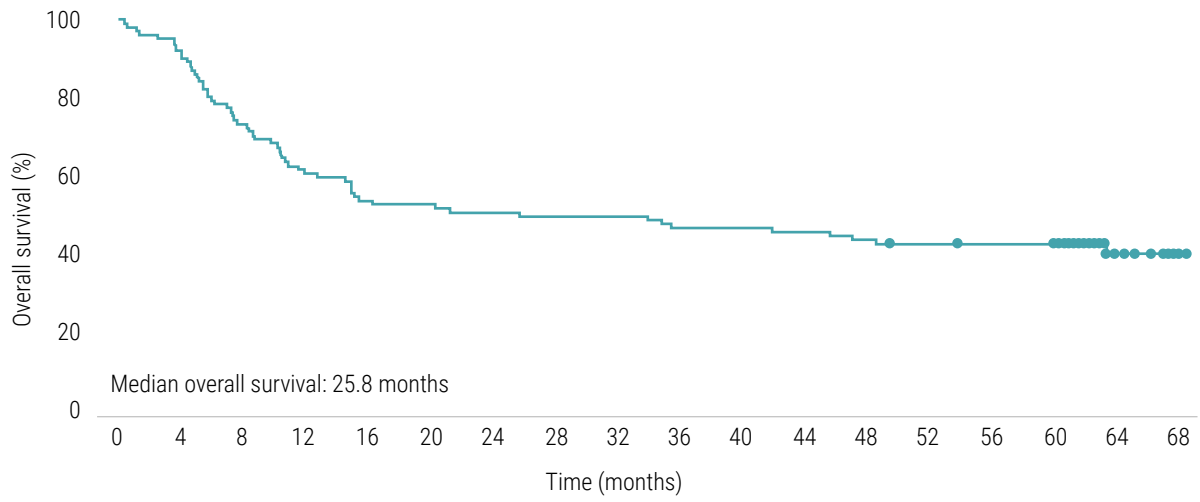
Abbreviations: **AADCD:** Aromatic amino acid decarboxylase deficiency; **ACF:** Sickle cell anaemia; **ADA-SCID:** Severe combined immunodeficiency syndrome due to adenosine deaminase deficiency; **SMA:** Spinal muscular atrophy; **DHR:** Hereditary retinal dystrophy; **DMD:** Duchenne muscular dystrophy; **DMD:** Duchenne muscular dystrophy; **DT1:** Diabetes type 1; **EAD:** Dystrophic epidermolysis bullosa: Hereditary retinal dystrophy; **DMD:** Duchenne muscular dystrophy; **EAD:** Dystrophic epidermolysis bullosa; **ELPT EBV+:** Epstein-Barr virus-positive post-transplant lymphoproliferative disease; **HGBL:** High-grade B-cell lymphoma; **MCL:** Mantle cell lymphoma; **MML:** Metachromatic leukodystrophy; **FL:** Follicular lymphoma; **FL3B:** Follicular lymphoma grade 3B; **DLBCL:** Diffuse large B-cell lymphoma; **ALL:** Acute lymphoblastic leukaemia; **MIM:** Metastatic unresectable melanoma; **MMR:** relapsed/refractory multiple myeloma; **PMBCL:** primary mediastinal B-cell lymphoma; **HSCT:** haematopoietic stem cell transplantation; **β-TDT:** β-transfusion-dependent thalassaemia.

Source: own elaboration adapted from FDA (2023)[933] and EMA (2019-2023)[361–364,405]

The approval by the FDA[952,953] and the EMA[954] of the first two CAR-T therapies (axicabtagene ciloleucell[955] and tisagenlecleucel[956]) represents a paradigm shift that opens the way to personalised medicine. It fills an important therapeutic need in patients with acute lymphoblastic leukaemia (ALL), diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma (FL), refractory or unresponsive to available therapeutic alternatives.

The efficacy of axicabtagene ciloleucel has been tested in the ZUMA-1 study in 101 patients with refractory DLBCL with a follow-up of 27.1 months. According to the results, 83% of patients had an objective response and 58% (59 patients) a complete objective response to treatment. Median duration of response was 11.1 months, median survival was not reached and progression-free survival was 5.9 months[957]. More recently, long-term results from the ZUMA-1 study were published, showing sustained long-term results with ciloleucel axicabtagene therapy in this group of patients (Figure 221)[958].

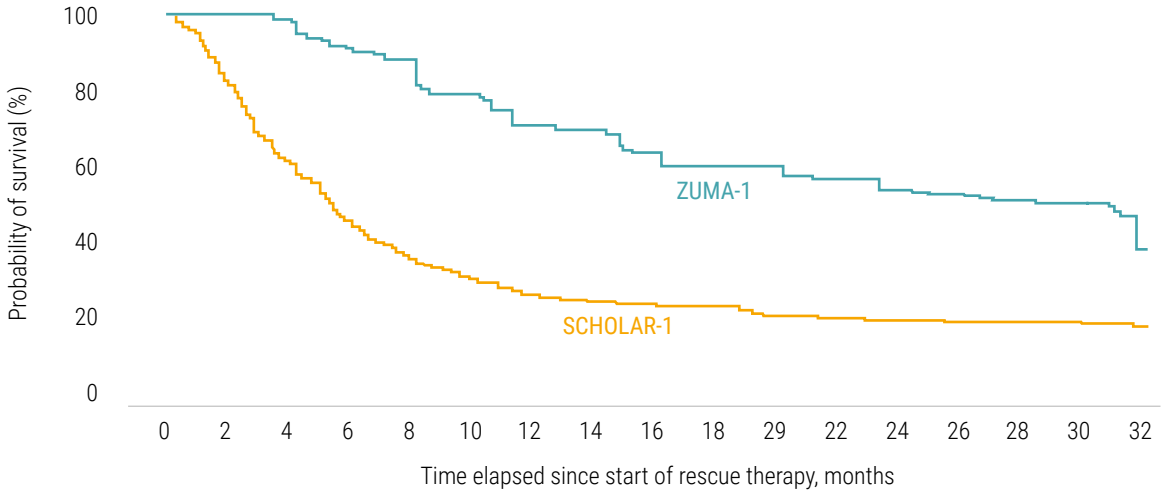
FIGURE 221. 4-YEAR OVERALL SURVIVAL OF DLBCL PATIENTS TREATED WITH AXICABTAGENE CILOLEUCEL (ZUMA-1 STUDY)



Source: Neelapu (2023)[958]

The paradigm shift is also seen in Figure 222, which compares the probability of survival of patients treated with axicabtagene ciloleucel (ZUMA-1 study) versus standard salvage therapy (SCHOLAR-1 study). Median overall survival was 31.0 months in ZUMA-1 and 5.4 months in SCHOLAR-1. The treatment difference suggested a 73% reduction in the risk of death in ZUMA-1 versus SCHOLAR-1. The 2-year survival rate was 54% and 20% in ZUMA-1 and SCHOLAR-1, respectively (Figure 222)[959].

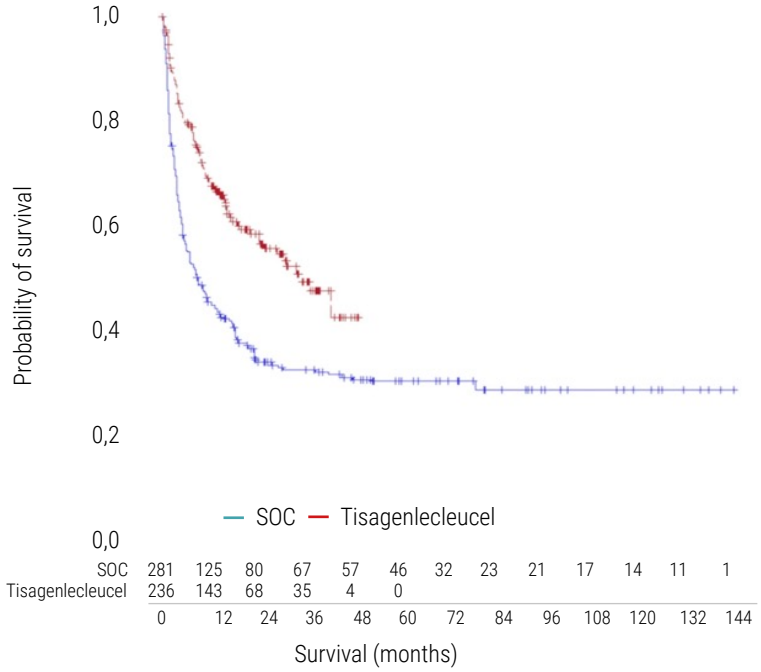
FIGURE 222. PROLONGED SURVIVAL WITH AXICABTAGENE CILOLEUCEL (ZUMA-1) AND STANDARD SALVAGE THERAPY (SCHOLAR-1) IN THE TREATMENT OF OF DLBCL



Fuente: Neelapu (2021)[959]

The results of tisagenlecleucel in ALL patients are evidenced by data from its use in actual clinical practice which reportedly show a 2-year adjusted overall survival probability of 59.49% (95%CI: 52.08 - 66.13) for tisagenlecleucel versus 36.16% (95%CI: 30.38 - 41.95) for the standard of care population (Figure 223). Improvements in event-free survival (EFS) and relapse-free survival (RFS) were also reported, with 42.31% versus 30.23% and 59.60% versus 54.57%, respectively[960].

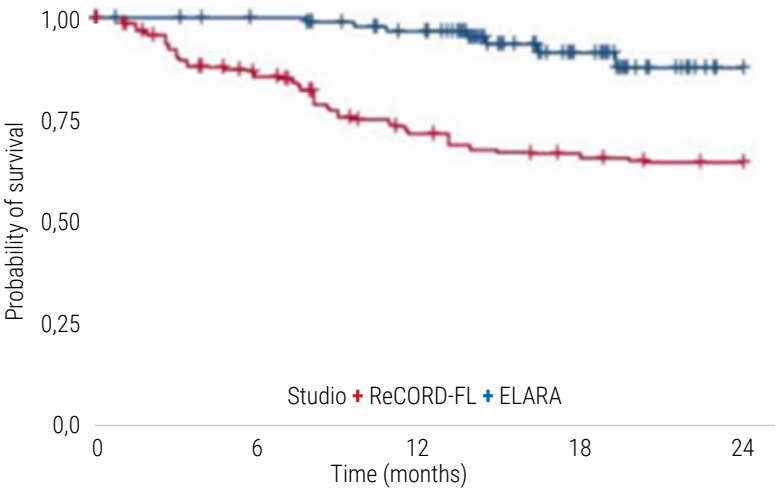
FIGURE 223. OVERALL SURVIVAL OF PATIENTS WITH LLA TREATED WITH TISAGENLECLEUCEL VERSUS TISAGENLECLEUCEL. TO THE STANDARD OF CARE



Abbreviation: SOC: standard of care.

Source: Stackelberg (2023)[960]

FIGURA 224. PROGRESSION-FREE SURVIVAL IN LF TREATMENT WITH TISAGENLECLEUCEL (ELARA) VS. TREATMENT AS USUAL (RECORD-FL)



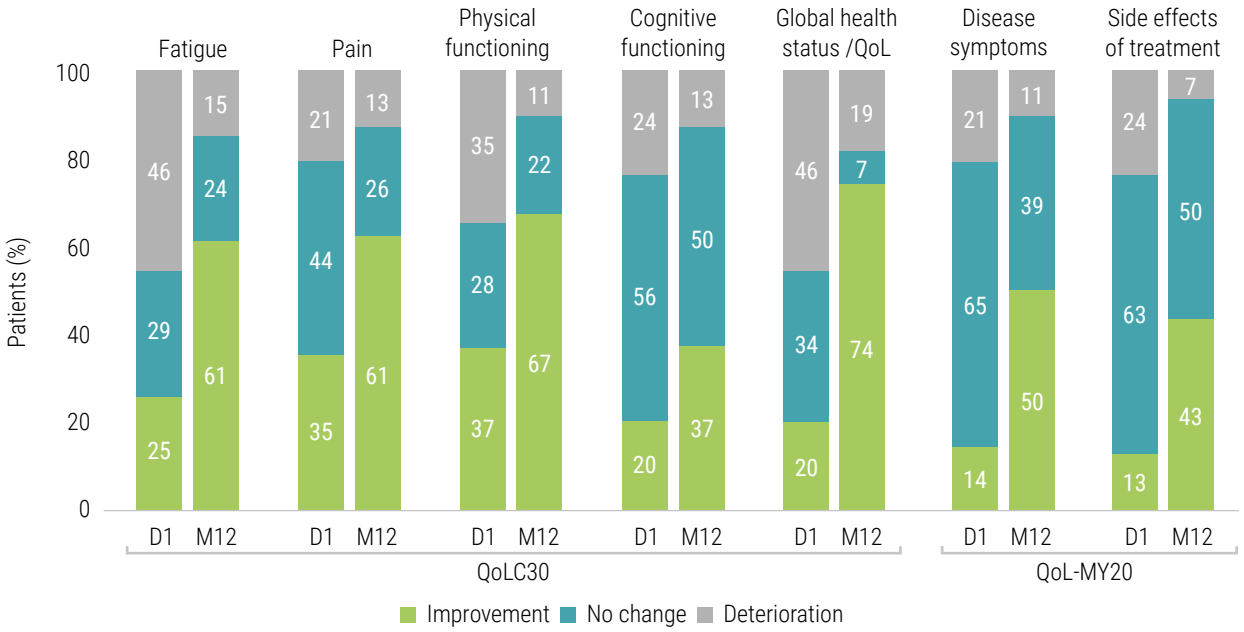
Source: Salles (2022)[961]

In addition, tisagenlecleucel is also indicated in the treatment of FL, where it has better health outcomes than usual care. Specifically, the probability of being progression/event free at 12 months was 70.5% for tisagenlecleucel versus 51.9% for usual care. Likewise, overall survival at 12 months was 96.6% versus 71.7% in the tisagenlecleucel and usual care groups, respectively (Figure 224)[961].

Since 2020, new CAR-T therapies have been approved for low-prevalence cancer indications with limited treatment options. For example, autoleukel brexucabtagene therapy was the first CAR-T therapy available for mantle cell lymphoma (MCL). Therapeutic options for this rare cancer include traditional chemoimmunotherapy for newly diagnosed cases, and targeted therapies (Bruton's tyrosine kinase (BTK) inhibitors) in the setting of relapsed/refractory disease. The early use of autoleukel brexucabtagene (before failure of BTK inhibitor therapy) in high-risk, poor-prognosis patients is a potentially viable new treatment option to delay disease progression. Its efficacy has been proven in the Phase II study (ZUMA-2), which evaluated patients with MCL who had already received multiple treatments, all with a BTK inhibitor, showing an objective response rate of 93%, with 67% of patients having a complete response[962].

The benefits of CAR-T therapies for refractory multiple myeloma in RMM patients also stand out, for example, idecabtagene vicleucel showed durable responses in MMR patients exposed to the three standard MM drug classes (immunomodulatory drugs, proteasome inhibitors and anti-CD38 antibodies), in the phase 2 KarMMa study[963]. The proportions of patients with clinically significant improvements over time increased from day 1 for fatigue, pain, physical functioning and global health status/quality of life according to the QLQ-C30 questionnaire. With regard to the QLQ-MY20, a 20-item supplementary module for MM, the proportions of patients who experienced clinically significant improvements in symptoms and side effects increased over time, while those with clinically significant worsening decreased from day one (Figure 225).

FIGURA 225. HRQL ASSESSMENTS AT DAY 1 (D1) AND MONTH 12 (M12) AFTER TREATMENT WITH IDECABTAGENE VICLEUCEL IN PATIENTS WITH MMR EXPOSED TO TRIPLE CLASS

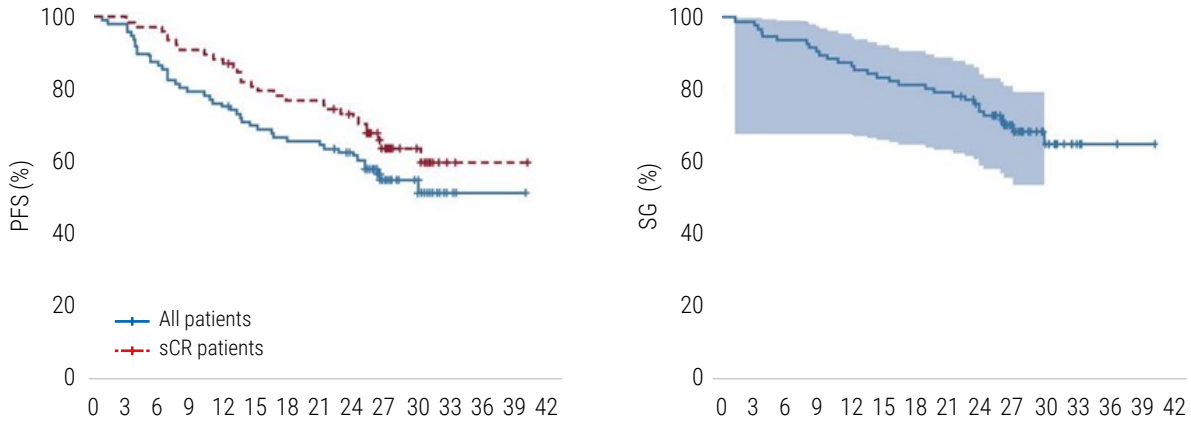


Abbreviations: **D:** day; **M:** month; **QoL:** quality of life.

Source: Delforge (2022)[963]

One of the latest advances in this pathology has been the approval in 2022 of ciltacabtagene autoleucel, a CAR-T therapy indicated for patients with RMM. The pivotal study of this therapy (CARTITUDE-1) was a single-arm, open-label, multicentre, phase Ib/II study that showed that treatment with was associated with a 27-month PFS and OS of 54.9% (95% CI 44.0 to 64.6) and 70.4% (95% CI 60.1 to 78.6), respectively. These results were consistent in both the standard and high-risk groups (Figure 226)[964].

FIGURE 226. PROGRESSION-FREE SURVIVAL (A) AND OVERALL SURVIVAL (B) IN PATIENTS WITH MULTIPLE MYELOMA TREATED WITH CILTACABTAGENE AUTOLEUCEL



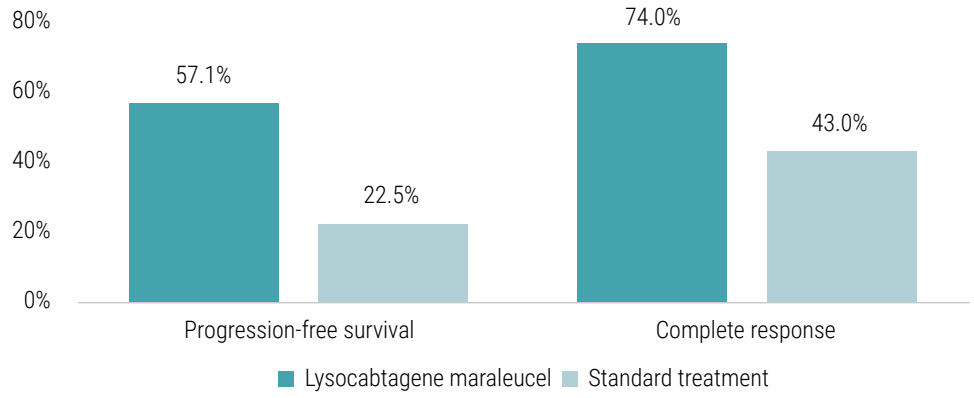
Abbreviations: **PFS:** progression-free survival; **OS:** overall survival; **ORR:** strict complete response; **PFS:** progression-free survival; **sCR:** stringent complete response.

Source: Martin (2023)[964]

Similarly, ciltacabtagene autoleukel has achieved clinically significant improvements in HRQoL and disease-specific symptom reduction in MM patients in first- through third-line patient populations. The CARTITUDE-4 study analysed 419 patients with MMR to lenalidomide and exposed to one to three prior treatments who received ciltacabtagene autoleukin, demonstrating the potency of this innovative therapy to significantly improve patients' HRQoL, including pain, fatigue and emotional functioning. In the primary analysis, a single infusion of the therapy significantly improved progression-free survival (hazard ratio [HR], 0.26; p<0.0001) and increased the rate and depth of response versus standard treatment[965].

On the other hand, treatment with maraleucel lysocabtagene CAR-T therapy approved in 2022 for primary refractory or early relapsed LB- DCG has achieved better response than standard treatment, both in progression-free survival at 12 months (57.1% vs. 22.5%) and in complete response to treatment at 18 months (74.0% vs. 43.0%) (Figure 227)[966].

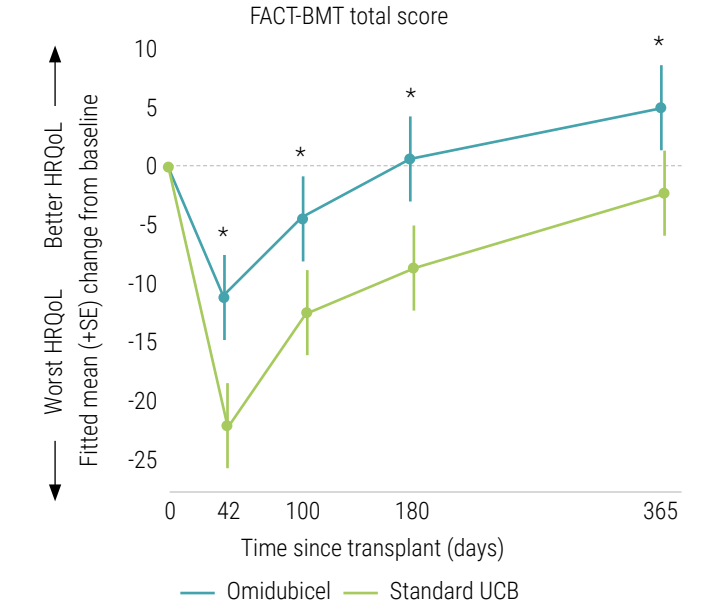
FIGURE 227. PROGRESSION-FREE SURVIVAL AND COMPLETE RESPONSE IN TREATMENT OF RELAPSED OR REFRACTORY DLBCL WITH MARALEUCEL LYSOCABTAGENE AND STANDARD THERAPY



Source: own elaboration based on Abramson (2023)[966]

In addition to CAR-Ts for oncology indications, an innovative cell therapy derived from umbilical cord blood (UCB) has also been approved in the United States in 2023 for use in allogeneic haematopoietic cell transplantation (HCT) in patients with haematological cancers. In a prospective, multicentre, randomised, multicentre, phase 3 clinical trial, 125 patients with advanced haematological malignancy were enrolled at 33 centres in North America, South America, Europe and Singapore and randomised to receive either omidubicel (n= 62) or SCU units (n= 63) for allogeneic HCT. Results showed that omidubicel significantly (p=0.01) improved HRQoL in allogeneic HCT recipients compared to those receiving SCU units, with mean differences between 7.2 and 11.0 points at different follow-up time points. Functional assessment of therapy was conducted using the 50-item cancer-specific FACT-BMT questionnaire that assesses physical, functional, emotional, social/family and HCT-specific well-being (Figure 228)[967].

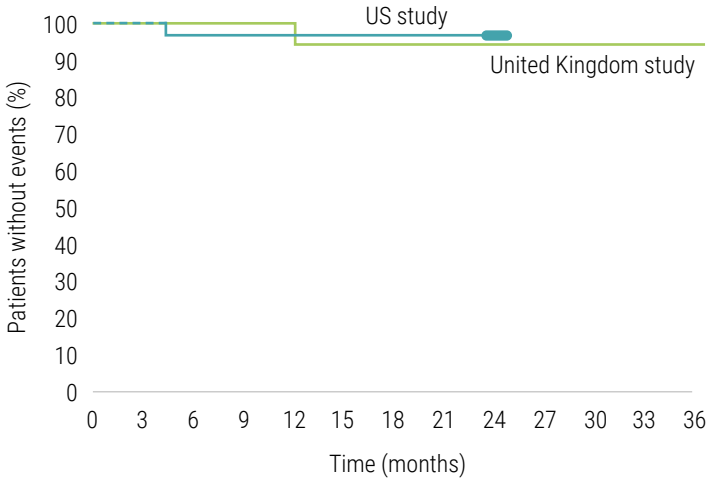
FIGURE 228. MEAN CHANGES FROM BASELINE HRQL MEASURES FOR THE FACT-BMT TOTAL SCORE IN PATIENTS PATIENTS WITH ADVANCED HAEMATOLOGICAL MALIGNANCY RECEIVING OMIDUBICEL (N= 62) OR UCB (N= 63)



Abbreviations: **ABC:** area under the curve; **UCB:** umbilical cord blood; **SE:** standard error.

Source: Lin (2023)[967]

FIGURE 229. PERCENTAGE OF PATIENTS WITH NO EVENTS IN ADA-SCID TREATMENT WITH CD34+ CELL MODIFYING CELL THERAPY, UNITED STATES AND UNITED KINGDOM



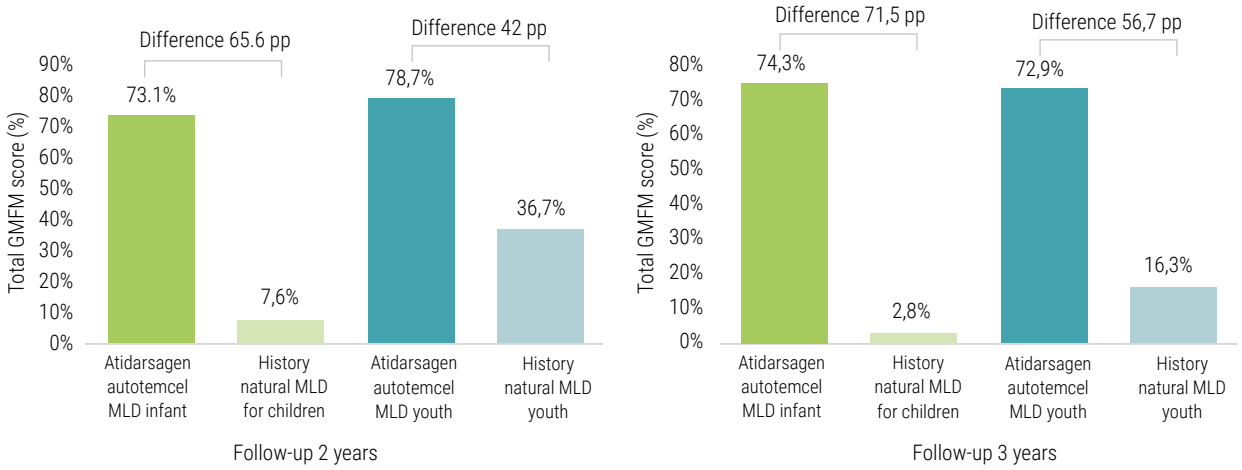
Source: Kohn (2021)[968]

Although primarily notable for their uses in oncology, advanced therapies have also provided new and more effective treatments for non-oncology RDs. First, the approval in 2016 of a gene therapy that modifies CD34+ cells in patients with a severe and rare condition called ADA-SCID, where this innovative drug has achieved promising results. ADA-SCID is a rare disease that affects the immune system, causing recurrent fungal, bacterial and viral infections and growth problems. Without treatment, children rarely survive more than 2 years. To make the drug, stem cells from the child's bone marrow are modified in the laboratory to insert a gene that produces the enzyme that the patient does not produce naturally. In a study with two different populations (in the UK and in the US), patients treated with the innovative drug achieved 100% overall survival in both groups at 24 and 36 months. Event-free survival was 97% (US group) and 100% (UK group) at 12 months and 97% and 95% at 24 months, respectively (Figure 229)[968].

Regarding innovative gene therapies with non-oncological indications, a relevant example is voretigen neparvovec therapy, approved in 2018 for hereditary retinal dystrophy (RHD), a rare disease that causes night vision loss, progressive peripheral visual field loss and blindness. After one year, patients treated with voretigen neparvovec performed better on the bilateral light test, achieving a 1.8-point improvement compared to a 0.2 point improvement in the control group. Voretigen neparvovec also achieved improvements over the control group in other tests, such as white light sensitivity. In this case, the control group showed no improvement compared to the start of the study while, after one year, there was a difference of 2.11 points between patients treated with voretigen neparvovec and the control group[969].

Another example to highlight is atidarsagen autotemcel, approved in 2020 for the treatment of children with metachromatic leukodystrophy (MLD). MLD is a rare inherited disease that causes symptoms such as difficulty walking, gradual mental deterioration and, ultimately, death. Atidarsagen autotemcel has been shown to be effective, achieving differences of up to 71.5 percentage points on the developmental motor function test (GMFM) compared to a cohort of untreated patients, who followed the natural history of the disease, at 3-year follow-up (Figure 230)[970].

FIGURE 230. MOTOR FUNCTION SCORES IN PATIENTS WITH LATE INFANTILE AND EARLY JUVENILE MLD TREATED WITH ATIDARSAGEN AUTOTEMCEL VS. NATURAL HISTORY OF THE DISEASE

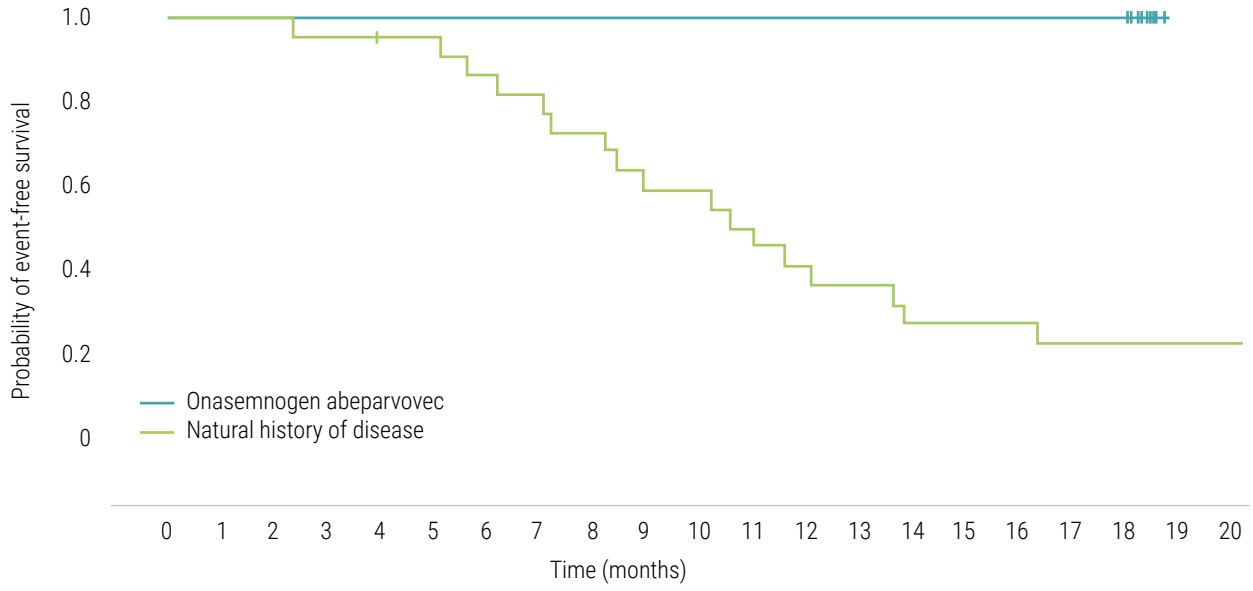


Abbreviations: **GMFM:** developmental motor function test; **MLD:** metachromatic leukodystrophy; **pp:** percentage points.

Source: Fumagalli (2022)[970]

Another gene therapy (onasemnogene abeparvovec) was approved in 2020 and has demonstrated improvements in both survival and achievement of motor milestones in SMA patients[971]. In a study completed in 2020, all children treated with onasemnogene abeparvovec achieved independent sitting for at least 30 seconds at any visit up to 18 months of age compared to none in the untreated group. Likewise, event-free and mechanical ventilation-free survival was 100% in children in the onasemnogene abeparvovec group compared to 26% in the untreated group (Figure 231)[972].

FIGURE 231. EVENT-FREE SURVIVAL IN THE TREATMENT OF PATIENTS WITH SPINAL MUSCULAR ATROPHY WITH ONASEMNOGENE ABEPARVOVEC VERSUS NATURAL DISEASE PROGRESSION



Source: Strauss (2022)[972]

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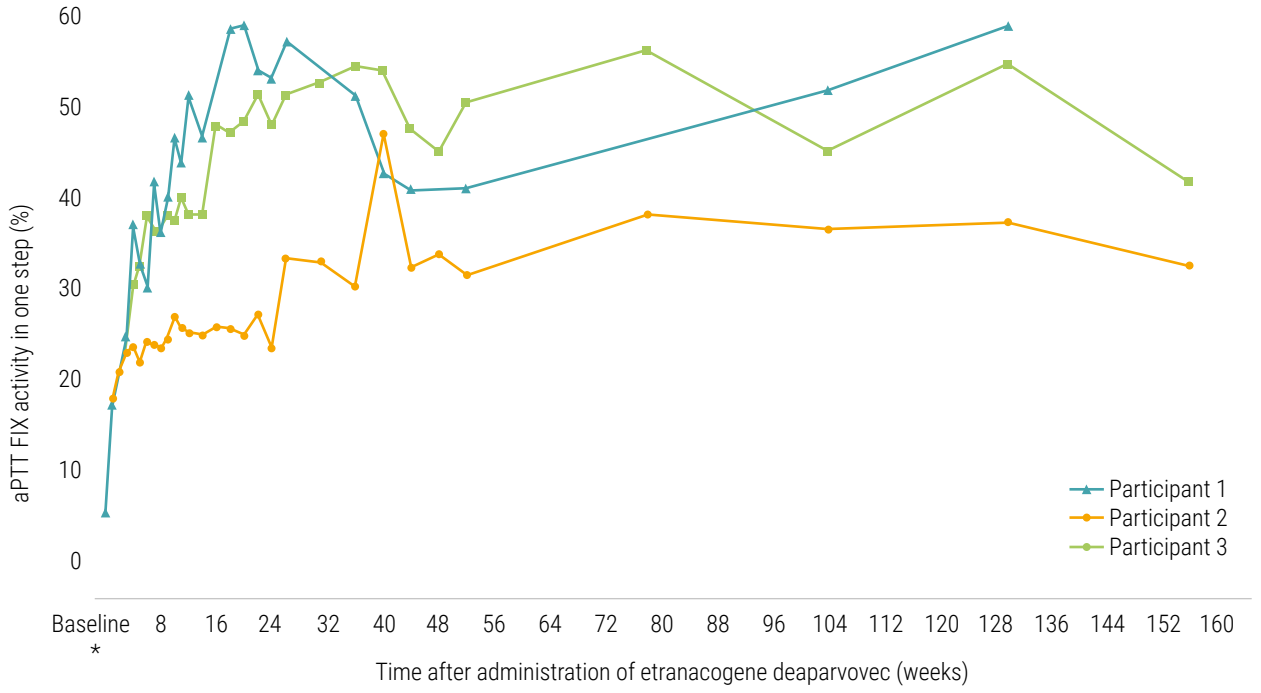
In 2022, significant milestones have been set in the field of gene therapies, with several major approvals in haematological indications, especially for haemophilia. First, valoctocogen roxaparvovec is the first gene therapy to treat severe haemophilia A, a rare heritable bleeding disorder caused by a lack of factor VIII. HRQoL in adult men with severe haemophilia A without inhibitors following valoctocogene roxaparvovec therapy has been analysed in the phase 3 GENEr8-1 trial. Improvements in HRQoL were achieved at 12 weeks and maintained for 2 years after gene transfer. For 132 seronegative participants, the mean increase from baseline in the total score on the haemophilia-specific quality of life questionnaire for adults with haemophilia (Haemo-QOL-A) was 7.0 (SD: 12.6) at week 104. In addition, at week 104, participants reported less disability for activity and work than at baseline [973].

Etranacogen dezaparvovec is the first gene therapy for the treatment of severe and moderately severe haemophilia B, an inherited disorder characterised by an increased bleeding tendency due to a partial or total deficiency of factor IX (FIX) activity. According to the results of a Phase 2b, open-label, single-arm, multicentre, phase 2b trial with 3 participants who were treated with a single infusion of the innovative therapy, stable, durable and clinically relevant increases in FIX activity were reported, and bleeding and the need for prophylaxis were avoided for 3 years. After therapy administration, FIX activity increased to a mean of 40.8% at year 1 and was maintained at 36.9% (min-max, 32.3%-41.5%) at year 3 (Figure 232)[974].

FIGURE 232. SUSTAINED INCREASE IN FACTOR IX ACTIVITY FOLLOWING ETRANACOGENE DEZAPARVOVEC ADMINISTRATION IN SEVERE HAEMOPHILIA B



Note: Uncontaminated FIX activity measured by a 1-step aPTT assay. *Samples at baseline and week 1 may have included exogenous FIX substitution activity.

Abbreviations: aPTT: activated partial thromboplastin time; **FIX:** factor IX.

Source: von Drygalski (2023)[974]

Among the most recent approvals, exagamglogen autotemcel stands out as the first gene therapy to use CRISPR/Cas9 technology, an innovative gene-editing tool, for the treatment of sickle cell disease (SCD) and transfusion-dependent β-thalassaemia (TDT)[975]. Its efficacy in patients with SCD has been tested in the recent CLIMB SCD-121 study, an ongoing phase 3 trial with patients receiving a single dose of exagamglogen autotemcel. Substantial and clinically meaningful improvements were observed in all patient-reported outcome measures assessed which included improvements in HRQoL, including physical, emotional, social/family and functional well-being, pain experience and general health status[976].

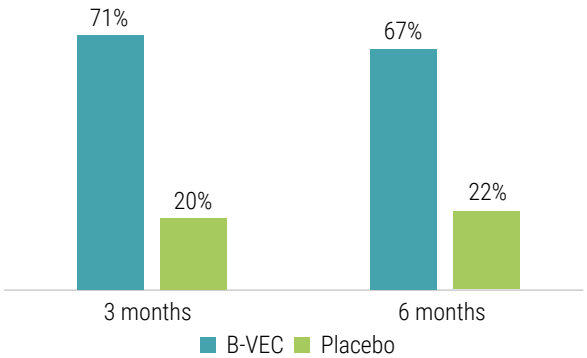
Regarding β-thalassaemia TDT, this is an inherited haematological disorder that involves chronic red blood cell transfusions and iron chelation therapy, and therefore has a negative impact on HRQoL. The advent of innovative gene therapy with exagamglogen autotemcel has brought significant benefits in the quality of life and symptomatology of these patients. The CLIMB TDT-111 study, an ongoing 24-month phase 3 trial, evaluated the impact of this therapy in patients with β-thalassaemia TDT receiving chronic red blood cell transfusions. According to the results, the therapy achieved substantial improvement in EQ-5D-5L and EQ VAS scores (mean changes at month 24 [n=15]: 0.12 [SD: 0.26] and 10.2 [SD: 20.9] points; minimum clinically important difference (MCID) 0.078 and 7 to 10, respectively). The FACT-G total score for functional assessment of cancer therapy improved from baseline to month 12 and was maintained until month 24 (mean change at month 24 [n=15] 10.3 [SD: 17.0] points; MCID 3 to 7), with improvements observed in all 4 subscales (physical, social/family, emotional and functional well-being). Also the BMTS score for transplant assessment improved at month 12 and was maintained until month 24 (mean change at month 24 [n=15] 6.8 [SD: 4.7] points; DMCI 2 to 3)[975].

Also for β-thalassaemia TDT, another potentially curative gene therapy called betibeglogen autotemcel has been approved. More than 90% of people who received this treatment in phase 3 studies did not need red blood cell transfusions during 8 years of follow-up. Prior to the advent of these gene therapies, the only curative alternative available for β-thalassaemia TDT was allogeneic haematopoietic stem cell transplantation, which was limited to patients with a donor with a human leukocyte antigen (HLA) match[977].

On the other hand, the gene therapy eladocagen exuparvovec approved in 2022 has been key in addressing aromatic amino acid decarboxylase deficiency (AADCD). In these patients, this advanced therapy has been shown to improve long-term survival, quality of life and resource use compared to patients treated with standard supportive care, which may alleviate certain symptoms but did not adequately improve long-term motor function[978].

The latest FDA approvals in 2023 include two innovative gene therapies for RDs. First, beremagen geperpavec for dystrophic epidermolysis bullosa (DEB), an extremely rare genetic skin disease that causes blistering and skin lesions. Secondly, delandistrogen moxeparvovec to treat a certain muscle disorder known as Duchenne muscular dystrophy (DMD).

FIGURE 233. COMPLETE WOUND HEALING RATE (%) IN DEB PATIENTS TREATED WITH BEREMAGEN GEPERPAVEC IN COMPARISON WITH THE PLACEBO GROUP AT 3 AND 6 MONTHS



Abbreviation: B-VEC: beremagen geperpavec.

Source: Guide (2022)[979]

The efficacy of beremagen geperpavec in wound healing has been proven in a phase 3, double-blind, randomised, placebo-controlled trial involving patients 6 months of age or older with genetically confirmed EAD. For each patient, a pair of primary wounds was selected, with the wounds matched for size, region and appearance. At 6 months, 67% of the wounds exposed to gene therapy were observed to achieve complete healing, in contrast to only 22% of the wounds exposed to placebo (Figure 233). This significant difference of 46 percentage points (95%CI 24-68, p=0.002) underlines the positive impact of this gene therapy[979].

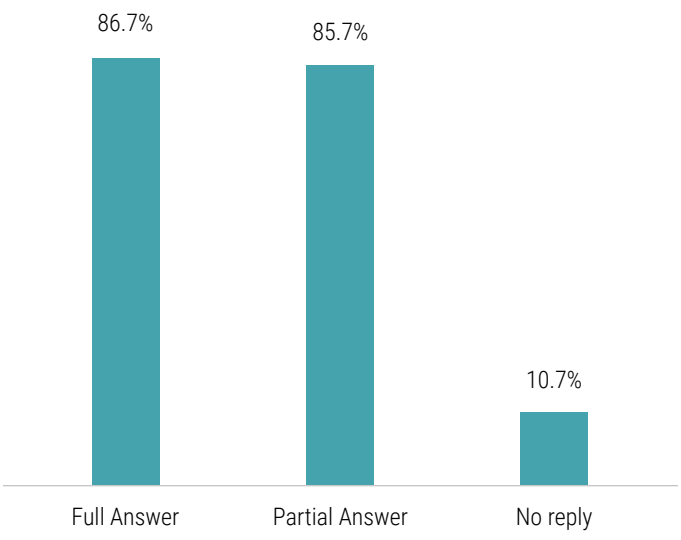
The delandistrogen moxeparvovec represents a significant breakthrough, as it is the first gene therapy approved to treat DMD in children. According to the available data, this gene therapy has been

shown to globally maintain the mean score on the North Star Ambulatory Assessment (NSAA), a 17-item scale used to assess functional motor abilities in children with DMD, even after 96 weeks of treatment. This result is remarkable, as functional decline would be expected based on the natural history of the disease. Furthermore, the findings indicate a maintenance of motor function for two years after treatment with delandistrogen moxeparvovec[980].

Also noteworthy is the FDA approval in 2021 of a new tissue therapy based on allogeneic processed thymus tissue for patients with congenital athymia. Treatment with the innovative tissue therapy in 100 patients with untreated congenital athymia led to the development of naive T-cells with a 1-year survival rate of 77% and a median follow-up of 7.6 years. Specifically, the estimated Kaplan-Meier survival rates at year 1 and year 2 after therapy administration were 77% (95%CI: 0.670-0.844) and 76% (95%CI: 0.657-0.834), respectively[981].

Finally, the latest cell therapies approved for non-oncology indications, such as tabelecleucel for Epstein-Barr virus-positive post-transplant lymphoproliferative disease (EBV+ ELPT) and donisleucel for type 1 diabetes (TD1), are worth highlighting.

FIGURE 234. OVERALL SURVIVAL RATES (%) 1 YEAR AFTER RECEIVING TABELECLEUCEL FOR VEB+ ELPT AS A FUNCTION OF THE RESPONSE TO THE TREATMENT

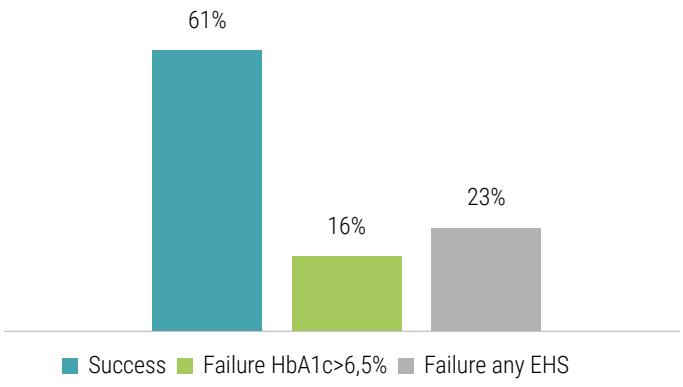


Source: HemOnctoday (2021)[983]

Survival in EBV+ PTLD is poor after initial treatment failure, indicating an urgent need for therapies. The 2022 EU approval of tabelecleucel marks a significant milestone in the treatment of this ultra-rare disease and offers hope for patients with relapsed or refractory disease, where therapeutic options are limited. Available data indicate a promising clinical benefit without the safety concerns associated with other allogeneic T-cell therapies[982]. One study analysed overall survival based on best response to treatment with tabelecleucel in 50 patients[983]. The results showed 1-year OS rates of 86.7% (95% CI 64.2-95.5) for patients with a complete response to treatment and 85.7% (95% CI 33.4-97.9) for those with a partial response (Figure 234). In addition, more than 80% of patients who responded to treatment with tabelecleucel for EBV+ PTLD were still alive two years after initial treatment, according to study results[983].

Donislecel, approved by the FDA in 2023, is the first allogeneic pancreatic islet cell therapy and has become a major breakthrough in the treatment of autoimmune type 1 diabetes (T1D)[418]. The primary efficacy and safety analysis of this therapy derives from its two main studies, UIH-001 and UIH-002, which used a composite efficacy endpoint of no severe hypoglycaemic events (HSEs) and glycated haemoglobin (HbA1c) values of ≤ 6.5%. The pooled analysis involved 30 adults with long-standing T1D1 who received up to three transplants of the minimum total predicted dose of 10,000 islet cell. Therapeutic success, as defined by the primary endpoint of the study, was achieved in 63% of patients, with a substantial improvement in glycaemic control and a reduction in insulin requirements. However, some limitations were observed, with 16.7% of patients not achieving the primary endpoint due to elevated HbA1c levels or 6.5% experiencing at least one EHS (Figure 235)[984]. Despite this, the majority of patients (83.3%) achieved insulin independence, with some maintaining this status for prolonged periods, supporting the long-term efficacy of the treatment[984].

FIGURE 235. FULFILLMENT OF THE PRIMARY EFFICACY ENDPOINT (%) 1 YEAR AFTER THE LAST TRANSPLANT WITH DONISLECEL CELL THERAPY IN PATIENTS WITH T1D (UIH-001 AND UIH-002 STUDIES)



Abbreviation: EHS: severe hypoglycaemic events.

Source: FDA (2021)[984]

Therapeutic success, as defined by the primary endpoint of the study, was achieved in 63% of patients, with a substantial improvement in glycaemic control and a reduction in insulin requirements. However, some limitations were observed, with 16.7% of patients not achieving the primary endpoint due to elevated HbA1c levels or 6.5% experiencing at least one EHS (Figure 235)[984]. Despite this, the majority of patients (83.3%) achieved insulin independence, with some maintaining this status for prolonged periods, supporting the long-term efficacy of the treatment[984].

Finally, based on the most recent data from ongoing clinical trials with orphan drugs, it is expected that specific treatments for many other rare diseases will be approved in the future. It is estimated that there are almost 800 potential ODs to treat various RDs currently in development, among which oncology therapies together account for 35%[985].

The remarkable increase in the approval of new ODs for the treatment of RDs has facilitated the introduction of treatments in pathologies that lacked therapeutic options. Although these innovative therapies do not achieve complete cure of the disease, they play a crucial role in reducing premature mortality and increasing the years of life gained for affected patients.

Mehta (2017)[918], Schultz (2018)[936], Wensink (2020)[919]

In recent years, innovative chemical molecules and biological therapies have been approved that have improved survival and quality of life in patients with rare and ultra-rare diseases with no therapeutic options. Advanced therapies have also been approved that have achieved unprecedented advances in rare oncological and non-oncological diseases. Highly effective targeted treatments for many other rare diseases are expected to be approved at a similar or higher rate in the near future.

Murtada (2023)[930]; Mahadeo (2024)[982]; Farrell (2021)[924]; Russo (2024)[943]; Garrelfs (2021)[946]; van de Donk (2023)[951]; Lin (2023)[967]; HemOnctoday (2022)[977]; PhRMA (2021)[985]

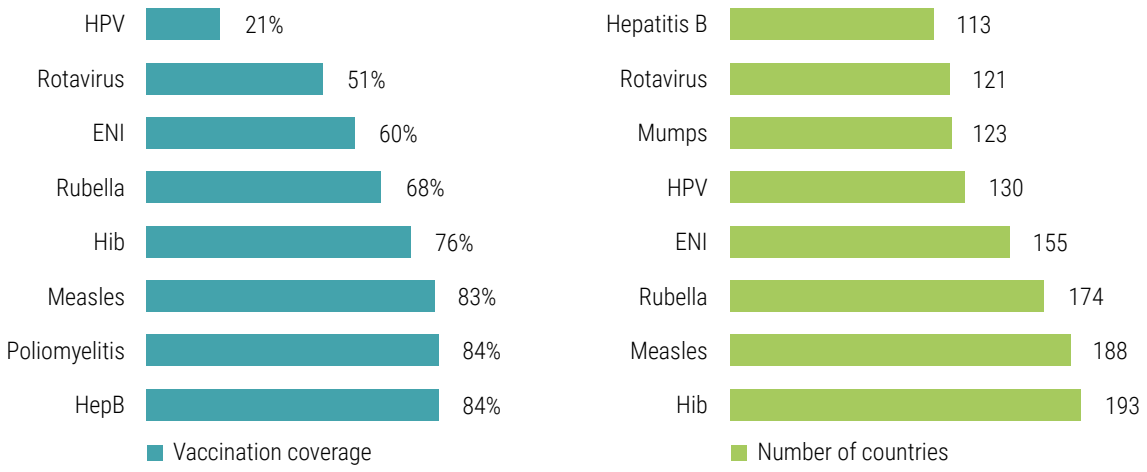
VACCINES

Vaccines are a crucial milestone in the prevention of infectious diseases, and have had an enormous impact on global health. With the exception of water purification, no other public health measure has contributed to reducing human morbidity and mortality as much as vaccination. It is clear that the global epidemiological landscape has evolved in line with the introduction of vaccines into our prophylactic arsenal.

Gradually, increased vaccine efficacy and safety have improved the prevention of various infectious diseases, especially in children, which caused high morbidity, mortality and sequelae. Systematic vaccination programmes have led, for example, to the eradication of smallpox, the interruption of polio transmission in much of the world, the reduction of measles by more than 95% in the Western hemisphere, and the control of diseases such as tetanus, diphtheria, rubella, pertussis, invasive Haemophilus influenzae disease, among others[152,986].

Today, more than 40 safe and effective vaccines are available to prevent disease, protect lifelong health and help prevent and mitigate disease outbreaks. Childhood immunisation prevents 4 million deaths worldwide each year, and it is estimated that more than 50 million deaths could be prevented through immunisation between 2021 and 2030[987]. Despite vaccination being one of the most effective public health interventions, vaccination coverage has stagnated compared to the decade before the COVID-19 pandemic, as the associated disruptions and vaccination efforts overburdened health systems in 2020 and 2021. However, from a global perspective, recovery to pre-pandemic levels is on the horizon. Diphtheria, tetanus and pertussis (DTP) vaccine coverage in 2022 is reported to be almost back to 2019 levels, with three doses of DTP administered to 84 per cent of infants worldwide (about 110 million) to protect them against these infectious diseases that could lead to severe disability and disability, and even death. In 2022, the global vaccination rate has shown variations by type of disease and number of countries in which it is introduced (Figure 236). Global vaccine coverage figures mask significant disparities between countries in different income strata, underscoring the need for a coordinated global approach to ensure equitable access to vaccines in both low- and high-income settings[988].

FIGURE 236. GLOBAL VACCINATION RATE AND NUMBER OF COUNTRIES WHERE VACCINES ARE INTRODUCED, BY DISEASE, 2022

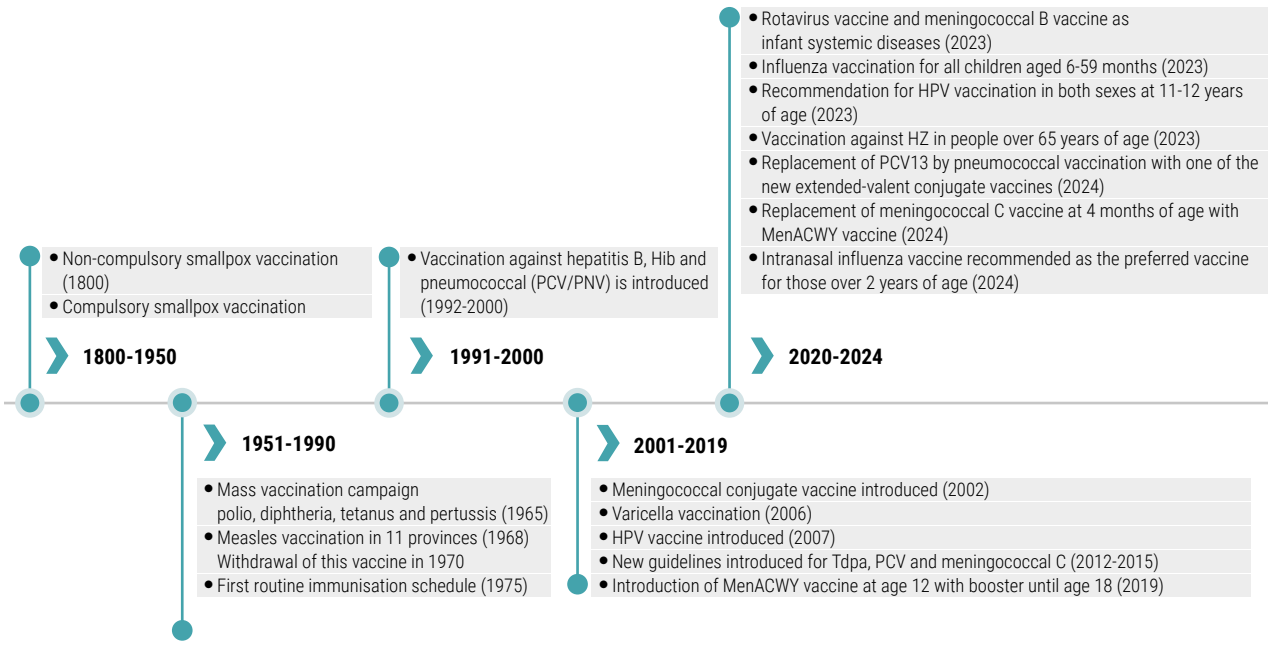


Abbreviations: **IPD:** Invasive pneumococcal disease; **Hib:** Haemophilus influenzae type b; **HPV:** Human Papillomavirus.

Source: own elaboration based on WHO (2023)[988]

Vaccination activity in Spain dates back to around 1800, although it was in 1975 that the first systematic vaccination schedule was implemented[986]. Since then, the schedule has undergone numerous modifications over time (Figure 237). Vaccines introduced in Spain include hepatitis B (HB, 1992-1996), Haemophilus influenzae type b (Hib, 1996-2000), pneumococcal (PCV, 1999-2009), meningococcal (MenC and MenACWY, 2000-2019), varicella (Var, 2006) and human papillomavirus (HPV, 2007). More recently, rotavirus and meningococcal B vaccines have been introduced as routine vaccines for infants[989]. In addition, influenza vaccination is recommended from the age of 6 months, with the intranasal option being preferred from the age of 2 yearss[990].

FIGURA 237. KEY MILESTONES IN THE EVOLUTION OF VACCINATION, SPAIN, 1800-2024



Abbreviations: **MenACWY:** meningococcal tetravalent conjugate vaccine (ACYW); **Hib:** Haemophilus influenzae type b; **HZ:** herpes zoster; **Tdpa:** diphtheria, tetanus and pertussis vaccine (low antigenic load); **PCV/PNV:** pneumococcal conjugate vaccine/pneumococcal polysaccharide vaccine; **HPV:** human papillomavirus vaccine.

Source: Own elaboration based on Álvarez García (2024)[990]; CAV-AEP (2023)[989]; Ministerio de Sanidad, Consumo y Bienestar Social (2015)[991] and Asociación Española de Pediatría (2020)[986]

Hepatitis B virus (HBV) infection affects 296 million people chronically, with an estimated 1.5 million new infections each year. According to WHO data, in 2019, hepatitis B caused an estimated 820,000 deaths worldwide, mainly from liver cirrhosis or liver cancer[992]. While acute hepatitis can be lethal in 1-2% of cases, the chronic forms are the most clinically relevant due to their frequency. Hepatitis B virus, together with human papillomavirus, is a proven cause of vaccine-preventable cancer. Worldwide, it is estimated that more than half of all cancers originating in liver cells are due to HBV[993].

Prevention of the disease relies primarily on immunisation, both active and passive, proper handling of blood, body fluids and blood transfusions, as well as prevention measures against sexually transmitted infections. Although safe and highly effective vaccines exist and have been included in most countries as part of the routine childhood immunisation schedule, achieving their adoption and timely coverage globally remains a major challenge[994]. It is estimated that scaling up HBV vaccination to 90% of newborns in 110 low- and middle-income countries by 2030 could prevent 710,000 (580,000 to 890,000) deaths in the 2020-2030 birth cohorts compared to the current situation, with the greatest benefits in Africa[995].

Spain is currently considered a country with a low burden of hepatitis B, with a prevalence of active infection of between 0.1% and 0.4% and a low incidence of neonatal and infant transmission, reflecting the effectiveness of the prevention and control measures implemented in the country[996]. This has been demonstrated in a study that analysed the impact of vaccination programmes after 20 years of use in Spain, concluding that, since their introduction, the incidence of HBV infection has halved from 2 cases per 100,000 inhabitants in 2002 to 1 case per 100,000 inhabitants in 2017[997]. The effective implementation of HBV vaccination programmes has resulted in a significant decrease in the HBV carrier rate as well as in hepatitis B-associated morbidity and mortality. Since their introduction, HBV vaccination programmes have prevented an estimated 210 million new HBV infections worldwide. These improvements in vaccination programmes are in line with the impact targets of reducing new HBV infections by 90% and HBV-related deaths by 65%[998].

Recently, the impact of HBV vaccination on patients with chronic liver diseases other than chronic hepatitis B has been analysed. The results showed that patients with these diseases who were vaccinated against HBV, including those with liver cirrhosis, had a significantly better survival (p=0.000)[999].

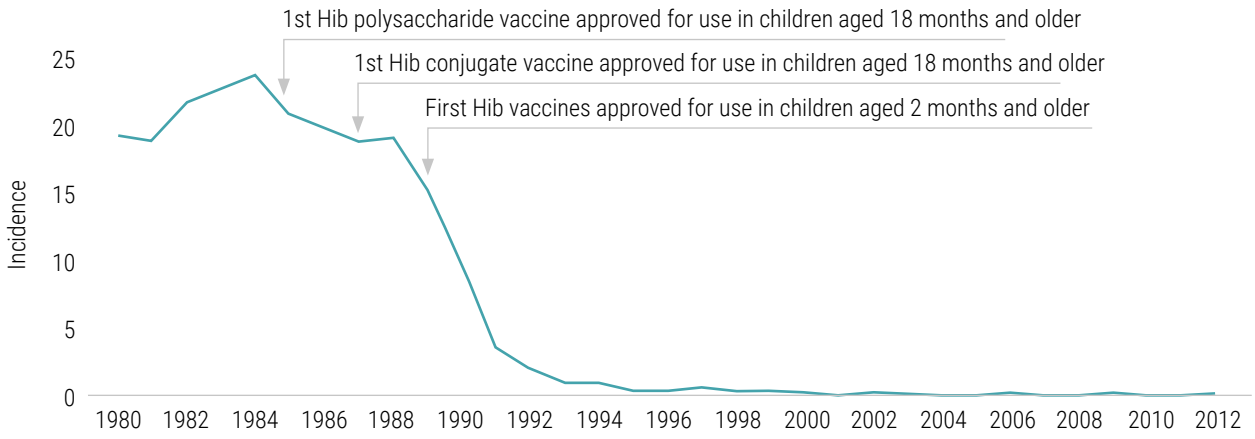
Another recent study analysed mortality as a function of immune response to the vaccine in dialysis patients who completed a course of HBV vaccination. Compared to non-responders, HBV vaccine responders had a lower risk of all-cause mortality (pooled relative risk (RR) 0.64, p<0.001) and a lower risk of cardiovascular mortality (pooled RR 0.74, p= 0.02)[1000].

For Haemophilus influenzae type b (Hib) disease, the main clinical pictures include meningitis, epiglottitis, pneumonia and osteoarticular infection, and generally affect children under 5 years of age. Hib meningitis is associated with mortality rates in industrialised countries of less than 5% but can be as high as 40% in developing countries[1001]. Before widespread immunisation, Hib was responsible for more than 95% of cases of epiglottitis986 and was the most common cause of bacterial meningitis in children in Europe. It remains the leading cause of meningitis morbidity and mortality in non-immunised populations worldwide[1001]. According to the latest data published by the European Centre for Disease Prevention and Control, in 2018, 3,982 cases of invasive Hib disease were reported in Europe, with a notification rate of 0.8 cases per 100,000 population, an increase compared to 2014, when it was 0.6[1002]. In Spain, 179 cases were reported in 2021 with a notification rate of 0.40. In 2022, a total of 462 cases were reported (rate of 0.97)[1003].

More than three decades have passed since Hib conjugate vaccines were first developed, and today several vaccine formulations with a Hib component are included in the immunisation schedule of almost every country in the world[1004]. The first two Hib-conjugated vaccines were licensed in Spain in 1993 and introduced into the vaccination schedule in December 1997. Since 2001, vaccination coverage in Spain has exceeded 94%[986]. In 2019, the average coverage of the three doses of Hib vaccine in Europe was 85%[1005].

The result of this process has been a significant decrease in the incidence rate of this disease, which before the vaccination campaign in 1996, had an incidence of between 8.3 and 26.3 cases per 100,000 inhabitants in the different Autonomous Communities (compared to the current 0.9)[1006]. In other countries, such as the United States, this reduction has been similar, from around 25 cases per 100,000 inhabitants in the pre-vaccination period to levels close to zero after the implementation of the vaccine (Figure 238)[1007].

FIGURE 238. EVOLUTION OF THE INCIDENCE RATE OF INVASIVE HIB DISEASE IN THE PRE- AND POST-VACCINATION PERIODS, UNITED STATES, 1980-2012

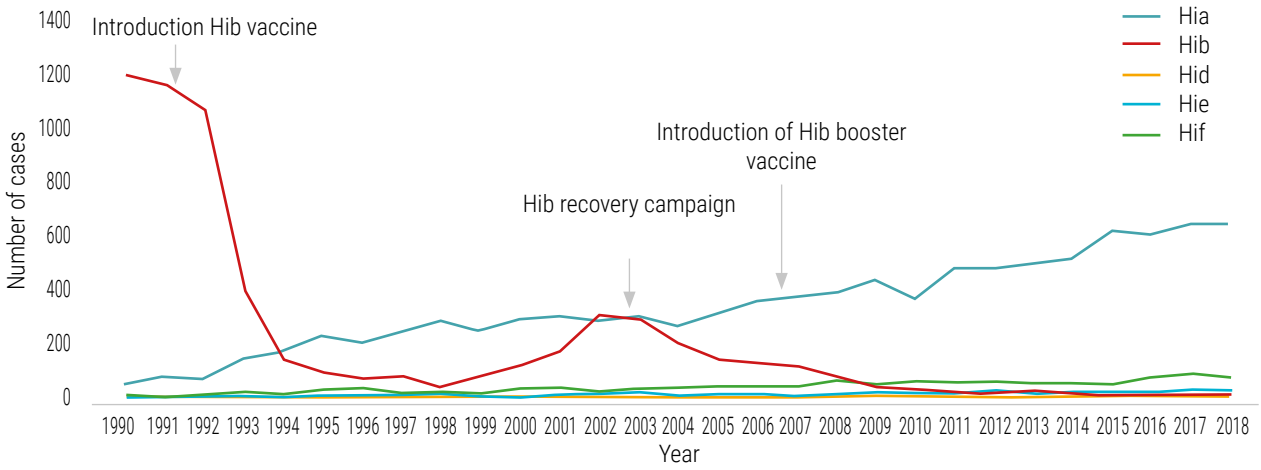


Source: American Academy of Pediatrics (2018)[1007]

A study in Sweden presents similar results after analysing data from 1986-2015, identifying reductions of up to 95% in the incidence rate of invasive Haemophilus influenzae disease following the introduction of vaccination in the population in one region of the country[1008]. More recently, the change in the epidemiology of Hib disease in The Gambia following the introduction of vaccination has been analysed. The Hib disease incidence of 5.0-8.0 per 100,000 children per year (analysed in children aged 2-59 months from May 2008 to December 2017), represents a reduction of more than 90% from the pre-vaccination Hib meningitis incidence of 60.0-70.0 per 100,000 children per year in the period 1990-1993[1009].

Also the introduction of Hib vaccine into the UK immunisation schedule in 1992 resulted in a rapid decline in invasive Hib disease in children under five years of age, from 23.8/100,000 in 1991-1992 to 1.8/100,000 in 1993-1994. This decline spread to other age groups due to the herd immunity effect, reaching an incidence of 0.63/100,000 in 1998. However, after 1999, cases of Hib infection in children increased, with 134 cases in 2002 compared to 22 in 1998, reaching an incidence of 4.60/100,000 in 2002 (Figure 239)[1004].

FIGURE 239. NUMBER OF CASES OF INVASIVE HAEMOPHILUS INFLUENZAE INFECTIONS BY SEROTYPE, ENGLAND, 1990-2018



Abbreviation: NTHi: non-encapsulated or non-typeable H. influenzae.

Source: Slack (2021)[1004]

Pneumococcus causes two forms of disease, invasive, such as meningitis, bacteraemia and sepsis, among others, and non-invasive, such as pneumonia, otitis media and sinusitis. According to the WHO, pneumonia is the leading single cause of infant mortality worldwide and pneumococcal disease is the most common cause of bacterial pneumonia in children[1010]. In Spain, pneumococcal infection is associated with high morbidity, related hospitalisation and mortality. According to a recent study, between 2016 and 2020, there were a total of 253,899 hospitalisations and a total of 35,716 deaths due to pneumococcal infection in Spain, with a case fatality rate of 14.07%[1011]. Specifically, the case fatality rate of invasive pneumococcal disease (IPD) is estimated at 15%-20% in young adults and 30%-40% in the elderly. In the Community of Madrid, the average annual incidence of IPD for the period 2018-2021 was 6.36 cases per 100,000 population[1012].

The introduction of pneumococcal conjugate vaccines (PCVs) has led to dramatic changes in the epidemiology of pneumococcal infections. There are currently four licensed vaccines in Spain: one polysaccharide with 23 serotypes (VNP23) and four conjugate vaccines with 13 (VNC13), 10 (VNC10), licensed in 2009 and the most recent with 15 (VNC15) and 20 serotypes (VNC20), licensed in 2022[1013]. Since its authorisation and commercialisation in Spain in 2022, different Autonomous Communities (CCAA) have included CNV20 as a funded vaccine in their routine vaccination schedule[1014].

Several studies have tried to analyse the impact of these vaccines on the incidence and hospitalisations caused by the disease. An example of this is the systematic review conducted by Alicino et al. (2017), with the aim of analysing the impact of the introduction of the NCV10 and NCV13 vaccines on hospitalisations of patients with clinically or radiologically confirmed pneumonia in children in two age groups, under 2 years of age and between 2 and 5 years of age[1015]. According to the authors, the introduction of these vaccines has reduced hospitalisations by 17% and 31% in children under 2 years of age with clinically and radiologically confirmed pneumonia, respectively, and by 9% (clinically confirmed pneumonia) and 24% (radiologically confirmed pneumonia) in children between 2 and 5 years of age.

On the other hand, Picazo et al. (2017) analysed the effectiveness of CNV13 versus CNV7 on the incidence of NIDs in the Community of Madrid, in children under 15 years of age, in periods with different vaccine financing policies, which varied between private, public or mixed financing. They concluded that public funding of the VCN13 vaccine led to high vaccine coverage (95%), drastically reducing NIDs caused by serotypes included (and not included) in the VCN13 vaccine. With the withdrawal of the public funding programme for this vaccine, there was a reduction in vaccination coverage from 95% to 68%, and a stagnation in the fall of NIDs, suggesting an immunological weakening of the population[1016].

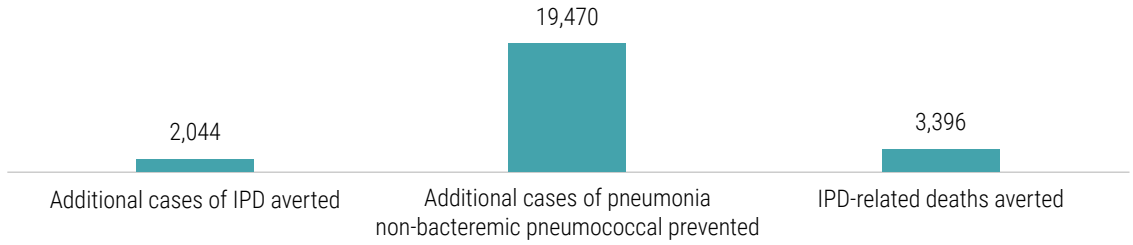
Between 1998 and 2021 in the United States, rates of IPD among children under 5 years of age declined by 95% overall and by 99% for disease caused by serotypes covered by CNV13. The declines were observed from 2001 onwards among adults and were due to the fact that the use of CNV in children generates a community or herd immunity effect[1017].

At the national level, all childhood and adult cases of IPD received at the Spanish Pneumococcal Reference Laboratory between 2009 and the first half of 2023 have been collected. The experts stressed the importance of surveillance of IPD, including the evolution of prevalent serotypes, to assess the impact of current and future PCVs, as well as the emergence of serotypes not covered by vaccines. Despite the marked reduction in cases of IPD in children under 2 years of age during the first year of the pandemic in 2020, a return to pre-pandemic levels (2009-2019 period) has been observed in 2022. In addition, between 2022 and 2023, there has been a significant increase in serotype 3 in children, becoming predominant also in adults over 65 years of age[1018].

More recently, in Spain it has been reported that, over a 10-year time horizon, vaccination with a single dose of CNV20 could prevent 2,161 additional cases of ENI (2,044 bacteraemias, 117 meningitis) compared to sequential vaccination with CNV15 followed by one dose of NPV23 in the population. Spanish

adults over 60 years of age. Overall, a single dose of CNV20 prevented an additional 19,470 cases of non-bacteremic pneumococcal pneumonia, of which 29.26% (5,700) required hospitalisation. In addition, the use of CNV20 progressively reduced ENI-related deaths, totalling 3,396 deaths averted (Figure 240)[166].

FIGURE 240. IMPACT OF PNEUMOCOCCAL 20-VALENT VACCINE (VCN20) USE IN ADULTS OVER 60 YEARS OLD IN SPAIN OVER 10 YEARS



Abbreviation: IPD: invasive pneumococcal disease.

Source : Cantarero (2023)[166]

Finally, it is worth mentioning the results of a systematic review that selected a total of seven studies published from 2017 to 2021, which found that pneumococcal PCV vaccination13 in children is associated with a 22% decrease in incidence and a 35% decrease in hospitalisation rates[1019]. Among the included studies, Jiménez et al. (2017)[1020] described trends in the incidence and outcomes of community-acquired pneumonia (CAP) hospitalisations among Spanish children from 2001 to 2014 and also assessed the effect of pneumococcal vaccination coverage in this period. They found a significant decrease of 3.67% per year in the incidence of CAP in children under 2 years of age, as well as in those aged 2-4 years after 2009. In addition, a reduction in Streptococcus pneumoniae isolates was observed over time, along with an increase in viral isolates. It was noted that increased vaccination coverage was associated with a decrease in the incidence of CAP hospitalisations in both age groups. In addition, overall crude hospital mortality following CAP decreased significantly from 4.1% in 2001-2003 to 2.8% in 2012-2014[1020].

Invasive meningococcal disease (IMD), caused by the meningococcus (Neisseria meningitidis), is the only cause of bacterial meningitis that can cause epidemics and can lead to the death of a previously healthy individual within hours (more than 95% of those affected have no detected risk factors). The most common forms of IMD are meningitis and sepsis, or a combination of both. Currently in Spain, IMD still has an average mortality rate of around 10%, with severe sequelae occurring in up to 30% of cases[1021].

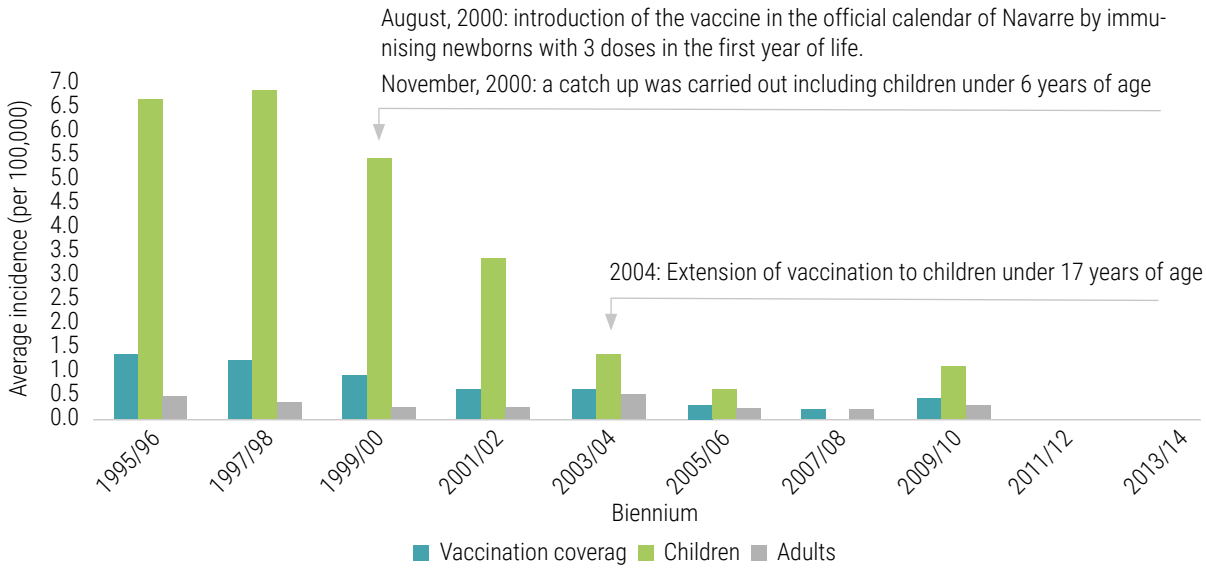
WHO estimates a total number of half a million cases and 50,000 deaths annually due to meningococcal disease. In 2021, 612 confirmed cases of IMD, including 48 deaths, were reported in 30 European Union (EU) countries. The overall notification rate in the EU was 0.1 cases per 100 000 inhabitants in 2021, the lowest since 2017. The notification rate decreased by 83.3% in 2021 compared to 2017 to 2019 (0.6 cases per 100 000 inhabitants)[1022]. In Spain, in the 2020-2021 season, there were 61 confirmed cases of IMD compared to 426 in the pre-pandemic season (-78.8%), corresponding to an incidence rate of 0.13 cases/100 000 population (0.62 in the previous season). In the 2021-2022 season, as is happening in other countries, cases of IMD are increasing, coinciding with the cessation of many of the pandemic containment measures[1021].

In 2000, the meningococcal C conjugate vaccine (MenC) was introduced into the Spanish childhood vaccination schedule, with a three-dose schedule at 2, 4 and 6 months of age. In 2013, the first vaccine against serogroup B was licensed for use in EU countries. MenACWY vaccines are being incorporated into European schedules and, like meningococcal B (MenB), are not funded for the general population. In September 2017, MenACWY vaccines, which were previously exclusively for hospital use, were authorised for sale in community pharmacies in Spain[986]. In 2024, the AEP has recommended the replacement of the MenC vaccine with the MenACWY

vaccine. Routine vaccination against MenB at 2, 4 and 12 months of age has also been recommended, as well as its use at any age in at-risk groups from one year of age onwards[990]. In recent years, several Autonomous Regions have included routine vaccination against MenB, as is the case of the Canary Islands and Castilla y León in 2019, or Andalusia, Catalonia and Galicia in 2022, which means that the vaccine is recommended in the routine vaccination schedule in 48.4% of the Spanish population under 2 years of age[1023]. It is expected that the rest of the Autonomous Regions will implement systematic vaccination against MenB throughout 2023 and at the latest until the end of 2024[1021].

Following the introduction of routine vaccination against MenC in Spain, a significant decrease in the incidence of IMD due to this serogroup was observed, from rates of 1.01 cases per 100,000 inhabitants in the pre-vaccination period 1999-2000 to rates of 0.28 cases per 100,000 inhabitants in 2004-2005 (71% reduction)[1024,1025]. A study conducted in Navarra showed a significant decrease in the incidence of the disease, from an incidence rate of 7.18 cases per 100,000 inhabitants in children under 15 years of age before vaccination (1995-1999) to no cases between 2011 and 2014, with an estimated vaccine effectiveness of between 96% and 99% (Figure 241)[1026] . In the first two years of the pandemic, the incidence of meningococcal disease in Spain fell, while the 2021-22 season saw an increase in incidence with 108 cases recorded, corresponding to a rate of 0.23 cases per 100,000 population for all serogroups, with MenB causing 45 cases (0.1/100,000), MenC 3 cases, MenW 6 and MenY 5[1027].

FIGURE 241. EVOLUTION OF THE INCIDENCE RATE OF INVASIVE MENINGOCOCCAL DISEASE IN THE PRE- AND POST-VACCINATION PERIODS, NAVARRA, 1995-2014

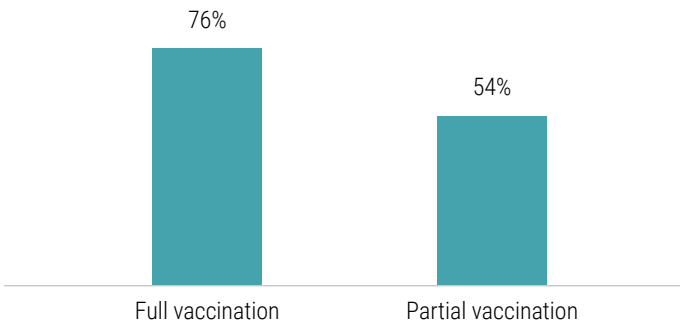


Source: Morales (2016)[1026]

Effectiveness studies of MenACWY vaccines are scarce in Spain, due to their recent inclusion in systematic schedules, uneven coverage, and the low incidence of IMD, although incidence rates per 100,000 population for serotypes W and Y have increased by 3-8 times in the period 2009-2018[986]. In England, the vaccine has been routinely recommended since late 2015, and during the first vaccination season (2015-2016), despite low coverage rates (36%), there was a reduction of up to 69% in the number of serogroup W cases, and subsequent seasons saw decreases of 15% in the number of annual casess[1025].

Two vaccines are currently available in Spain for the prevention of serogroup B IMD authorised by the EU: the four-component vaccine (4CMenB) and the vaccine with two variants of factor H-binding proteins (MenB-fHbp)[1023]. A new study in Spain has demonstrated the effectiveness of the 4CMenB vaccine in reducing the risk of invasive meningococcal disease in children under 5 years of age from 2015 to 2019. According to the results obtained, the effectiveness of full vaccination with 4CmenB against IMD caused by any serogroup was 76% (95%CI: 57%-87%), while for partial vaccination an efficacy of 54% (95%CI: 18%-74%) was observed (Figure 242). Children under 5 years of age who had received the full vaccination schedule had a 71% (95% CI 45%-85%) lower risk of MenB IMD than unvaccinated children. On the other hand, the effectiveness of vaccination with at least one dose of 4CMenB was 64% (95%CI: 41%-78%) against serogroup B disease and 82% (95%CI: 21%-96%) against non-B1028 serogroup B disease[1028].

FIGURE 242. EFFECTIVENESS OF MENINGOCOCCAL B VACCINATION IN MENINGOCOCCAL DISEASE INVASIVE DISEASE CAUSED BY ANY SEROGROUP, SPAIN, 2015-2019



Source: Castilla (2023)[1028]

Chickenpox is the clinical expression of primary varicella-zoster virus (VZV) infection. In the absence of vaccination, the disease is very common, with up to 95% of children having had the disease by the age of 12. In Spain, it is estimated that more than 90% of adults have developed chickenpox and may have the complete VZV genome latent in 5% of their neurons[1023] . Herpes zoster (HZ) is the local manifestation that appears when a latent VZV infection is reactivated, the most important complication of which is the pain that accompanies acute neuritis and post-herpetic neuralgia, especially in immunocompromised individuals.

Systematic reviews and meta-analyses of numerous studies have found that the effectiveness of one dose of VZV vaccine in children aged 9 months to 12 years is 81-83% against any form of the disease and 95-100% against moderate and severe forms[1029,1030]. This has been demonstrated in a study on lessons learned during the first 25 years of the varicella vaccination programme in the United States. According to the results, one dose of varicella vaccine offers moderate protection of 82-85% against the disease in general and high protection of 100% against severe cases. However, this protection may decrease over time. The one-dose programme, implemented between 1995 and 2006, significantly reduced the incidence of varicella and severe cases, with a decrease ranging from 71% to 90%, although it did not completely prevent outbreaks in highly vaccinated communities. The administration of two doses improved the effectiveness of the vaccine by at least 10%, further reducing the incidence of disease and severe cases, as well as the number and size of outbreaks[1031].

A recent study in Slovenia considered the long-term benefits of six two-dose varicella vaccine strategies versus no vaccination over a 50-year time period, including monovalent vaccination at 12 and 24 months of age, or monovalent vaccination at 15 months followed by monovalent or tetravalent vaccination at 5.5 years. Over 50 years, depending on the vaccination strategy, universal varicella vaccination reduced varicella cases by 77-85% and was associated with substantial reductions in varicella deaths (39%-44%), outpatient cases (74%-82%) and hospitalisations (74%-82%)[160].

On the other hand, a study carried out in Spain analysing the annual incidence of HZ in the period 2014-2019 estimates it to be 351.6 cases per 100,000 inhabitants, showing an increase with age, especially from the age of 50 years and reaching the maximum value in the 80-84 age group. In addition, they found that 97.2% of deaths from HZ occur in people aged 65 years or older and that 91.4% of hospitalisations for postherpetic neuralgia (PHN) occur in people aged 50 years or older[1032]. In this regard, the incorporation in 2023 of the vaccine against HZ in people over 65 years of age in the vaccination schedule is noteworthy[1023].

Two vaccines are currently licensed in Spain: a live attenuated vaccine and a subunit vaccine containing VZV glycoprotein E produced by DNA recombination techniques (VVZr vaccine), both vaccines are indicated for the prevention of HZ and post-herpetic neuralgia in people aged 50 years and older[1023]. The efficacy of VVZr was evaluated in two randomised phase 3 clinical trials versus placebo (ZOE-50 and ZOE-70). Pooled analysis of the two studies showed that efficacy in adults aged 70-79 years was 91.3% (95%CI 86.0-94.9) and 91.4% (95%CI 80.2-97.0) in those aged ≥80 years. In addition, vaccination reduced the incidence of PHN significantly, with an efficacy of 88.8% (95%CI: 68.7-97.1) in those aged 70 years and older[1031]. According to long-term data, the efficacy against HZ and immune responses of the VVZr vaccine remained high for at least 7 years after vaccination[1033].

The most common pathology caused by **human papillomavirus** (HPV) infection is genital warts, benign lesions affecting both men and women, produced in more than 90% of cases by low-risk HPVs. In addition, HPV is associated with several types of cancer, including rectal-anal, penile, throat, cervical, vaginal and vulvar cancers. HPV vaccination has proven to be a crucial tool in the prevention of these cancers. In Spain, the prevalence of this disease is 182 cases per 100,000 people. Cervical cancer is the most relevant clinical expression of HPV infection, being the second most frequent cancer worldwide in women aged 15-44 years, after breast cancer. Its incidence in developed countries as a whole is estimated to be 15 cases per 100,000 women. 100,000 women per year. In Europe, there are an estimated 60,000 cases per year. In Spain, the incidence and mortality rates are among the lowest in Europe, at 7.1 and 3.1 per 100,000 women per year, respectively (approximately 2,000 cases and 739 deaths per year)[1034].

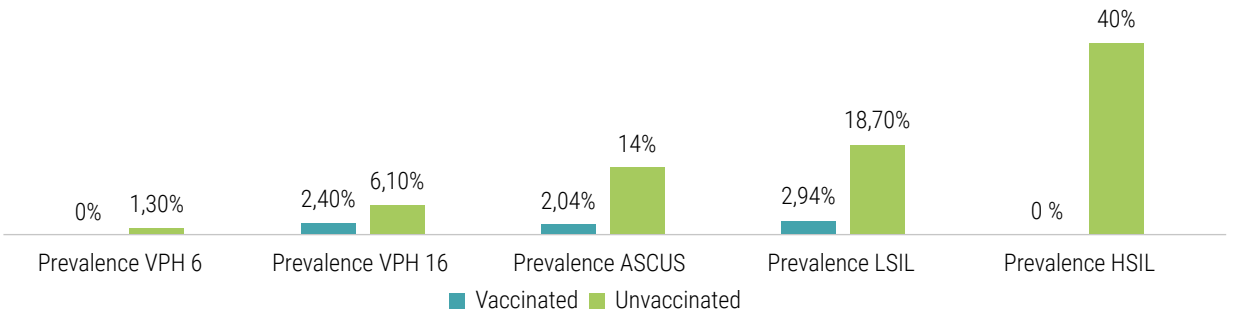
Both women and men can be asymptomatic carriers and vehicles of HPV infection. It is estimated that about 80% of women will have been infected with at least one type of HPV in their lifetime. In Europe, the average prevalence of HPV infection is 8.2%, being higher in young women (25% in women aged 25 years or younger)[1034]. At the end of 2007, the first two HPV vaccines were marketed in Spain, a bivalent HPV 16/18 and a tetravalent HPV 6/11/16/18 vaccine, which were introduced into the routine vaccination schedule for girls. Currently, as of 2023, it will be 15 years since the start of this vaccination in Spain, and precisely to coincide with this anniversary, this recommendation has been extended to boys[1035].

Among the systematic reviews to assess the impact of HPV vaccination on the prevalence of various HPV diseases in the global population, the study by Drolet et al. (2019)[1036] analysed 65 studies from 14 countries, including data from 60 million people. They found that, after 5-8 years of vaccination, the prevalence of HPV 16 and 18 was significantly reduced by 83% (RR: 0.17; 95% CI: 0.11-0.25) in females aged 13-19 years, and by 66% (RR: 0.34; 95% CI: 0.23-0.49) in females aged 20-24 years. For HPV and 66% (RR: 0.34; 95% CI: 0.23-0.49) in females aged 20-19 years. 24 years. For HPV 31, 33 and 45, there was a 54% reduction (RR: 0.46; 95% CI: 0.33-0.66) in their prevalence in women aged 13-19 years. Genital wart diagnoses decreased by 67% (RR: 0.33; 95% CI: 0.24-0.46) in women aged 15-19 years and by 31% (RR: 0.69; 95% CI: 0.53-0.89) in women aged 25-29 years. Among boys aged 15-19 and young adults aged 20-24, these diagnoses decreased by 48% (RR: 0.52; 95% CI: 0.37-0.75) and 32% (RR: 0.68; 95% CI: 0.47-0.98), respectively.

On the other hand, several studies have shown that the use of two doses of HPV vaccine results in similar immune system responses as three doses[1037–1040]. Recently, a systematic review has been published showing that the HPV vaccine is more effective against HPV-related disease outcomes when administered at younger ages, underscoring the importance of early vaccination. According to the results, for younger adolescents aged 9-14 years the efficacy of the HPV vaccine ranged from approximately 74-93% and 12-90% for adolescents aged 15-18 years[1041].

Finally, it is worth mentioning that the first evidence has been published on the effectiveness of the HPV vaccine in Spain[1042]. This is an ambispective cohort study, conducted in 790 women aged 25 and 26 years, which compares the prevalence rate of HPV and cytological abnormalities according to vaccination status. The results showed a significant reduction in the prevalence of HPV 6 (0% vs. 1.3%) and 16 (2.4% vs. 6.1%), as well as in the prevalence of HPV16-related cytological abnormalities: atypical squamous cells of undetermined significance (ASCUS) (2.04% vs 14%); low-grade squamous intraepithelial lesion (LSIL) (2.94% vs 18.7%); and high-grade squamous intraepithelial lesions (HSIL) (0% vs 40%), in the vaccinated group vs the unvaccinated group (Figure 243).

FIGURE 243. EFFECTIVENESS OF THE TETRAVALENT HPV VACCINE IN WOMEN IN SPAIN



Abbreviations: **VPH:** human papillomavirus; **ASCUS:** atypical squamous cells of undetermined significance; **LSIL:** low-grade squamous intraepithelial lesion; **HSIL:** high-grade squamous intraepithelial lesions.

Source: Hernandez-Aguado (2022)[1042]

With regard to influenza, the WHO estimates that there are around one billion cases of seasonal influenza worldwide each year, of which 3-5 million are severe cases. In addition, it causes between 290,000 and 650,000 respiratory deaths annually[1043]. The most effective way to prevent the disease is vaccination. However, influenza viruses are highly susceptible to variation and the vaccine needs to be updated every year[1023]. Influenza has always been the infection with the highest morbidity and mortality in Europe, compared to other communicable diseases, until the advent of SARS-CoV-2. Influenza has a high burden of disease (30-40%) in children who play a major role in the transmission of disease to the rest of the environment, especially vulnerable groups[990]. Recently, the indication for influenza vaccination has been extended to children between 6 and 59 months of age for their individual protection and to prevent contagion to other people of older ages, with a schedule of one dose each influenza season[989].

In Spain, the latest data from the Spanish Acute Respiratory Infection Surveillance System (SiVIRA) show that, in mid-December 2022, the influenza incidence rate stood at 160 per 100,000 inhabitants. The season has consisted of two distinct peaks: the first, due to an influenza A subtype (H3N2); and the second, influenza B[1044]. Currently, different types of inactivated influenza vaccines and an attenuated vaccine are available in Spain for use in the paediatric population from the age of 6 months or 2 years and older. All these vaccines contain antigens from two influenza A virus subtypes (H1N1 and H3N2) and antigens from two influenza B virus genetic lineages (Victoria and Yamagata)[1023]. Recently, the EMA has issued a statement recommending the transition from quadrivalent to tri-valent vaccines that do not include the B/Yamagata component. This recommendation is due to the fact that the B/Yamagata strain of influenza B virus has not been detected in circulation since March 2020, which is attributed, in part, to public health measures implemented to limit the spread of COVID-19 during the pandemic[1045].

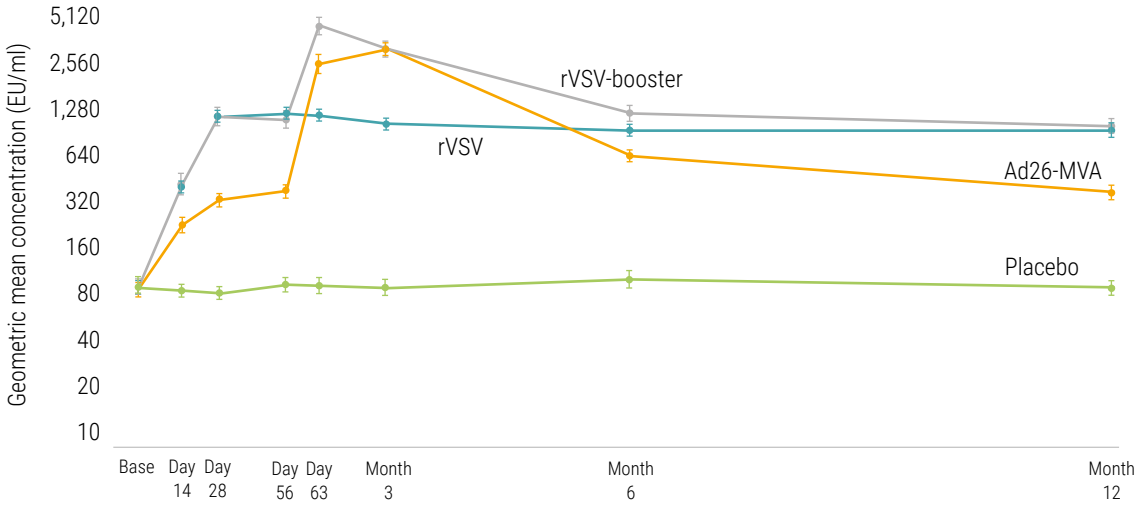
Immunogenicity-enhancing vaccines prevent the risk of influenza and its complications, especially in populations with weaker immune systems. There is evidence of their efficacy, reduction of medical visits and hospitalisations or reduction of outbreaks, demonstrated in clinical trials and meta-analyses with real-life data[1044].

In addition, it is worth mentioning that the use of the intranasal attenuated virus vaccine (LAIV) has recently been recommended as the preferred vaccine for all children aged 2 years and older, as it is a faster, simpler and more convenient way of administering prophylaxis[989]. The safety and efficacy of this vaccine has been analysed in a recent systematic review and meta-analysis including 22 studies, which showed that LAIV was associated with an increased likelihood of seroconversion compared to placebo and taking into account serotype A/H1N1 [pooled odds ratio (OR) = 2.26 (95%CI: 1.12-4.54), p= 0.022; based on 488 participants, no heterogeneity (I2 = 0.0%)][1046].

In addition, the approval in 2020 of the two components of a new vaccine that provides active immunisation to prevent Ebola virus disease (EVD) in people aged one year and older is worth mentioning[361]. The average case fatality rate of Ebola virus disease is around 50%, and in some outbreaks has ranged from 25% to 90%, depending on the circumstances and response. Good outbreak control depends on many types of measures, including the use of vaccines[1047]. It is expected that the use of vaccines will lead to a survival of about 53% in case of infection with a lethal dose of EVD[1048].

A study based on two randomised placebo-controlled trials, one in adults and one in children, has been published to assess the safety and immune responses of three vaccine regimens to prevent EVD. In both adults and children, antibody responses with the different vaccine regimens differed from those with placebo from day 14 onwards. Among adults at month 12, the percentages of participants with an antibody response were 41% and geometric mean concentrations 401 EU per millilitre in the Ad26-MVA group, 76% and 992 EU per millilitre in the rVSV group, 81% and 1037 EU per millilitre in the rVSV-booster group, and 3% and 93 EU per millilitre in the placebo group (p<0.001 for all comparisons) (Figure 244)[1049].

FIGURE 244. ADULT ANTIBODY RESPONSE (GEOMETRIC MEAN CONCENTRATIONS) OF THREE VACCINE REGIMENS TO PREVENT EBOLA VIRUS DISEASE, BY VISIT OF THE ESSAY



Notes: Ad26-MVA group received Ad26.ZEBOV followed by MVA-BN-Phyl 56 days later; rVSV group received rVSVΔG-ZEBOV-GP followed by placebo 56 days later; and rVSV-booster group received rVSVΔG-ZEBOV-GP followed by rVSVΔG-ZEBOV-GP 56 days later. Geometric mean concentration was based on log10 concentration with basal log10 titre and assay site as covariates. Antibody response was defined as an antibody concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per millilitre and an increase in antibody concentration from baseline of at least a factor of 4. I-bars indicate 95% confidence intervals.

Source: PREVAC Study Team (2022)[1049]

Finally, in 2023, two vaccines for the prevention of lower respiratory tract disease due to **respiratory syncytial virus** (RSV) were approved for use in adults over 60 years of age and in children through immunisation of the mother during pregnancy[364]. RSV in considered the main agent of respiratory infection globally and is seasonal like influenza. Worldwide, RSV causes an estimated 33 million lower respiratory tract infections, 3.2 million hospitalisations and some 49,000 deaths each year in children under 5 years of age, 99% of them in countries with lower Human Development Index (HDI). Both hospitalisations and deaths are most common in children under 6 months of age[1050].

According to a recent study, in Europe, one in 56 children under 2 years of age who were born at term are admitted to hospital due to RSV infection, making it the second leading cause of infectious mortality globally in children aged 1-12 months, behind only malaria[1051]. In Spain, it is estimated that RSV infections cause between 15,000 and 20,000 paediatric emergency visits and 7,000 to 14,000 hospitalisations per year. In addition, the number of children in Spain who die from RSV infections is estimated to be between 70 and 250 per year[1052].

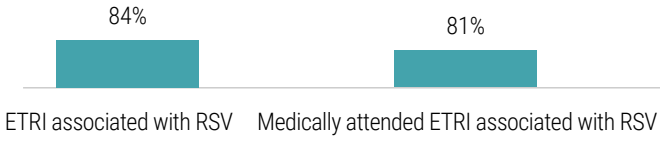
Beyond its impact on children, its impact on the adult population is increasingly described, especially in those over 65 years of age, where RSV is responsible for approximately 1.5 million episodes of lower respiratory tract infection[1050]. The efficacy of a single dose of an RSV vaccine has been tested in adults older than 60 years over two seasons, with rates of 84.4% (95%CI: 59.6%-95.2%) in the prevention of RSV-associated lower respiratory tract disease (LRTD) and 81.0% (95%CI: 43.5%-95.2%) in the prevention of RSV-associated LRTD requiring medical attention (Figure 245)[1053].

On the other hand, the recent recommendation for the use of nirsevimab (monoclonal antibody against RSV) in infants under 6 months and up to 2 years of age in at-risk groups for this disease is also noteworthy[989]. The MELODY study (randomised clinical trial comparing nirsevimab versus placebo in term and late preterm infants) demonstrated a decrease in medically attended RSV disease at 150 days by 74.5% (95%CI 49-87). When the analysis was extended to 3,000 participants, hospitalisation was reduced by 75% (95%CI 49-89) and "severe" admissions (oxygen and/or serum therapy) by 78.6% (95%CI 48.8-91)[1054].

Among the new developments in recent years in the vaccination schedule in Spain, a change of name from vaccinations to immunisations has been proposed, driven by the new monoclonal antibody to prevent RSV disease[989]. In addition, the use of systematic immunisation schedules for healthy individuals and another for those belonging to risk groups has been proposed, as well as the inclusion of a specific section for vaccination recommendations for pregnant women[990].

In the specific chapter related to the disease caused by COVID-19 we detail the main health results achieved thanks to the development of vaccines for the prevention of this disease, responsible for one of the greatest health, economic and social crises of the last 100 years.

FIGURE 245. EFFICACY OF A SINGLE DOSE OF THE VACCINE AGAINST DISEASE ASSOCIATED WITH RESPIRATORY SYNCYTIAL VIRUS IN ADULTS ≥60 YEARS OLD. MULTIPLE COUNTRIES, 2021-2023



Abbreviations: **ETRI:** lower respiratory tract disease; **RSV:** respiratory syncytial virus.

Source: Melgar (2023)[1053]

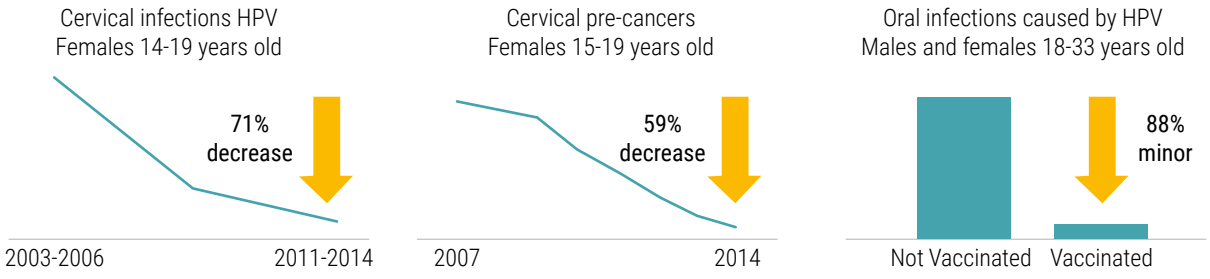
Finally, it is worth noting the number of vaccines currently in various stages of development in Europe (103 by mid-2023), most of them targeting infectious diseases caused by different viruses. More than 80% of candidate vaccines target the adult population, especially those at higher risk of infection with serious diseases. In addition, 43% of candidate vaccines target diseases for which vaccines are not yet registered and 58% are existing vaccines that are still under development, applying new therapeutic approaches[1055].

Finally, It is also important to note that some conventional vaccines, such as those that prevent hepatitis B and HPV, are also considered cancer vaccines, as they prevent infections related to the development of certain types of cancer. The most relevant example of this, and the one that has been used most extensively, is the human papillomavirus (HPV) vaccine in the prevention of **cervical** and other **cancers** related to the female reproductive system. Over the past decade, the impact of HPV vaccination has been demonstrated in real-world settings, especially among girls vaccinated prior to HPV exposure in countries with high vaccination coverage. Peak reductions of about 90% in HPV 6/11/16/18 infections, about 90% in genital warts, about 45% in low-grade cytological cervical abnormalities, and about 85% in biopsy-confirmed high-grade histological cervical abnormalities have been reported[1056].

Another study estimated that, assuming complete vaccination in 47 million women and that the vaccine protects throughout life, the HPV vaccine prevented 379,000 cases of cervical cancer and 156,000 related deaths in 2014. Due to differences in international coverage rates, where high-income countries achieved a higher percentage of vaccinated women, all women vaccinated with at least one dose of vaccine were taken into account. As a result, the numbers of cases and deaths averted increased to 444,600 cases and 184,000 deaths, respectively[1057].

A number of studies have examined the effectiveness of this type of public health programme over the first decade of its implementation. Australia, the United States and New Zealand were among the first countries in the world to adopt it widely among adolescent girls, and much of the subsequent work was conducted for these countries. Australia was a pioneer in vaccination where rapid reductions in HPV infections and genital warts occurred. Data collected four years after the start of the programme showed a 92.6% reduction in genital wart diagnoses among women under 21 years of age (from 11.5% in 2007 to 0.85% in 2011). Among women aged 21-30 years, this proportion is 72.6%[1058]. Subsequent data estimated that the prevalence of associated infections was reduced by 86% among women aged 18-24 years who received all three doses, and by 76% among those who received one or two doses[1056]. Notable, though mixed, results were also achieved in the USA, with reductions in infections ranging from 36% to 91%[1056], although the prevalence of HPV infection has been on a downward trend since the HPV vaccine era (Figure 246)[1059].

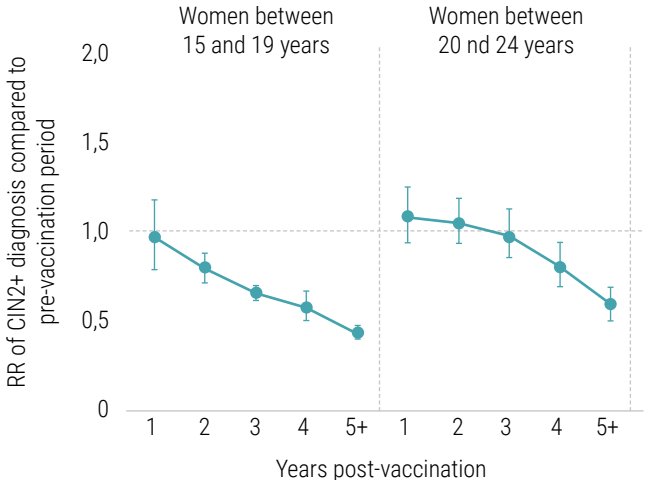
FIGURE 246. PREVALENCE OF CERVICAL VPHV INFECTION, CERVICAL PRECANCERS AND ORAL VPHV INFECTION IN THE VPHV VACCINE ERA, 2003-2017



Source: President's cancer panel (2018)[1059]

A systematic review highlights the result on the effect of HPV vaccination on cervical intraepithelial neoplasia grade 2+ (CIN2+), which is the main intermediate variable used to measure cervical cancer. In the meta-analysis conducted by the same authors 4 years prior to the publication of the current study, the number of years post-vaccination had been insufficient to examine this impact, as CIN2+ can take several years to develop. In the updated review, which looked at follow-up periods of 5-9 years, they concluded that vaccination reduced CIN2+ by half (RR: 0.49; 95% CI: 0.42-0.58) in women aged 15-19 years, and by 31% (RR: 0.69; 95%CI: 0.57-0.84) in women aged 20-24 (Figure 247)[1036].

FIGURE 247. IMPACT OF HPV VACCINATION ON CERVICAL CANCER PREVENTION, MEASURED BY CHANGES IN CIN2+ AMONG WOMEN AGED 15 TO 24 YEARS, OVER MORE THAN 5 YEARS. AUSTRALIA, CANADA, DENMARK, SCOTLAND, AND THE USA



Abbreviations: CIN2+: Cervical Intraepithelial Neoplasia Grade 2+ relative risk.

Source: Drolet (2019)[1036]

Recently, the results of an individual and dynamic model of transmission of HPV infection and disease of multiple HPV types, calibrated with specific data from four low- and middle-income countries, have been published. According to the results, the two-dose schedule offers a reduction in cervical cancer incidence of 79-86%, depending on the country, compared to no vaccination. For an expanded 5-year schedule, with the second dose administered to previously vaccinated girls at age 9 years, assuming 30% coverage at age 14 years among girls vaccinated at age 9 years, the incidence reduction is 71%-78%. However, if the 14-year dose is administered regardless of vaccination status, the incidence reduction is 71%-78%.vaccination coverage and assuming 70% coverage at age 14, the projected reduction is 86-93%, exceeding the efficacy of the two-dose schedule even with a decrease in vaccination coverage[1060].

On the other hand, hepatitis B vaccination remains essential to prevent hepatocellular carcinoma (HCC) and as part of the global response to hepatitis B elimination. Especially given that there are still more than 1.5 million new preventable hepatitis B infections each year and an estimated 296 million people living with chronic hepatitis B infection worldwide, resulting in more than 820,000 deaths annually from liver cirrhosis and HCC. Recently, significant reductions in the incidence rates of hepatitis B-related HCC and the relative risk of developing HCC have been reported in a vaccinated cohort compared to an unvaccinated cohort ranging from 0.31 to 0.38 in the age groups 6-9 years, 10-14 years and 15-19 years (p<0.001) (Figure 248)[994].

FIGURE 248 COMPARISON OF HEPATOCELLULAR CARCINOMA INCIDENCE RATE RATIOS (95CI%) BY AGE GROUP COHORTS BORN BEFORE AND AFTER THE START OF THE UNIVERSAL HEPATITIS B VACCINATION PROGRAMME IN TAIWAN

Source: Flores (2022)[994]

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The development of vaccines has had a significant impact on public health, enabling the eradication of diseases such as smallpox and drastically reducing the prevalence of others, such as polio and measles. It has also facilitated the control and prevention of diseases such as tetanus, diphtheria, rubella, pertussis, invasive Haemophilus influenzae type b disease and human papillomavirus. As vaccination coverage has increased and changes and expansions in vaccination schedules have been implemented, greater control of these diseases has been achieved.

Ekwueme (2000)[152], Arístegui Fernández (2015)[997], Drolet (2019)[1036] Alcino (2017)[1015], Picazo (2017)[1016]

In recent years, it has been recommended in Spain to systematically vaccinate infants with the meningococcal B vaccine, to include the herpes zoster vaccine in people over 65 years of age and to vaccinate against influenza from the age of 6 months, with the intranasal option being preferred from the age of 2 years, as it allows a quicker, simpler and more convenient prophylaxis. At the European level, new vaccines have been approved to prevent Ebola virus disease and respiratory syncytial virus disease. In the future, it is expected that new vaccines will be developed for diseases for which there are no registered vaccines and that existing vaccines will be further improved.

Castilla (2023)[1028]; Melgar (2023)[1053]; EMA (2023)[1048]; CAV-AEP (2024)[1021]

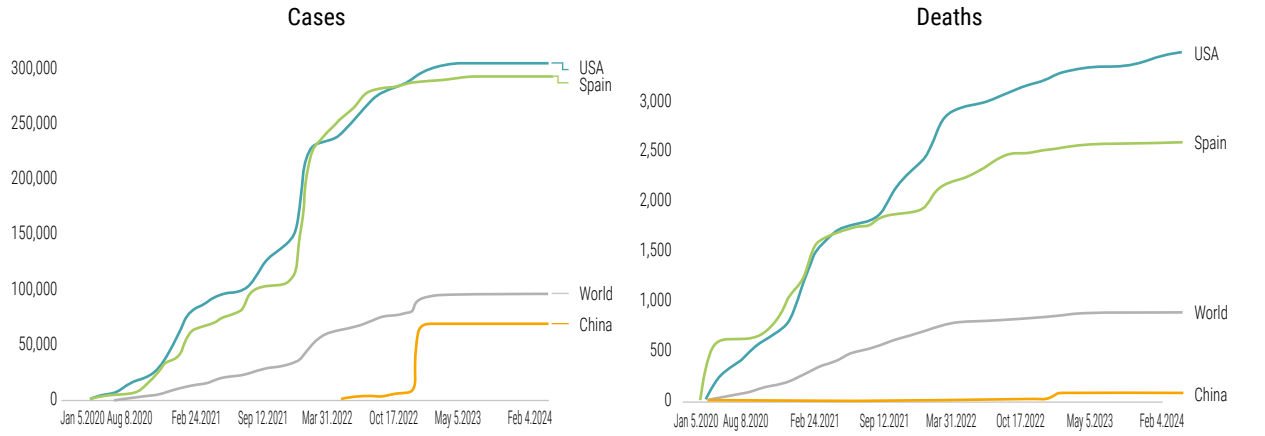
COVID-19

SARS-CoV-2 caused the largest global pandemic in the last 100 years in 2020, with unprecedented effects not only in terms of health, but also in the economic, health care and social spheres. Coronaviruses are a family of viruses that cause infection in humans and various animals and can be transmitted from animals to humans[1061]. Between 1960 and 2018, six coronaviruses had been described in humans, with more or less severe symptoms, but a reduced impact on mortality[1062,1063]. The seventh human coronavirus, named SARS-CoV-2, is the third in this family of highly pathogenic viruses, causing coronavirus disease (COVID-19). It was first reported to WHO on 31 December 2019 by the Wuhan Municipal Health and Sanitation Commission (China)[1061].

On 11 March 2020, the WHO declared a global pandemic, due to the levels of spread and severity of the disease, which at that time had already affected 118,319 people, with 4,292 deaths, almost a third of which occurred outside China, in a total of 114 countries in all regions of the world[1064]. On 14 March, the Spanish Council of Ministers declared a state of alarm throughout the national territory, initially established for a period of 100 calendar days[1065].

Until February 2024, a total of 774.5 million confirmed cases of COVID-19 have been reported worldwide (14.0 million in Spain) and 7.02 million deaths have been reported worldwide (121,852 deaths in Spain) (Figure 249)[1066].

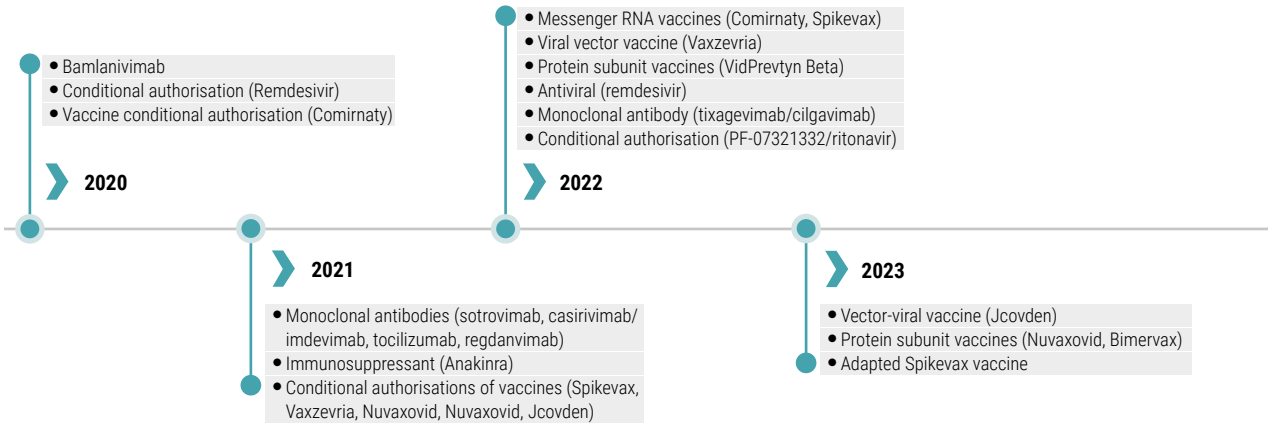
FIGURE 249. CUMULATIVE NUMBER OF COVID-19 CONFIRMED CASES AND DEATHS PER MILLION POPULATION IN THE WORLD, USA, CHINA AND SPAIN, JANUARY 2020-FEBRUARY 2024



Note: RNA (ribonucleic acid). **Source:** Our World in Data (2024)[1066]

The main milestones in the evolution of COVID-19 treatments are shown in Figure 250.

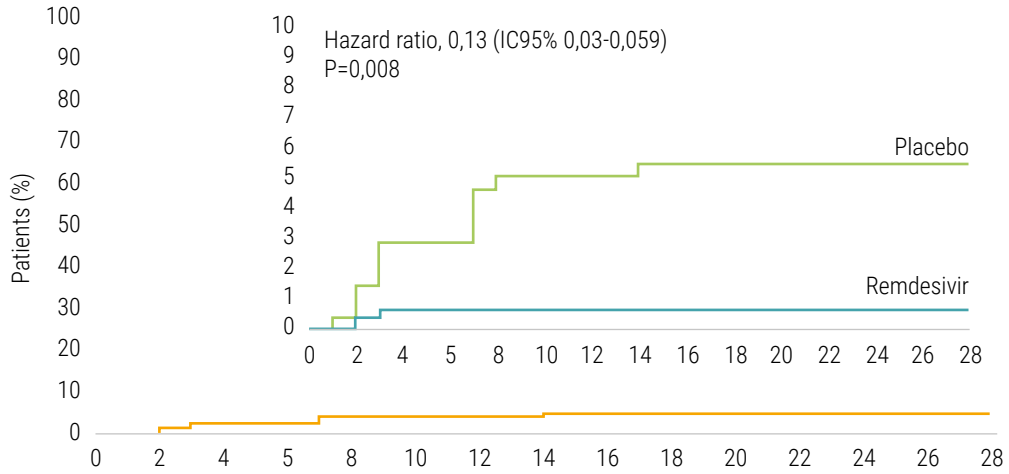
FIGURE 250. EVOL UTION OF COVID-19 TREATMENTS



Source: own elaboration based on (2024)[1067]

One of the first treatments available against COVID-19 was remdesivir, an antiviral treatment that was conditionally approved by the EMA for inpatient treatment in July 2020 (in August 2022 as standard). The treatment had previously been tested as a treatment for Ebola and had generated promising results in animal studies for MERS-CoV and SARS[1068]. In the pivotal clinical trial of remdesivir, conducted in 397 patients admitted with severe COVID-19 infection, it was observed that, after 14 days from the start of the study period, 60% of patients who received treatment with this antiviral had been discharged from hospital[1069]. Another trial, involving 584 patients with moderate COVID-19 and pneumonia, showed that patients treated with COVID-19 were 65% more likely to perceive clinical improvement at day 11 than patients receiving treatment as usual (OR 1.65; 95%CI 1.09 - 2.48)[1070]. A third trial, involving 1,063 patients, which evaluated the efficacy of Remdesivir versus placebo, found that the recovery time for patients treated with Remdesivir was 11 days (95%CI 9-12), compared to 15 days for patients in the placebo group (95%CI 13-19)[1071]. A subsequent study evaluated the effect of the drug in 584 non-hospitalised patients at high risk of hospitalisation due to underlying health problems. Treatment for 3 days, when initiated within 7 days of first symptom onset, reduced the risk of hospitalisation by 87%. Over the 28 days analysed, 0.7% of patients treated with remdesivir (2 out of 279) were hospitalised, compared to 5.3% of patients (15 out of 283) receiving placebo (Figure 251)[1072].

FIGURE 251. COVID-19-RELATED DEATH OR HOSPITALISATION UNDER TREATMENT WITH REMDESIVIR, COMPARED TO PLACEBO



Source: Gottlieb (2022)[1072]

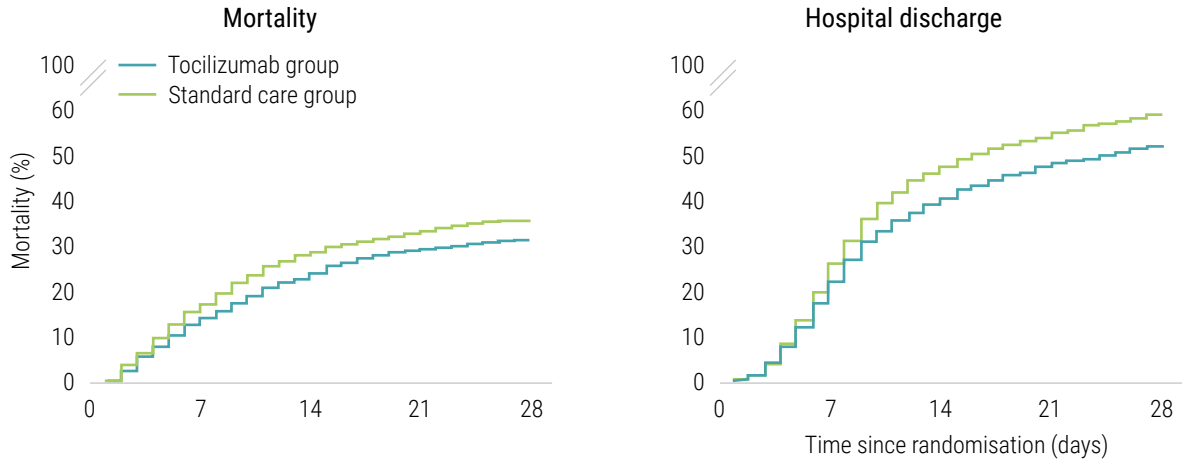
Approved treatments for COVID-19 include a number of monoclonal antibodies, which have been shown to be effective in reducing hospitalisations and/or deaths related to the disease.

Thus, in a randomised clinical trial of 1,057 participants, treatment with a single intravenous dose of sotrovimab (approved by the EMA in December 2021), compared to placebo, resulted in a statistically significant reduction in the proportion of patients who experienced a composite outcome of all-cause hospitalisation lasting more than 24 hours or death up to day 29 (1% vs. 6%, respectively; adjusted relative risk, 0.21)[1073].

The combination of casirivimab and imdevimab (approved in November 2021) demonstrated benefits in terms of both treatment and prevention of COVID-19. According to a systematic review and meta-analysis of the treatment effect in a total of 19.819 patients, these monoclonal antibodies effectively reduced the mortality rate (Odds ratio [OR] = 0.62; 95%CI: 0.40-0.98; p = 0.04) and reduced the progression of clinical symptoms (OR = 0.86; 95%CI: 0.79-0.93; p = 0.0003) versus placebo or standard of care, as well as improving viral load clearance and hospital discharge[1074].

In severe cases of COVID-19, treatment with tocilizumab (approved by the EMA in December 2021), given together with standard treatment, has been shown to reduce the risk of mortality compared to standard treatment alone. In the pivotal treatment trial, 31% of patients treated with this combination (621 out of 2022) died within 28 days of treatment, compared to 35% of patients receiving standard treatment alone (729 out of 2094). In addition, 57% of patients (1150 of 2022) who received tocilizumab were able to leave the hospital within 28 days, compared to 50% of patients (1044 of 2094) who received standard treatment alone (Figure 252)[1075].

FIGURE 252. EFFECT OF TOCILIZUMAB VERSUS STANDARD TREATMENT ON 28-DAY MORTALITY AND HOSPITAL DISCHARGE IN CRITICALLY ILL PATIENTS WITH COVID-19



Source: RECOVERY Collaborative Group (2021)[1075]

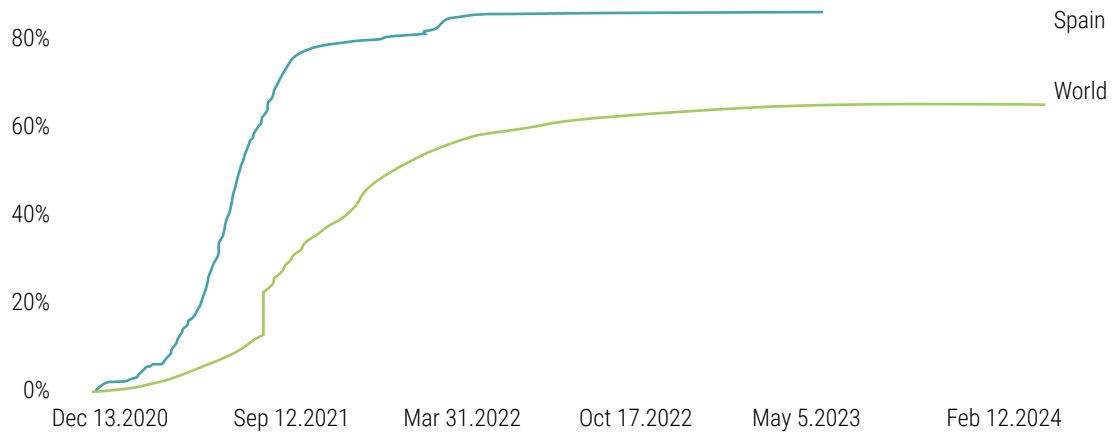
The combination of tixagevimab and cilgavimab (approved by the EMA in March 2022) has been shown to reduce the risk of COVID-19 infection by 77%, with an estimated duration of protection against the virus of at least six months[1076]. Another study showed that of patients who were not hospitalised at the time of treatment, 4.4% (18 out of 407) of those treated with these monoclonal antibodies developed severe COVID-19 or died within 29 days of treatment, compared to 8.9% (37 out of 415) of those receiving placebo[1077].

Beyond treatments for critically ill patients, a key therapeutic innovation in the field of COVID-19 has been the development of different types of vaccines against the disease. In Europe, the first - conditional - approval of a vaccine for COVID-19 came in late 2020, with Comirnaty. Since then, the EMA has approved seven vaccines[1067], which have demonstrated high effectiveness rates.

Overall, vaccine effectiveness against COVID-19 hospitalisation was estimated to be 52.2% (95%CI 51.4% to 52.9%) for a first dose, 55.7% (95%CI 55.2% to 56.1%) for a second dose, and 77.6% (95%CI 77.3% to 80.0%) for a third dose. The vaccine efficacy against COVID-19 morbidity was 58.7% (95%CI 52.7% to 65.9%) for a first dose, 88.6% (95%CI 87.5% to 89.5%) for a second dose, and 93.2% (95%CI 92.9% to 93.5%) for a third dose[1078].

Some studies conclude that, by March 2023, vaccines had reduced deaths due to COVID-19 by 57%, with an estimated 1.4 million lives saved in Europe alone, of which 96% would be in people aged 60 years and over, and 52% in people aged 80 years and over[1079]. This has been helped by the high vaccination rates experienced in Europe in general and in Spain in particular (Figure 253)[1066].

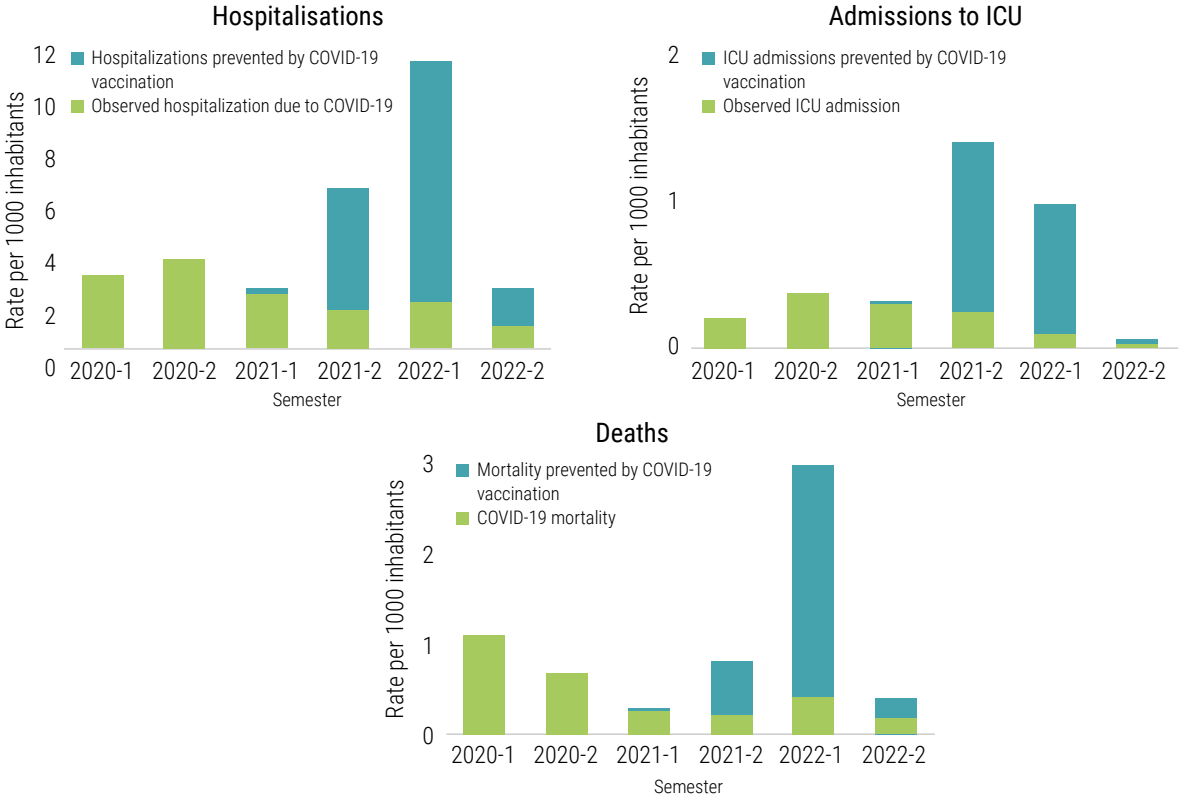
FIGURE 253. PERCENTAGE OF PEOPLE VACCINATED AGAINST COVID-19 IN THE WORLD AND IN SPAIN, JANUARY 2020-FEBRUARY 2024



Source: Our World in Data (2024)[1066]

According to a study in Navarra, full COVID-19 vaccination coverage of 86% and 56% with a booster dose resulted in estimated vaccine-prevented event rates of 16.3 hospitalisations and 3.4 deaths per 1,000 population, which were 70.9% and 74.7% of the events expected without vaccination, respectively. Most of the hospitalisations and deaths averted by vaccination occurred in people aged 80 years or older or with severe chronic diseases. One hospitalisation and one death due to COVID-19 were averted for every 53 and 258 people vaccinated, respectively (Figure 254)[1080].

FIGURE 254. OUTCOMES PREVENTED BY VACCINATION AGAINST COVID-19 IN TERMS OF HOSPITALISATION, ICU ADMISSION AND DEATHS (RATES PER 1,000 POPULATION). NAVARRA, 2021-2022



Source: Martínez-Baz (2024)[1080]

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In any case, the evolution of the virus has in many cases compromised the efficacy of vaccines[1081], inevitably leading to new infections and reinfections, and efforts to develop new vaccines and drugs continue[1082].

By the mid-2020s, a first drug had already demonstrated favourable results on the reduction of mortality in patients with COVID-19. Since then, an enormous joint effort has been made to rapidly develop effective treatments and vaccines against the infection.

Goldman (2020)[1069], Spinner (2020)[1070], Beigel (2020)[1071]

The rapid and effective vaccination against COVID-19 has made it possible to curb the consequences of the pandemic. In addition, the dozen or so treatments (including antivirals, immunosuppressants and monoclonal antibodies) available have also reduced the risk of infection, hospitalisations and deaths among patients already infected with the virus.the risk of infection, hospitalisations and deaths among patients already infected with the virus.

WHO European Respiratory Surveillance Network (2024)[1079], Martínez-Baz (2024)[1080], RECOVERY (2021)[1077], Elias (2023)[1076]

CONCLUSIONS

Pharmaceutical innovation has been one of the most significant contributions of the modern era, extending human life and improving the general well-being of the population. However, its benefits transcend individual health, extending to the healthcare system, labour productivity and the economy as a whole in both direct and indirect ways. Thus, medicines have positive effects on multiple dimensions, which must be taken into account when trying to approximate their value from a global perspective.

Throughout this detailed report we have presented, based on an extensive narrative literature review, a multitude of examples illustrating the economic, clinical and social contribution of medicines and the pharmaceutical industry. In this new update of the report, we have placed particular emphasis on developments from 2020 to date. Below is a summary of the main contributions made.

Firstly, in **the economic sphere**, the biopharmaceutical industry is one of the main sectors of activity in terms of quality employment generation, added value, research and competitiveness in developed economies. The following considerations related to the pharmaceutical industry have been highlighted throughout the report:

- It is a source of skilled employment. In Spain, the pharmaceutical industry employs more than 51,000 people, almost two thirds of whom are university graduates. It is the high-tech sector that generates the most jobs. Worldwide, the industry directly employs more than 5.5 million people.
- It is a sector with high productivity. In Spain, it is the second industrial sector with the highest productivity per employee (€116,000), 62% more than the industry average. The added value of the pharmaceutical industry worldwide is equivalent to the economy of a country like the Netherlands.
- It has powerful multipler effects on other economic sectors. For each unit of direct production in the pharmaceutical sector in Spain, two additional units are generated in other sectors; and for each direct job, 4 additional indirect and induced jobs are generated.
- It is a benchmark in R&D&I. It is the industrial sector that invests the most in R&D in Spain, approximately 1,206 million euros per year, which represents 19.3% of R&D expenditure in the total industrial sector. 78% of companies in the sector carry out innovation activities, compared to 23% of the industrial average. It is also one of the leaders in terms of innovation intensity (4.6% of turnover).
- It plays a very important role in terms of external competitiveness. In 2022, pharmaceuticals became Spain's third most exported product, behind only automobiles and fuels. At the European level, pharmaceuticals is the industrial sector that contributes most to the trade balance, with a positive trade balance of €125 billion.
- It contributes to public finances through tax payments. Pharmaceutical companies based in Spain contributed €611 million in 2022 in corporate taxes and €493 million in social security contributions.
- In summary, pharmaceutical companies in Spain represent only 0.2% of the country's industrial companies, but contribute 2.2% of employment, 2.8% of turnover, 3.5% of added value, 5.6% of exports and 18.9% of research and development expenditure in the industrial sectors.

Secondly, the use of more effective innovative drugs compared to previous ones is an investment that can result in cost savings, both public and private, in healthcare and non-healthcare costs and both direct and indirect. Freeing This allow resources for other uses, improving the efficiency of the healthcare system, boosting economic growth and generating in multiple benefits from a social perspective. Examples of this are detailed below:

- Investment in innovative medicines can be more than offset by potential savings in healthcare resources, especially hospitalisation costs. There are examples of this potential compensatory effect of new medicines in many developed countries, including Spain, and it appears to be greater in the long term than in the short term. In the United States, it is estimated that, biotechnological innovation has been associated with a compensation effect of 56%. In Spain, a 10% increase in pharmaceutical expenditure would generate a net saving of 1.1 euros per capita in hospital spending.
- Although they may not achieve full cost compensation but rather partial compensation, many medicines are cost-effective interventions worth investing in. Globally, it has been estimated that the cost of new medicines ranges from $14,000 to $36,000 per year of life gained, which places them as an efficient intervention. There are also multiple specific examples in particular diseases that need to be reviewed on an individual basis.
- The use of more effective innovative medicines can also generate savings for the public sector and patients through a reduced burden of formal and/or informal personal care required by patients due to the improved health status achieved. The benefits can be particularly relevant for age-related conditions such as dementia, Alzheimer's disease or Parkinson's disease. It has been estimated that, if these items were included in economic evaluations, 85% of the cost-effectiveness ratios would tend to be more favourable or even demonstrate net cost savings.
- Pharmaceutical innovation also brings value to society through the avoided labor losses by improving patients' self-perceived health status and quality of life. It is estimated that medicines approved between 2006 and 2010 are responsible for a reduction of 37 million lost workdays in the US alone.
- Furthermore, treatment adherence can also generate direct healthcare cost savings for the system and labour productivity gains for the patient and society. In Spain, it is estimated that a 10 percentage point increase in adherence rates for four chronic diseases would result in savings of more than €500 million per year in direct healthcare costs.
- Vaccines are one of the most cost-effective public health interventions, with benefits that typically far exceed their development and implementation costs, especially in the long term. In Spain, it is estimated that for every €1 invested in childhood vaccination, €22 is saved in direct and indirect costs. For every €1 invested in COVID-19 vaccination, benefits of €1.4 are generated from a healthcare system perspective and €3.4 from a social perspective.

Third, the ultimate purpose of medicines is to **improve population health**. Throughout history, medicines, along with medical advances and public health measures, have radically changed the lives of modern societies, enabling us to live longer and in better conditions. The following are some examples of the clinical benefits of innovative medicines in different pathologies:

- Life expectancy has increased over the years, largely due to pharmaceutical innovation, and currently stands at 83.2 years in Spain. Between 2006 and 2016, 1.7 years of life expectancy were gained, of which approximately three-quarters are attributed to the effect of pharmaceutical innovation, with the remainder due to to other factors.
- In the field of HIV/AIDS, antiretrovirals have managed to turn this acute and fatal disease into a chronic condition with high survival and quality of life. Drug treatments have prevented 21 million deaths worldwide between 1996 and 2022, and more than 120,000 deaths in Spain. The life expectancy of these patients now closely resembles that of the general population, and patients report an increasing self-perceived quality of life. In recent years, new drugs and drug combinations have been approved,

as well as pre-exposure prophylaxis as a preventive strategy, and research ongoing into a potential effective vaccine against the disease.

- Cancer is no longer a death sentence for many patients, thanks to increased knowledge about the disease and advances in diagnosis and treatment. In the last 10 years, more than 115 new cancer drugs have been approved, and patient survival rates has continued to increase. It is estimated that 96% of the increase in the average age of death from cancer in Spain in 1999-2016 is attributable to new treatments. Recently, treatments are being personalised according to the genetic characteristics of each patient and tumour, significantly improving success rates and reducing associated side effects.
- Cardiovascular disease treatments developed in recent decades have significantly reduced the incidence of cardiovascular events and associated mortality, although they remain the leading cause of death worldwide. New treatments have reduced the risk of death from heart disease by 10% and the risk of cardiovascular events by 25%.
- The therapeutic arsenal for diabetes has undergone considerable evolution over the last decades, with the development of new insulins and delivery methods to improve disease control and prevent medium- and long-term vascular complications, Non-insulin antidiabetic therapies have also been developed, offering oral alternatives with advantages in effectiveness, adherence, accuracy, functionality and satisfaction.
- Regular use of medications for respiratory diseases such as COPD and asthma achieves effective symptom reduction and improved lung response, in turn improving the patient's quality of life. Newer treatments, including new delivery methods, improve adherence, reduce the risk of exacerbations and improve disease control. The future lies in targeted molecules and biomarkers that open up new possibilities for treating the disease and predicting treatment response.
- Direct antiviral agents have ushered in a new era in hepatitis C virus treatment, achieving a sustained viral response approaching 98% in real life. Results are positive even among the most difficult-to-treat profiles. In Spain, treatments approved since 2015 have halved the prevalence of hepatitis C, preventing more than 8,600 cases of cirrhosis, 5,400 cases of hepatocellular cancer and 1,100 long-term liver transplants. In turn, improvements in sustained viral response translate into improved quality of life.
- Mental disorders are the world's leading cause of disability. Various antidepressant and antipsychotic treatments approved over the past decades have sought to reduce the severity of symptoms to prevent relapse and improve quality of life. Recently introduced drugs improve prospects for conditions such as schizophrenia and bipolar disorder, and offer new options for patients resistant to existing therapies, as well as alternative and stepwise forms of administration.
- In Parkinson's disease, disease-modifying treatments delay the onset of motor symptoms and improve quality of life. New gel formulations and their combination with other drugs are the main therapeutic innovation in recent years, and research is ongoing into treatments targeting specific biological pathways involved in the disease process.
- In the field of multiple sclerosis, the introduction of disease course modifiers, some of them in oral forms, has led to improvements in flare prevention and progression of disability, which have been transferred to self-perceived quality of life. New therapeutic agents have opened up new possibilities for patients not adequately controlled with standard treatments. In the coming years, treatments directed at new targets are expected, along with improved specificity and tolerability of available strategies.
- Disease-modifying drugs have also made important therapeutic advances in rheumatoid arthritis, improving the likelihood of achieving clinical remission, quality of life and functional status of patients, as well as preventing structural damage and associated long-term disability. In recent years, new therapies and indications have been approved, with improved outcomes in patients with an inadequate response or intolerance to other biologics.

- Autoimmune dermatological diseases, such as atopic dermatitis, cutaneous lupus erythematosus, nodular prurigo, vitiligo, dermatomyositis, pemphigus and epidermolysis bullosa acquisita, have new biologic drugs that offer greater specificity and efficacy in disease control, reducing disease burden and improving patients' quality of life.
- In recent years, patients with psoriasis have seen an expansion of the therapeutic arsenal available for moderate to severe cases, which has improved the degree of clearance achieved, its speed and its persistence over time, with a very significant impact on patients' quality of life.
- The treatment of inflammatory bowel diseases, including ulcerative colitis and Crohn's disease, has advanced significantly until the advent of biologic drugs and advanced therapies, achieving symptom control in patients unresponsive to first-line therapies or in advanced stages of the disease.
- In recent years, novel preventive therapies for migraine have been approved, as well as acute treatments for immediate and long-lasting relief of pain and other symptoms. Increased understanding of the disease's pathophysiology has led to the development of new, more specific and effective drugs that reduce the duration of attacks and lengthen the time between episodes.
- Rare diseases represent the focus of pharmacological innovations in recent years, at least in terms of the number of drugs developed (10% of the total since 1995). Over the last few years, innovative small-molecule drugs and biological therapies have been approved that have improved survival and quality of life in patients with rare and ultra-rare genetic diseases with no therapeutic options. Advanced therapies achieved unprecedented progress in both oncological and non-oncological rare diseases.
- Vaccines are one of the public health measures that have contributed most to reducing morbidity and mortality in humans. There are currently more than 40 vaccines for the prevention of 25 diseases. Childhood vaccines prevent 4 million deaths worldwide each year, as well as epidemics and major health consequences. In developed countries, immunisation schedules continue to be updated with new vaccines and age groups, as well as new preventive strategies such as the use of monoclonal antibodies. Thousands of vaccines are in the research pipeline, almost half of them targeting diseases for which no vaccines have been registered.
- COVID-19 vaccines are a paradigmatic case of recent therapeutic innovation, enabling a return to normality after the largest global pandemic in the last 100 years, which has so far caused 7 million deaths and the paralysis of economies on a global scale. The seven approved vaccines have reduced deaths from COVID-19 by 57%, saving 1.4 million lives in Europe alone. In addition, the dozen or so treatments (including antivirals, immunosuppressants and monoclonal antibodies) available have also reduced the risk of infection, hospitalisations and deaths among patients already infected with the virus.

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CONTRIBUTION TO THE ECONOMY

GO TO PAGE 10

Measuring the economic footprint of the pharmaceutical industry

Ostwald D & Knippel J.

Feasibility study Wirtschaftsforschung (2013)

OBJECTIVE:

- To estimate the direct effects of the pharmaceutical industry on the global economy, as a first step in examining the sector's "economic footprint".

METHOD:

- **Countries:** 68 countries worldwide.
- **Reference period:** 2006-2011.
- **Data sources:** United Nations (United Nations System of National Accounts), OECD (Database for Structural Analysis), Eurostat (IO tables), etc.
- **Variables:** gross value added, employment, output, compensation of employees, capital expenditure, R&D investment. The entire pharmaceutical industry is considered (both branded and generic companies).
- **Type of analysis:** Previous literature review to analyse the main works on the economic footprint, studying the methodological approach, the economic indicators used, the database used and the economic sector of application. Direct effects are estimated using publicly available official statistics and a value-added approach.

RESULTS:

- There is no uniform and comprehensive data on the global economic impact of the pharmaceutical industry.
- Macroeconomic data for the global pharmaceutical industry in 2011 are:
  - Gross value added of $441 billion, with an average annual growth since 2006 of 7.5%.
  - 4.23 million directly employed, with an average growth of 3.3%.
  - Production worth $941 billion, with an average growth of 8.2%.
  - Total employee compensation of $93.3 billion, with an average wage per employee of $22,100, up 18.2% from 2006.
  - A capital investment intensity of 23.5% of gross value added.
  - R&D investment intensity of 19.7% in 2007.

CONCLUSIONS:

- Globally, the pharmaceutical industry has a very large and growing direct impact on the economy, but this represents only a part of its overall "economic footprint".

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The Pharmaceutical Industry in Figures. Key Data 2023

EFPIA – European Federation of Pharmaceutical Industries and Associations

Report (2024)

OBJECTIVE:

- Presenting the macroeconomic data of the European pharmaceutical industry and its contribution to economic development and health, identifying the main challenges.

METHOD:

- **Countries:** 32 of the 53 countries in Europe (includes EU-27, except Luxembourg, and includes Iceland, Norway, Russia, Switzerland, Turkey and the UK).
- **Reference period:** 2020, 2021 y 2022 (estimated data).
- **Data sources:** Eurostat, IQVIA, OECD, WHO, ECDC, PhRMA, EFPIA member associations.
- **Variables:** R&D expenditure, employment, sales, exports, imports, number and cost of new molecules, value added, market share of generics, pharmaceutical expenditure.
- **Type of analysis:** Descriptive analysis of secondary data.

RESULTS:

- The pharmaceutical industry is a key asset of the European economy, being one of the leading technology sectors:
  - It made an estimated R&D investment of 44.5 billion euros by 2022.
  - It is the most R&D intensive sector, investing 12.4% of its sales, followed by the technology sector of services (9.3%) and products (7.0%).
  - In 2022, North America accounted for 52.3% of global pharmaceutical sales, compared to 22.4% for Europe.
  - It directly employed around 865,000 people and generated approximately three times as many jobs indirectly.
  - With exports of 567,009 million euros and imports of 395,250 million euros, it has a positive trade balance, far superior to that of other high-tech sectors.
  - On average, pharmaceutical expenditure accounts for 18.4% of total public health expenditure.
- The sector faces major challenges:
  - Fiscal austerity measures prompted by the crisis have had a major impact on the sector.
  - Bringing a new drug to market cost an average of €1,926 million in 2014 and an average of 12-13 years from the first synthesis of the new active substance.
  - Competition from emerging economies is increasing.
  - Market fragmentation results in parallel trade worth €6.28 billion in 2021.

CONCLUSIONS:

- The pharmaceutical industry has played an important role in increasing the well-being of Europeans. Progress in biopharmaceutical research has led to a decrease in the mortality rate and an improvement in the quality of life.

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The Global Economic Impact of the Pharmaceutical Industry

Ostwald D, Cramer M, Albu N, Tesch J.

Wifor report (2020)

OBJECTIVE:

- Assess the economic impact of the pharmaceutical industry worldwide, with an emphasis on the United States, considering the direct, indirect and induced effects on value added and employment generated.

METHOD:

- **Country:** Global, mainly United States.
- **Periodo:** 2006-2017.
- **Sample:** Economies worldwide, mainly the United States.
- **Sources:** United Nations Statistical Division, Eurostat, OECD, Asian Development Bank (ADB), World Input-Ou- tput Database (WIOD), EFPIA, PWC, PhRMA.
- **Variables:** Added value generated and employment.
- **Analisys:** Literature review, descriptive and temporal analysis, Wifor calculations.

RESULTS:

- The global pharmaceutical industry directly contributed $532 billion to global GDP in 2017.
- The global pharmaceutical industry directly employed more than 5.5 million highly productive people in 2017. It employed another 45 million jobs along the global supply chain, particularly benefiting Asian and other developing countries due to structural differences in these regions.
- The global pharmaceutical industry purchased direct inputs from other sectors worth more than $800 billion. This triggered effects in global supply chains, resulting in an additional contribution of $791 billion to GDP.
- Private consumption generated income (directly and indirectly) resulting in an additional $515 billion contribution to GDP.

CONCLUSIONS:

- This report highlights the positive and significant impact that the pharmaceutical industry has globally both in economic terms and in terms of employment generation, and how it contributes to sustainable development according to the United Nations goals.

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Economic and societal footprint of the pharmaceutical industry in Europe

EFPIA (European Federation of Pharmaceutical Industries and Associations) & PwC (PricewaterhouseCoopers)

Report (2019)

OBJECTIVE:

- Demonstrate the economic, health and social impact of the pharmaceutical industry in the European Union and the importance of intellectual property incentives for R&D.

METHOD:

- **Region:** European Union.
- **Reporting year:** 2016.
- **Data sources:** Eurostat, European Medicines Agency, World Health Organisation, EFPIA member associations.
- **Variables:** Value added and employment (direct, indirect and induced), employment distribution by gender, labour productivity gains, cost savings.

RESULTS:

- The pharmaceutical industry is a key value-adding asset for the EU economy, health sector and society:
  - It generated an added value of 206 billion euros, of which 106,074 million euros were generated indirectly or induced (multiplier of 1.06). In Spain, the total value added was 14,759 million euros, with a multiplier of 2.09 (9,976 million euros were generated indirectly or induced).
  - For each of the 642,000 direct jobs generated, 2.9 additional jobs were generated in other sectors, indirectly and induced. In Spain, for each of the 41,000 direct jobs, 4 additional jobs were generated.
  - Forty-six per cent of workers in the sector are women, compared to between 15 and 30 per cent in other sectors, such as aeronautics, automotive or telecommunications.
  - It was responsible for treating more than 650,000 people with cancer or HIV between 2007 and 2017. These treatments generated €27 billion in labour productivity, and €13 billion in cost savings.
  - The dismantling of the current system of intellectual property incentives could reduce total industrial R&D investment in the region by 25%.

CONCLUSIONS:

- The pharmaceutical industry has contributed significantly to the EU economy, society and the health sector, both directly (employment, R&D) and indirectly (productivity, leverage effect).

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The pharmaceutical sector in the Spanish economy: contribution to GDP, employment and to tax revenues

Bosch J, Villar JG, Puig-Junoy J.

Working Paper Series (2024); 13

OBJECTIVE:

- To quantify the economic impact of the pharmaceutical sector's activity on the Spanish economy in terms of production, gross value added (GVA) and employment.

METHOD:

- **Country:** Spain.
- **Period:** 1995-2019.
- **Sources:** National Statistics Institute (INE).
- **Variables:** Output, GVA, GDP, employment, imports and exports, carry-over, support and driver effects, tax revenues.
- **Analisys:** Analysis of the evolution of the main economic magnitudes of the pharmaceutical sector. The input-output methodology is used, and the usual indicators from the literature derived from it, using data from the Annual National Accounts of Spain, produced by the INE. Indicators are calculated to measure both the intensity (effect of each euro of production in the sector) and the capacity (effect, taking into account the size of the sector) of drag and support that the pharmaceutical sector has on the other sectors of the economy.

RESULTS:

- Stability of the sector: The GVA of the sector represents approximately 0.6-0.7% of the Spanish economy.
- Contribution to the economy: The pharmaceutical sector generates approximately 1% of Spanish GDP (carry-over effect discounting own effect) and around 204,463 full-time equivalent jobs (taking into account the three types of effects: direct, indirect and induced).
- R&D investment: The pharmaceutical sector accounts for more than 5% of total R&D in Spain in 2019.
- Productivity: In 2019, the sector's productivity is 1.15 times that of the industry and 1.61 times that of the economy as a whole.
- Imports and exports: Imports account for more than 85% of the pharmaceutical sector's final demand, while exports account for about 26%.
- Drag effects: The multiplier effect of the pharmaceutical sector (direct, indirect and induced effect) is higher than the industry average (1.11 vs. 1.03) in relation to GVA.

CONCLUSIONS:

- The study highlights the key contribution of the pharmaceutical sector to the Spanish economy between 1995 and 2019, highlighting its stability, R&D investment, productivity, external competitiveness, multiplier effect on the economy, tax revenue generation and job creation.

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Biopharma Economic Impact on the US Economy

PhRMA

SSRN Electron Journal (2023)

OBJECTIVE:

- To estimate the size and structure of the US biopharmaceutical industry, as well as its capacity for innovation and economic impact on the US economy.

METHOD:

- **Country:** United States, including state-by-state breakdown.
- **Period:** 2018-2021.
- **Sample:** United States Economy.
- **Sourcess:** Bureau of Labor Statistics (BLS), TEConomy Partners, IMPLAN model, US Bureau of the Census, PwC, IPC.
- **Variables:** Direct, indirect and induced impacts of employment, wages, value added, output, taxes and R&D.
- **Analisys:** Literature review, descriptive and temporal analysis, author's calculations (e.g. adjusting for inflation, percentage change over time).

RESULTS:

- The biopharmaceutical industry has experienced significant growth in recent years, including during the COVID-19 pandemic.
- Employment increased by 16.8% and labour income by 31.2% between 2018 and 2021.
- Value added grew by 28.7% from 2018 to 2021, and has grown faster than US GDP every year since 2018.
- Total labour income amounted to $54 billion in 2021.
- In 2021 alone, the biopharmaceutical industry has supported more than 1,490,000 jobs in the US, with a multiplier of 5.12.
- In 2020, the US industry spent 16.6% of its revenues on research and development, a total of almost $91.8 billion.
- In 2021, US exports recorded over $92.5 billion, the highest level during the 2018-2021 period covered in this study.

CONCLUSIONS:

- This report highlights the growing importance of the biopharmaceutical industry to the US economy, in terms of employment, value added, exports and research and development.

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The Economic Impact of the U.S. Biopharmaceutical Industry: 2020 National and State Estimates

PhRMA & Teconomy Partners

Report (2020)

OBJECTIVE:

- To provide new empirical evidence on the economic impact of the biopharmaceutical sector in the United States at state, regional, and local levels.

METHOD:

- **Country:** United States, including state-by-state breakdown.
- **Reference year:** 2020.
- **Data sources:** US Food and Drug Administration (FDA), Bureau of Labor Statistics (BLS), Current Population Survey (CPS), TEConomy Partners, IMPLAN model, US Bureau of the Census.
- **Variables:** Direct, indirect and induced impacts of employment, wages, value added, output, imports and R&D.
- **Analysis:** Descriptive analysis of secondary data.

RESULTS:

- The biopharmaceutical industry in the United States directly employed more than 903,000 workers, with an employment multiplier of 4.92. Thus, the industry generates more than 3.5 million additional jobs in the United States with a total employment impact of more than 4.4 million jobs across the US economy by 2020.
- The industry has been a stable employer during economic downturns.
- With average annual wages and benefits of over $145,000, almost $60,000 more than the average wage in US manufacturing and more than double the average across all industries, jobs in the biopharmaceutical industry are both high-paying and high quality.
- From an overall productivity perspective, the research and production nature of the US biopharmaceutical industry generates a productivity level of nearly $381,000 per employee, more than twice that of the average US manufacturing worker and more than three and a half times the average worker overall.
- The US biopharmaceutical industry exceeded $710 billion in direct output in 2020, with a ripple effect of $700 billion in output through its suppliers and other sectors of the economy, totalling more than $1.4 trillion. This combined impact on total output represents 3.7% of total US output.

CONCLUSIONS:

- The US biopharmaceutical industry plays a key role in US innovation, with a highly developed research, manufacturing and distribution infrastructure that generates significant economic impact nationally compared to other industries.

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The 2023 EU Industrial R&D Investment Scoreboard

Nindl E, Confraria H, Rentocchini F, Napolitano L, et al.

The 2023 EU Industrial RandD Investment Scoreboard, Publications Office of the European Union (2023)

OBJECTIVE:

- To analyse comparatively the investment in research and development (R&D) of the 2,500 companies with the highest R&D expenditure worldwide. Evaluate the trend over the last decade.

METHOD:

- **Country:** World.
- **Reference year:** 2022. Evolution since 2008.
- **Data source:** Profit and loss accounts of companies.
- **Sample:** 2,500 industrial companies, of which 367 European companies (12 Spanish), 827 from the USA, 679 from China, 229 from Japan and 398 from the rest of the world (22 countries).
- **Variables:** Sales, employment, R&D expenditure, operating profit, capital investment.
- **Analysis:** Comparative descriptive analysis.

RESULTS:

- The health sector is the largest sector in the Scoreboard in terms of number of companies and the second largest in terms of R&D expenditure.
- The number of health companies increased by a factor of 1.5 between 2012 and 2022 to 584 companies, and R&D investment increased by a factor of 2.1.
- Biotech companies are the main driver of the total growth of companies in the sector, and their number has more than doubled since 2012 (from 125 to 271 companies); the number of pharma companies increased by 36%, while the number of companies in other health sectors decreased slightly (-5%).
- The top 50 of the 2,500 companies produced 25% growth in research by 2022. Between 2012 and 2022, pharmaceutical R&D grew by an average of 5.3% per year, biotech R&D by 14.5%, and R&D in other aspects of health by 6.5%, compared to an average value of 7% for the health sector as a whole. ICT services, on the other hand, grew by 6.9% in 2022.
- Pharmaceutical companies invest 64% of total R&D in the sector, amounting to 261.4 billion euros, while biotech companies invest 25.4%.
- EU-based companies account for 11.8% of companies and 16.8% of R&D in the sector.
- The healthcare industry has historically had the highest R&D intensity (R&D investment over sales) with approximately 11.5%, followed by ICT services with 8%.

CONCLUSIONS:

- R&D investment by the 2,500 companies accounts for 80% of global business investment. The health sector is the sector with the highest number of companies and, by a small margin, the second largest in terms of R&D.

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Despite high costs, specialty drugs may offer value for money comparable to that of traditional drugs

Chambers JD, Thorat T, Pyo J, Chenoweth M, et al.

Health Affairs (2014); 33(10): 1751-1760

OBJECTIVE:

- Assess the health outcomes and additional costs of new specialised (biotech) medicines compared to standard treatment, as compared to traditional medicines.

METHOD:

- **Country:** United States.
- **Reference period:** 1999-2011.
- **Population:** The entire population of the United States. Sample of 102 new molecules, of which 58 are speciality medicines and 44 are traditional medicines.
- **Data source:** Federal Drug Administration website, cost-utility studies published in Pubmed and not funded by industry.
- **Variables:** Specialty drugs included in CVS Caremark and Express Scripts; Quality Adjusted Life Years (QALYs), cost of drugs over pre-existing treatment.
- **Analysis:** Comparison of mean QALYs and costs using non-parametric statistical tests. Sensitivity analysis using the highest and lowest QALYs and costs reported in the studies.

RESULTS:

- Specialty medicines offer a greater health gain than traditional medicines in terms of QALYs gained: for all approved medicines, median 0.031 and mean 0.17; for specialty medicines, median 0.183 and mean 0.25; for traditional medicines, median 0.002 and mean 0.08.
- Specialty medicines are associated with higher cost increases: mean $42,561 and median $2,950 for all new medicines; mean $72,917 and median $12,238 for speciality medicines; mean $3,237 and median $784 for traditional medicines.
- No significant differences are found between the cost-effectiveness ratios associated with traditional and specialised medicines.
- 2 speciality medicines and 5 traditional medicines are dominant options (more effective and cheaper than their comparators).
- 15 of the specialised and 4 of the traditional ones have ratios of at least $150,000/QALY.
- The social value of specialised medicines may be greatest when they target diseases with unmet clinical needs and few treatment options (e.g. cancer, multiple sclerosis).

CONCLUSIONS:

- Specialty medicines tend to offer greater health gains than traditional medicines over existing medicines, but at a higher incremental cost.

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National and International Tests of the New Drug Cost Offset Theory

Santerre R.

Southern Economic Journal (2011); 77(4): 1033-1043

OBJECTIVE:

- To analyse whether there is an offsetting effect on the cost of new medicines on aggregate health care costs in developed countries.

METHOD:

- **Countries:** United States and 7 OECD countries (Belgium, Canada, Finland, Germany, Japan, Sweden, United Kingdom).
- **Reference period:** 1960-2007 for the USA other periods between at most 1971 and 2004 for the other OECD countries.
- **Data source:** Centers for Medicare and Medical Services, Bureau of Labour Statistics, Bureau of Economic Analysis, Bureau of the Census, Department of Health and Human Services, Federal Food and Drug Administration, OECD data.
- **Variables:** Demand for prescription drugs, demand for medical services (visits and hospitalisations), demand for medical devices, per capita income, people over 65, number of new molecules approved by the FDA.
- **Analysis:** Regression analysis to jointly estimate growth in demand for prescribed medicines and medical services per capita as a function of growth in demand in the previous period, relative prices of medicines and medical services, growth in the percentage of people over 65, life expectancy at birth, income per capita and the number of new molecules marketed, assuming that medicines and medical services are substitutes.

RESULTS:

- In the United States, in the short term, the approval of an additional drug accelerates per capita pharmaceutical spending growth by 0.136% and reduces per capita health care spending growth by -0.123%, resulting in an overall reduction in per capita health care spending of -0.095%. In the long run, the reduction in overall health spending would be -0.183%.
- In the short term, one additional new drug would raise pharmaceutical spending in the US by $1.02 (or 309 million euros at the aggregate level), but would save $6.62 in medical services. Total healthcare spending (including demand for medical devices) would be reduced overall by $5.91 per person, allowing a national saving of $1.8 billion. In the long run, one additional new medicine would generate net health care savings in the US of $11.38 per person, or 3.4 billion euros at the aggregate level.
- In the OECD countries analysed, the net effect of marketing an additional new medicine on health care spending is -0.065% in the short run and -0.087% in the long run, i.e. slightly lower than the rates found for the United States.

CONCLUSIONS:

- The offsetting effect of new medicines on net health expenditure in developed countries is confirmed, with larger marginal effects in the long run than in the short run. In the long run, marketing one additional medicine would generate net savings in non-pharmaceutical health expenditure up to 6 times greater than the additional pharmaceutical expenditure generated.

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Benefits and costs of newer drugs: an update

Lichtenberg FR.

Managerial and Decision Economics (2007); 28(4-5): 485-490

OBJECTIVE:

- Update and extend previous work to estimate the impact of drug novelty on total health spending among the US population.

METHOD:

- **Country:** United States.
- **Reference period:** 1996-1998.
- **Data source:** Medical Expenditure Panel Survey.
- **Variables:** Health expenditure (drug expenditure, hospitalisations, home care, doctor visits, emergencies) associated with each disease; age of the drug measured as the time since its commercialisation by the FDA.
- **Analysis:** Econometric model to estimate each of the items of health expenditure associated with disease i of person j in year t based on the age of the medicine consumed, a fixed effect per year and disease, and an individual effect per patient.

RESULTS:

- Among the general population, replacing an older drug (15 years old) with a newer drug (5.5 years old) would increase pharmaceutical spending by about $18 per person, but reduce non-pharmaceutical healthcare spending by $129, generating a net saving of $111 per person. These savings are generated by savings on hospitalisations (62% of savings), doctor visits (27%) and home care (10%) and, to a lesser extent, emergency visits (2%). In total, the savings ratio for each additional monetary unit invested in the medicine is 7.2.
- Among the Medicare-covered population, replacing an old drug (15 years) with a new drug (5.5 years) would increase pharmaceutical spending by about $21 per person, but reduce non-pharmaceutical health spending by $176, generating a net saving of $155 per person. Hospitalization savings alone would account for $102, representing 58% of the total savings. The savings ratio for each additional monetary unit spent on the medicine is 8.3.
- The average age of drugs used depends on the degree of drug insurance coverage. Among people covered by Medicare with private drug insurance, the average age of drugs used is 8.6% lower than that of drugs used by people covered by Medicare but with public or private drug insurance.

CONCLUSIONS:

- Investment in a new medicine reduces non-pharmaceutical health expenditure by 7.2 to 8.3 times.

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The Impact of New Drugs on US Longevity and Medical Expenditure, 1990-2003: Evidence from Longitudinal, Disease-Level Data

Lichtenberg FR.

The American Economic Review (2007); 97(2): 438-443

OBJECTIVE:

- To examine the effect of changes in the age of medicines on longevity and health spending in the United States during the period 1990-2003.

METHOD:

- **Country:** United States.
- **Reference period:** 1990-2003.
- **Data source:** Microdata on mortality by cause from the National Center for Health Statistics; Hospitalisations by cause from HCUPnet; annual prescription drug data by condition from the Medical Expenditure Panel Survey.
- **Analysis:** Econometric Weighted Least Squares (WLS) model to estimate mortality or health service utilisation as a function of a measure of novelty of drug i in year t, and a fixed effect per year. First approach using data for all available years between 1996 and 2003 and second approach using data only for the first and last year of the period.
- **Variables:** Years of potential life lost before age 65 and before age 75; number of hospital admissions by condition and year, number of admissions to nursing homes, number of days of hospitalisation in which the patient died, by condition and year. Degree of drug novelty defined as the percentage of prescribed medicines used to treat condition i in year t that contain active ingredients approved after 1990 (and after 1993).

RESULTS:

- Medical conditions with higher rates of pharmaceutical innovation are statistically significantly ($p<0.0001$) associated with greater falls in mortality before the age of 65 and before the age of 75, both when considering short-term ($t= -0.349$ and $t= -0.210$) and long-term effects ($t = -1.125$ and $t = -0.788$).
- If the degree of pharmaceutical innovation in 2003 were the same as in 1993, hospital and nursing home expenditures would have been 11% higher ($58 billion and $9.5 billion respectively).
- The use of new medicines has reduced the number of potential years of life lost by 1.57 million for Americans under 65 (and by 1.7 million for those under 70) and saved $58 billion in hospitalisations and $9.5 billion in health care.
- Taking into account the lower hospital admissions generated in the short term, the net cost of the new drugs is about $27 billion. The net cost per year of life saved before age 75 is $15,974.

CONCLUSIONS:

- In the short term, new drugs prescribed in the US have had a net cost of $27 billion. In contrast, the long-term effect is $2.4 in savings for every $1 invested in new medicines.

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The impact of new drug launches on hospitalization in 2015 for 67 medical conditions in 15 OECD countries: a two-way fixed-effects analysis

Lichtenberg FR.

Forum for Health Economics & Policy (2019); 20180009

OBJECTIVE:

- Re-examine the impact that pharmaceutical innovation has had on hospitalisations in different developed countries.

METHOD:

- **Countries:** 15 OECD countries.
- **Reference period:** 1982-2015.
- **Sample:** 67 pathologies.
- **Sources:** IMS Health MIDAS, IMS Health New Product Focus, OECD Health Statistics, Theriaque, International Agency for Research on Cancer.
- **Variables:** Cost of hospitalisations in 2015; pharmaceutical innovation measured as the number of new chemical entities marketed in the period 1982-2015 in each country for each pathology analysed.
- **Analysis:** Fixed effects regression models by country and pathology, controlling for the propensity of each country's population to be hospitalised for each pathology. Assumes a lagged effect of innovation on hospitalisations. Analysis by time subgroups.

RESULTS:

- The number of hospital discharges in 2015 is inversely related to the number of drugs released in the period 1982-2000 and in the period 2001-2005, but not to those released between 2006 and 2015.
- One additional medicine marketed in 2001-2005 for a given pathology is associated with a 10% reduction in the number of hospital discharges for that pathology in 2015.
- If no new drugs had been marketed after 1981, the total number of hospital days and discharges in 2015 would have been 163% and 91% higher, respectively, than actually produced.
- The estimated reduction in 2015 hospital expenditure attributable to drugs launched after 1981 is 5.3 times greater than the 2015 expenditure on those drugs.

CONCLUSIONS:

- Pharmaceutical innovation has had an offsetting effect on hospital costs in the developed countries analysed.

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Has pharmaceutical innovation reduced the average cost of U.S. health care episodes?

Lichtenberg FR.

International Journal of Health Economics and Management (2023); 24(1): 1–31

OBJECTIVE:

- To investigate the impact that pharmaceutical innovation had on the average cost of health care episodes.

METHOD:

- **Country:** United States.
- **Reference period:** 2000-2014.
- **Population:** The entire population of the United States.
- **Data source:** Bureau of Economic Analysis Health Care Database (US), e-Drug 3D (US), IQVIA MIDAS. Agency for Healthcare Research and Quality Medical Expenditure Survey (US).
- **Variables:** Average cost per episode of care (days of hospitalisation).
- **Analysis:** Double fixed effects model. We analyse the relationship between approximately 200 diseases, the growth in the number of drugs approved to treat the disease and the subsequent growth in average expenditure per episode of care, controlling for growth in the number of episodes and other factors.

RESULTS:

- Drugs approved during 1986-1999 reduced the average cost per episode by 4.7%, and drugs approved during 1996-2009 reduced the average cost per episode by 2.1%.
- If drug approvals had not affected the number of episodes, drugs approved during 1986-1999 would have reduced medical spending in 2014 by approximately $93 billion.
- Drugs approved during 1984-1997 reduced the number of hospital days by 10.5%. The number of hospital days is inversely and significantly related to the number of drugs approved 10-19 years earlier, controlling for the number of episodes of illness.
- The reduction in hospital costs ($110 billion) was greater than the reduction in drug spending ($42 billion).

CONCLUSIONS:

- Drugs approved during 1986-1999 and 1996-2009 were shown to significantly reduce subsequent average costs per episode, with important implications for hospital utilisation and healthcare costs. This decrease in hospital expenditure outweighed the investment in medicines, thus demonstrating a full compensatory effect.

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Prescription drug coverage and elderly Medicare spending

Shang B & Goldman DP.

The Geneva Papers (2010); 35: 539-567

OBJECTIVE:

- Analyse the potential of Medicare Part D (prescription drugs) to improve projections for Medicare Parts A (hospitalisations, etc.) and B (doctor visits, etc.).

METHOD:

- **Country:** United States.
- **Reference period:** 1992-2000.
- **Data source:** Medical Current Beneficiary Survey, with 12,000 Medicare beneficiaries (public health insurance programme for people over 65).
- **Variables:** Expenditure on hospitalisations, nursing facilities, residential care and some home health care (Part A Medicare); expenditure on doctor visits, physical and occupational therapists and some home care (Part B Medicare); expenditure on prescription drugs (Part D Medicare); control variables: functional status, risk factors, age, sex, race, educational level, area of residence, income level.
- **Therapeutic group:** The analysis focuses on those chronic diseases most related to drug use and medical expenditure: diabetes, cancer (excluding skin cancer), heart disease (myocardial infarction, heart attack, angina, coronary heart disease, heart failure), stroke, hypertension, lung disease (emphysema, asthma, COPD), Alzheimer's disease and osteoarthritis.
- **Analysis:** Two alternative types of models where the dependent variables are spending on Medicare Part A, Medicare Part B and Medicare Part D, adjusting for observed differences in the control variables.

RESULTS:

- With the simple two-part model, benefiting from prescription drugs raises drug spending by $157 and doctor visit spending by $31 (Part B), but reduces hospitalisation spending by $135 (Part A), resulting in a net cost increase of $53.
- If the interaction with income is introduced to control for adverse selection (more complex model), at steady state benefiting from drug prescribing raises drug spending by $148 (+15%), while reducing spending on hospitalisations (Part A) by $350 (-22%) and spending on doctor visits (Part B) by $74 (-4%), resulting in a net saving of $276.
- Under the more complex model, each additional $1 of drug spending is associated with an average reduction of $2.06 in hospitalisations and $0.44 in physician visits.

CONCLUSIONS:

- After controlling for self-selection of the poorest Medicare recipients, the results indicate that prescription drugs (Part D) are a substitute for physician services and hospitalisations (Part B and A).

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The effect of newer drugs on health spending: do they really increase the costs?

Civan A & Köksal B.

Health Economics (2010); 19: 581-595

OBJECTIVE:

- To analyse the influence of technological improvement in pharmaceutical markets on levels of healthcare spending in the United States.

METHOD:

- **Country:** United States.
- **Reference period:** 1993-2004.
- **Data source:** Center for Medicare and Medicaid Services. US Census Bureau and Bureau of Economic Analysis.
- **Variables:** Different alternative measures of per capita health expenditure: personal health care, hospital care, medical services, other professional services, dental services, home care, prescribed medicines, durable and non-durable medical products, home nursing care and other personal health care. Weighted average age of the active ingredient of the medicine. Regional population and GDP. Public and private health coverage.
- **Analysis:** Panel data model for all 50 states in the country during the reference period. Measure of per capita health expenditure as a function of weighted average age of the active ingredient, state GDP per capita, health coverage, proportion of population over 65 and a state fixed effect.

RESULTS:

- A 1-year reduction in the average drug age is associated with an $8.2 increase in per capita pharmaceutical spending and a $45.4 reduction in per capita healthcare spending, mainly due to a reduction in hospital spending.
- The age of the medicine correlates positively and statistically significantly with total health expenditure (t=45.43) and with non-pharmaceutical health expenditure (t=54.15). On the other hand, its correlation is negative and statistically significant with respect to pharmaceutical expenditure (t=-8.17).
- The health expenditure categories most affected by the age of the medicine are hospital care (t=18.85), followed by dental services (t=8.98), nursing home care (t=8.52) and pharmaceutical expenditure (t= -8.17).

CONCLUSIONS:

- Although innovative medicines are more expensive than their predecessors, their greater efficacy leads to a reduction in total health expenditures by reducing the need for other types of medical services.

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Is There a Link Between Pharmaceutical Consumption and Improved Health in OECD Countries?

Miller RD & Frech HE.

Pharmacoeconomics (2000); 18(1): 33-45

OBJECTIVE:

- To determine the effect of per capita pharmaceutical spending on life expectancy and infant mortality in OECD countries.

METHOD:

- **Countries:** 21 OECD countries.
- **Reference period**: 10-year lag for explanatory variables (used for the years 1985- 1993).
- **Data sources:** OECD Health Data.
- **Variables:** Life expectancy (at birth, at 40 years, at 60 years) and infant mortality, as a function of real per capita pharmaceutical expenditure (in purchasing power parity or PPP), per capita income, lifestyle factors (smoking, alcohol consumption, dietary richness) and sex.
- **Analysis:** Multivariate double-log regressions where the coefficients are interpreted as elasticities.

RESULTS:

- Being female has a positive and statistically significant effect on life expectancy at birth (0.039) at age 40 (0.100) and at age 60 (0.137).
- The effect of pharmaceutical expenditure on life expectancy at 40 and 60 years of age is statistically significant and increases with age, with elasticities of 0.017 and 0.040, respectively. The effect tends to be larger the lower the country's level of pharmaceutical consumption.
- Non-pharmaceutical expenditure has no effect on life expectancy at birth, and a small negative effect at age 40 and 60.
- Lifestyle habits have significant effects on life expectancy: smoking and alcohol consumption reduce life expectancy at birth and at 40.
- GDP per capita has positive (0.057 and 0.088) and statistically significant effects on life expectancy at age 40 and 60, respectively.
- No statistically significant effects on infant mortality are found.

CONCLUSIONS:

- Increased pharmaceutical consumption would contribute to increased life expectancy in developed countries, especially for middle-aged and older people.

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The Productivity of Pharmaceuticals in Improving Health: An Analysis of the OECD Health Data

Shaw JW, Horrace WC, Vogel RJ.

WUST economics working paper archive (2002); 0206001: 1-42

OBJECTIVE:

- To estimate the effect of pharmaceutical spending on health status (life expectancy at older ages) in OECD countries.

METHOD:

- **Countries:** 29 OECD countries.
- **Reference period:** Year 1997 for life expectancy. 13-year lag for pharmaceutical and non-pharmaceutical expenditure (year 1985). Time lag of 7 and 17 years for lifestyle factors.
- **Data sources:** OECD Health Database 2000.
- **Health variables:** Life expectancy (at 40, 60 and 65 years), by sex, real per capita pharmaceutical expenditure (in purchasing power parity or PPP), GDP per capita and lifestyle factors (smoking, alcohol consumption, diet).
- **Analysis:** Multivariate regressions with log-linear functional form. Marginal effects were calculated as the average number of days of life expectancy gained in 1997 for each additional dollar spent in 1985 on drugs, and alternatively as the average number of years of life gained in 1997 for each additional 1% of GDP spent in 1985 on drugs.

RESULTS:

- Being male is associated with a lower life expectancy than being female (12.4% less).
- Tobacco, alcohol, butter and fruit/vegetable consumption have a significant effect on life expectancy, after controlling for health consumption and wealth of the country: -0.1019; -0.0336 (men); 0.0189; 0.0943, respectively.
- GDP per capita is a significant predictor of life expectancy at age 60 and 65. The marginal effects increase with age: 0.03 at 60 and 0.05 at 65.
- Per capita pharmaceutical consumption is associated with a positive effect on life expectancy. Elasticities increase with age (0.028 at age 60 and 0.031 at age 65).
- The consumption of non-pharmaceutical expenditure does not appear to have a statistically significant effect.

CONCLUSIONS:

- Additional increases in per capita pharmaceutical spending can help to increase the life expectancy of the elderly population.

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The impact of pharmaceutical innovation on longevity and medical expenditure in Sweden, 1997-2010: Evidence from longitudinal, disease-level data

Lichtenberg FR.

CESIFO Working paper Social Protection (2012); 3894

OBJECTIVE:

- To estimate the impact of pharmaceutical innovation on longevity and health expenditure in Sweden during the period 1997-2010.

METHOD:

- **Country:** Sweden.
- **Reference period:** 1997-2010.
- **Data type:** Longitudinal, aggregated to disease level.
- **Data source:** Thèriaque, Läkemedelsverket, IMS Health MIDAS, Eurostat, OECD Health Database, World Health Organization Mortality Databse.
- **Variables:** longevity measured as the average age of death or as the percentage of deaths occurring at a given age; pharmaceutical innovation measured as the number of chemicals previously marketed to treat a disease; number of days of hospitalisation; pharmaceutical expenditure as the value of medicines for each disease sold each year.
- **Analysis:** Cost-effectiveness analysis to determine the cost of pharmaceutical innovations per life year gained (LYG), and weighted least squares regression analysiss.

RESULTS:

- Between 1997 and 2010, the median age at death increased from 78.4 to 80.28 years in Sweden, an increase of 1.88 years. Of this increase, 31.6% (0.60 years) is attributable to pharmaceutical innovation. Without the new drugs, the average age of death in 2009 would have been 0.47 years lower.
- Between 2000 and 2009, the number of hospital days fell by 6%, from 10.1 to 9.6 million days. Without innovative medicines, hospitalisations in 2009 would have been 12% higher, costing an additional $112 per capita per year ($1,047 instead of $935).
- A 10% increase in the number of molecules for a given disease is associated with an 8.9% increase in pharmaceutical spending three years later. The increase in the number of drugs marketed between 1997 and 2006 is associated with a 37.2% increase in pharmaceutical spending in 2009, resulting in an additional $91 per capita annual pharmaceutical expenditure.
- Without pharmaceutical innovation, average health expenditure per capita would have been $21 ($112-91) lower for one year of a patient's life and $109 lower over a patient's lifetime.
- The average cost per LYG with the new drugs is $233 in the base case. If no hospital savings had been achieved, the ICER would be $19,192/AVG.

CONCLUSIONS:

- Pharmaceutical innovations have contributed to a 0.47-year increase in longevity in Sweden between 1997-2010, representing an investment with an average cost of $233 per year of life gained.

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The impact of pharmaceutical innovation on longevity and medical expenditure in France, 2000–2009

Lichtenberg FR.

Economics and Human Biology (2014); 13: 107-127

OBJECTIVE:

- Estimate the impact of pharmaceutical innovation on longevity and healthcare expenditure in France during the period 2000-2009.

METHOD:

- **Country:** France.
- **Reference period:** 2000-2009.
- **Data source:** Thèriaque, IMS Health MIDAS, Eurostat, World Health Organization.
- **Variables:** Mean age at death; age-adjusted annual rate of hospital admissions per 100,000 population; age-adjusted rate of hospital days per 100,000 population; pharmaceutical expenditure each year, by type of medicine; pharmaceutical innovation measured as the number of chemical substances previously marketed to treat each disease; delays since marketing of innovations.
- **Analysis:** Weighted least squares regression analysis:
  - Longevity model in which the mean age at death in each year depends on the logarithm of the stock of subgroups of chemicals marketed each year to treat the different diseases, controlling for disease and year.
  - Two models of resource use in which hospitalisations per year by disease subgroups and pharmaceutical expenditure per year depend on the stock of marketed medicines.

RESULTS:

- The increase in longevity in 2000-2009 attributable to pharmaceutical innovation ranges from 0.15 to 0.42 years (average 0.29 years). This accounts for about one fifth of the total increase in longevity over this period.
- The average time lag between marketed substances and the average age of death from the disease is 9.94 years.
- Pharmaceutical innovation during the period under review reduced the number of days of hospitalisation by 9.3% in 2010.
- A 10% increase in the number of molecules for a given disease is associated with a 13.5% increase in pharmaceutical spending three years later.
- Pharmaceutical innovation during the period 1997-2006 cost an average of $125 per capita, but 87% of this was offset by lower hospital spending (-$109), reducing the cost of innovation to $16 per capita per year.
- Pharmaceutical innovation has meant that total health expenditure per capita in 2009 increased by $16 and lifetime health expenditure per capita increased by $2,309, implying a cost-effectiveness ratio of $8,065 per life-year gained.

CONCLUSIONS:

- Pharmaceutical innovations have contributed to increasing life expectancy by 0.29 years in France between 2000-2009, representing a cost-effective intervention.

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How many life-years have new drugs saved? A three-way fixed-effects analysis of 66 diseases in 27 countries, 2000–2013

Lichtenberg FR.

International Health (2019); 11(5): 403–416

OBJECTIVE:

- To analyse the impact of the commercialisation of new drugs on the number of years of life lost due to 66 pathologies in 27 countries.

METHOD:

- **Countries:** 27 countries, including Spain.
- **Period:** 2000-2013.
- **Sample:** 66 pathologies.
- **Sources:** IQVIA MIDAS, OECD Health Statistics, Theriaque, Mundial, International Federation of Pharmaceutical Manufacturers & Associations.
- **Variables:** Standardised rates of years of life lost before the ages of 65, 70, 75, 80 and 85; cost of hospitalisations in 2015; premature mortality; pharmaceutical innovation measured as the number of new chemical entities marketed in the period in each country for each pathology analysed; incremental cost-effectiveness ratio.
- **Analysis:** Fixed effects regression models by country, pathology and year, controlling for the improvement in the premature mortality rate for each pathology in each country. Analysis by time subgroups.

RESULTS:

- The premature mortality rate (before the age of 5) for a pathology is inversely related to the number of medicines launched for that pathology in the country.
- A medicine marketed between 0 and 11 years before a given point in time is associated with a 3% reduction in the rate of years of life lost before age 85 at that point in time, while for a period of 12 years or more, the effect would be 5.5%. For other age subgroups, the estimates are qualitatively similar, but larger in magnitude.
- If no new drugs had been marketed after 1981, the total years of life lost before the age of 85 in 2013 would have been 2.16 times higher than it actually was. For the 22 countries analysed, this translates into a gain of 149 million years.
- Spending in 2013 on drugs launched after 1981 is $421.8 billion.
- The cost-effectiveness ratio associated with post-1981 pharmaceutical spending is $2,837 per year of life gained before age 85.

CONCLUSIONS:

- Investment in pharmaceutical innovation has been a cost-effective strategy in terms of life years gained in the developed countries analysed.

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The effect of pharmaceutical innovation on longevity: patient-level evidence from the 1996-2002 medical expenditure panel survey and linked mortality public-use files

Lichtenberg FR.

Forum Health Econ Policy (2013); 16(1): 1-33

OBJECTIVE:

- To estimate the effect of drug technology change on longevity in the elderly population in the United States, based on individual patient data.

METHOD:

- **Country:** United States.
- **Reference period:** 1996-2002.
- **Data sources:** Medical Expenditure Panel Survey, public mortality files.
- **Health variables**: Survival of those over 64 years of age, according to the novelty of the drugs consumed by the person (3 alternatives: average year of FDA approval; proportion of drugs post 1975; proportion of drugs post 1985), their sex, their age group, their region of residence, their educational level, their income level, their race, their degree of disability, their degree of health insurance and risk factors.
- **Analysis:** Three models for estimating individual survival time (number of years to death) as a function of a measure of the age of drugs prescribed for that individual and a vector of other individual attributes. Calculation of the cost-effectiveness ratio of a unit increase in drug novelty from the ratio of its cost (increase in expenditure) to its benefit (increase in life expectancy).

RESULTS:

- The novelty of medicines increased over time: for example, the proportion of prescribed medicines containing drugs approved after 1985 increased from 26% in 1996 to 57% in 2008, and the measure of novelty increased by 6.6 years over the period.
- The coefficient of drug novelty is positive and statistically significant in all three alternative modes, fluctuating between 0.0052 and 0.0058, indicating that for each additional year of drug novelty, the life expectancy of older people increases by 0.52% to 0.58%.
- The use of novel medicines is estimated to increase lifetime medical expenditure by an average of $6,046 and life expectancy by 0.47 years, which translates into a cost-effectiveness ratio of $12,863 per life-year gained.

CONCLUSIONS:

- The introduction of novel drugs in the United States has accounted for two-thirds of the total increase in life expectancy of the elderly, which, given its cost, translates into a cost-effective health intervention.

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Number of drugs provided by the Pharmaceutical Benefits Scheme and mortality and hospital utilization in Australia

Lichtenberg FR.

SSM - Population Health (2023); 12(24): 101514

OBJECTIVE:

- To analyse the impact that pharmaceutical innovation has had on mortality and hospital utilisation in Australia.

METHOD:

- **Country:** Australia.
- **Reference period:** 1994-2019.
- **Data source:** PBS Item Reports, PBS Item Drug Map, IQVIA MIDAS and Thériaque databases for medicines. WHO mortality database. OECD Health Statistics.
- **Variables:** Premature mortality, years of life lost (YLL) and number of days of hospitalisation.
- **Analysis**: Two-way fixed effects model of the effect of the current or delayed number of medicines on various measures of mortality and hospitalisation.

RESULTS:

- The increase in the number of medicines in 1996-2013 was associated with a reduction in the number of DALYs before age 85 of 359,026 in 2019.
- If the number of medicines had not increased during the study period, the number of DALYs before the age of 85 would have been 21.2% higher.
- If the number of medicines had not increased between 2000 and 2017, the average age at death would have decreased by 0.61 years (29.9% of the total increase over the period).
- The addition of an additional medicine for a disease was associated with a reduction in the number of DALYs for the disease before the age of 85 years of 2%.
- The increase in the quantity of medicines from 1994-2011 was associated with a reduction in the number of hospital days of 2.48 million in 2019 and a reduction in hospital expenditure of 5.97 billion Australian dollars.
- If the number of medicines had not increased between 1994 and 2011, the number of hospital days in 2019 would have been 10.6 per cent higher.

CONCLUSIONS:

- The increase in the number of new medicines available in Australia is associated with lower premature mortality and fewer days of hospitalisation, leading to a reduction in hospital expenditure.

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The effect of pharmaceutical innovation on longevity: Evidence from the U.S. and 26 high-income countries

Lichtenberg FR.

Economics and Human Biology (2022); 46: 101124

OBJECTIVE:

- Examine the impact that pharmaceutical innovation has had on longevity.

METHOD:

- **Countries:** Analysis (1): USA. Analysis (2): 26 high-income countries, including Spain.
- **Reference period:** Analysis (1): 2006-2018. Analysis (2): 2006-2016.
- **Sample:** 150 pathologies. The total population of the countries under analysis.
- **Data source:** IQVIA MIDAS, Drug Central and Thériaque databases. OECD Health Statistics. United States National Bureau of Economic Research. WHO Global Health Estimates.
- **Variables:** mean age at death; cost of hospitalisations; pharmaceutical innovation measured as the number of new chemical entities marketed in the period in each country for each pathology analysed; mean age (year of initial launch worldwide) of these drugs; cost per life-year gained.
- **Analysis:** Two types of two-way fixed effects analysis: (1) Long-term (2006-2018) changes in longevity associated with different diseases in the USA; (2) Relative levels of longevity associated with different diseases in 26 high-income countries over a single time period (2006-2016).

RESULTS:

- Analysis of the US data indicates that the lower the average age of medicines, the higher the average age at death of the patient. The reduction in drug age between 2006 and 2018 increased the average age at death in the US population by approximately 6 months (66% of the observed increase).
- Analysis of data from 26 high-income countries indicates that a reduction in the age of medicines was associated with a 1.23-year increase in the average age at death between 2006 and 2016, accounting for 73% of the observed increase. In 2016, 9.37 million years of life were gained due to the increase in the number of medicines marketed in the period.
- Estimates of the cost per life-year gained for the United States and the 26 countries are $35,817 and $13,904, respectively. Both figures are well below the GDP per capita in the respective regions, suggesting that, overall, pharmaceutical innovation was highly cost-effective.

CONCLUSIONS:

- The reduction in the shelf life of medicines is positively correlated with the increase in life expectancy in the populations of the nations under analysis, suggesting that investment in pharmaceutical innovation is a cost-effective strategy.

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Cost-Effectiveness of Colchicine for Recurrent Cardiovascular Events

Boczar KE, Beanlands R, Wells G, Coyle D.

CJC Open. 2023;5(5):348-56

OBJECTIVE:

- To determine whether the use of colchicine, both in the long and short term, is cost-effective for the prevention of recurrent cardiovascular events in patients who have suffered a myocardial infarction (MI).

METHOD:

- **Country:** Canada (Ontario region).
- **Reference period:** 2022.
- **Population:** Adults (mean age: 62 years) who have experienced a MI and are being treated with colchicine or the standard of care (comparator).
- **Data source:** Two randomised clinical trials (COLCOT and LoDoCo 2). Literature data. MONICA/KORA registry.
- **Variables:** Direct costs (hospitalisations, medical visits, etc.), quality-adjusted life years, and life years gained.
- **Analysis:** A probabilistic Markov model was used in conjunction with a Monte Carlo simulation, with a time horizon of the patient's lifetime. The payer's perspective was adopted, with a 1.5% discount rate for costs and benefits. A probabilistic sensitivity analysis was performed, and methodological uncertainty was explored by varying the discount rates applied (0% and 3%).

RESULTS:

- Both prolonged (lifetime [LT]) and short-term (20 months [ST]) colchicine use emerge as dominant strategies compared to standard care (SC), showing a lower average cost per patient (LT: $91,552 CAD; ST: $96,636 CAD and SC: $97,085 CAD) and an increase in the average number of quality-adjusted life years per patient (LT: 19.92; PC: 19.86 and ST: 19.80).
- Life years gained were 23.62, 23.77 and 23.75 with long-term and short-term colchicine treatment and standard clinical practice, respectively.
- In another comparison, long-term use of colchicine was found to be a dominant option over short-term use, with lower lifetime costs and greater lifetime QALY gains.
- Under a willingness-to-pay per QALY threshold of CAD$50,000, long-term use of colchicine had a 72.2% probability of being cost-effective (i.e., the ICER was greater than CAD$50,000 in 72.2% of the 5,000 simulations). Short-term use of colchicine had a 25.8% probability of being the most cost-effective strategy..

CONCLUSIONS:

- Treatment with colchicine after myocardial infarction appears to be cost-effective compared to the standard of care.

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How cost-effective are new cancer drugs in the U.S.?

Lichtenberg FR.

Expert review of pharmacoeconomics & outcomes research (2020); 20(1): 39–55

OBJECTIVE:

- To evaluate the cost-effectiveness of FDA-approved cancer drugs in the United States during the period 2000-2014.

METHOD:

- **Country:** United States.
- **Period:** 2000-2014.
- **Sources:** IMS Health, HCUPnet, National Cancer Institute, Compressed Mortality Database, SEER Reseach Data.
- **Variables:** Premature mortality; 5-year survival; hospitalisations; pharmaceutical innovation measured as the number of oncology drugs marketed by the FDA; incremental cost-effectiveness ratio.
- **Analysis:** Three fixed-effects regression models on years of potential life lost before age 75, survival rate and days of hospitalisation.

RESULTS:

- Cancer medicines marketed between 2000 and 2014 are associated with a reduction of 719,133 years of potential life lost (before age 75) in 2014.
- Cancer drugs approved in 1989-2005 have reduced hospital costs in 2013 by $4.8 billion. Meanwhile, in 2014, the net societal cost of cancer drugs approved after 1999 is €7.5 billion, taking into account the lower expenditure on older drugs and hospitalisations resulting from their use.
- In the base case, the cost per life-year gained in 2014 from cancer medicines approved in 2000-2014 is estimated at $7,853.

CONCLUSIONS:

- Investment in oncology pharmaceutical innovation can be considered a cost-effective strategy.

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The Relationship Between Pharmaceutical Innovation and Cancer Mortality in Spain, from 1999 to 2016

Lichtenberg FR.

Value in Health (2023); 26(12): 1711-20

OBJECTIVE:

- To examine the impact that pharmaceutical innovation has had on reducing cancer mortality in Spain. Spain.

METHOD:

- **Country:** Spain.
- **Reference period:** 1999-2016.
- **Sample:** 58 types of cancer.
- **Sources:** Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), CI5plus (Cancer Incidence in 5 Continents Time Trends), IQVIA, Theriaque and WHO mortality database.
- **Variables:** Pharmaceutical innovation measured as the number of new chemical entities marketed in the period 1999-2016 for each type of cancer analysed, mean age at cancer death, number of years of life lost at 65, 75 and 85 years of age.
- **Analysis:** 25 two-way fixed effects regression models (by cancer site and year) on morbidity and numbers of years of life lost at 65, 75 and 85 years.

RESULTS:

- Cancer medicines approved during the period under review were associated with a reduction of 42,138 cancer deaths in 2016 in our country.
- New cancer drug approvals produced between 1997 and 2014 were associated with a 29.2% reduction in the number of cancer deaths in 2016.
- Pharmaceutical innovation in oncology was associated with a 2.77-year increase (96% of the observed increase) in the median age of death from cancer between 1999 and 2016.
- New drug approvals were associated with a 29.7%, 35.1% and 35.2% reduction in the number of years of life potentially lost before the age of 65 years, 75 years and 85 years, respectively.
- Pharmaceutical expenditure per year of life gained before the age of 75 in 2016, from new cancer drugs authorised between 2000 and 2016, amounted to €3,269.

CONCLUSIONS:

- Pharmaceutical innovation in oncology has had a significant impact on reducing cancer mortality in Spain, and is a cost-effective strategy.

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The Burden of Rare Diseases: An Economic Evaluation

Andreu P, Karam J, Child C, Chiesi G, et al.

Chiesi Global Rare Diseases (2022)

OBJECTIVE:

- Investigate the direct, indirect and mortality-related costs of rare diseases, comparing the situation where treatment is available with the situation where no specific treatment exists.

METHOD:

- **Country:** United States.
- **Reference period:** 2022.
- **Population:** 584,000 patients with 24 rare diseases in five therapeutic areas (metabolic, haematological, immunological, congenital and neurological disorders).
- **Data source:** IQVIA database of 373 rare diseases, related to 8.4 million patients (18% of the total) in the United States. Review of 500 scientific articles. Expert opinion
- **Variables:** Direct costs, indirect costs and costs associated with mortality.
- **Analysis:** Direct costs include medication, medical devices, hospitalisation, home care, professional services (e.g. nursing visits) and administrative costs. Indirect costs include productivity costs: patient and caregiver, work loss, changes in household, secondary treatment costs, travel and accommodation. Mortality-related costs consider a value of life of $130,000 per year.

RESULTS:

- The burden of the 24 selected rare diseases ($125-334 thousand, per patient, per year) is approximately 10 times higher than that of the 24 selected prevalent diseases ($26 thousand), including diabetes, cardiovascular diseases, Alzheimer's disease, arthritis and back pain, cancers and others.
- The absence of treatment for a rare disease is associated with a 21.2% increase in total annual costs per patient (direct costs per patient/year: $63k with treatment vs. $118k without treatment; indirect costs: $40k vs. $73k; costs associated with mortality: $36k vs. $49k).
- The cost to the 8.4 million patients affected in the US by the 373 rare diseases considered in this analysis is estimated to be $2.2 billion per year.
- The introduction of targeted treatments can significantly reduce costs, especially in metabolic and immunological diseases, where direct costs were reduced by 71-84%, partially offsetting the increased costs of drug procurement.

CONCLUSIONS:

- The economic burden attributed to patients affected by rare diseases significantly exceeds the burden associated with patients diagnosed with more prevalent diseases. Furthermore, the lack of treatment correlates with a clear increase in the costs inherent to the disease.

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The impact of direct acting antivirals on hepatitis C virus disease burden and associated costs in four European countries

Mennini FS, Marcellusi A, Robbins Scott S, Montilla S, et al.

Liver international (2021); 41(5): 934–948

OBJECTIVE:

- To assess the clinical and economic impact of direct-acting antiviral therapy (DAA) for hepatitis C virus (HCV) in England, Italy, Romania and Spain.

METHOD:

- **Countries:** England, Italy, Romania and Spain.
- **Reference period:** 2015-2019.
- **Population:** A total of 1,000 standard patients with 13 disease states (5 stages of fibrosis, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), transplantation in the first year and years post-transplantation, 4 stages of sustained virological response (SVR), SVR of irreversible liver damage (ILD)), plus HCV-related death and death from other causes were considered.
- **Variables:** Direct costs related to the management of HCV-related diseases, including outpatient visits, biochemical tests, instrumental procedures, management and treatment of decompensated cirrhosis, hepatocellular carcinoma and liver transplantation, together with the costs of DAAs.
- **Analysis:** A Markov model capturing multiple morbidity and mortality states, based on country-specific parameters, was used to assess HCV disease progression and costs to treat (vs. not treat) 1,000 standard patients over a 20-year time horizon. To estimate the uncertainty of economic outcomes, probabilistic and deterministic sensitivity analyses were conducted. In addition, 5,000 Monte Carlo simulations were performed to provide 95% confidence intervals.

RESULTS:

- The estimated number of avoided hepatocarcinomas, decompensated cirrhosis and liver transplants over a 20-year time horizon was 1,057 in England; 1,221 in Italy; 1,211 in Romania; and 1,103 in Spain for patients treated during 2015-2016, and 640 in England; 626 in Italy; 739 in Romania; and 643 in Spain for patients treated during 2017-2019.
- Cost savings ranged from 45 to 276 million euros:
  - **Romania:** €45.4 million (95%CI: 7.7-116.0)
  - **Italy:** 63.4 million (95% CI: 30.4-108.6)
  - **England:** €81.5 million (95%CI: 51.3-118.6)
  - **Spain:** 275.6 M€ (95% CI: 170.9-404.9)
- It is estimated that the investment needed to expand access to DAAs in 2015-2019 would be recouped in 6.5 years in England; 5.4 years in Italy; 6.7 years in Romania; and 4.5 years in Spain.

CONCLUSIONS:

- Direct-acting antivirals could generate significant clinical benefits and substantial economic savings over the next 20 years, reaching a break-even point in a short period of time.

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Real-world Impact of Fremanezumab on Migraine-Related Health Care Resource Utilization in Patients with Comorbidities, Acute Medication Overuse, and/or Unsatisfactory Prior Migraine Preventive Response

Buse D, Krasenbaum L, Seminerio M, et al.

Pain Therapy (2024);13 (3):511-532

OBJECTIVE:

- To assess the effect of fremanezumab on migraine-related medication use, healthcare resource utilisation (HCRU), costs in patient populations with comorbidities, acute medication overuse (AMO) and previous unsatisfactory preventive response to migraine.

METHOD:

- **Country:** United States.
- **Period:** 2018-2019.
- **Sample:** 3,193 patients with major depressive disorder and/or generalised anxiety disorder (n = 1183), potential for SMA (n = 1458) or prior erenumab use (n = 422). Eligible adults with migraine who initiated fremanezumab between 1 September 2018 and 30 June 2019 (date of first fremanezumab prescription is the index date), had ≥ 12 months of continuous insurance enrollment prior to baseline (pre-index period) and ≥ 6 months of data after baseline (post-index period; variable follow-up after 6 months).
- **Sources:** Commercial insurance claims database (Merative® and MarketScan®) and supplementary databases.
- **Variables:** Charlson Comorbidity Index, excessive use of medication for a specific or short-term illness, previous unsatisfactory preventive response to migraine, and health care costs of medical visits.
- **Analysis:** Retrospective analysis of health insurance claims.

RESULTS:

- Pre- and post-index, the mean number per patient per month (PPM) of insurance claims for disease-specific or short-term medications and migraine-related preventive medications (excluding fremanezumab) decreased from 0.97 (SD: 0.90) to 0.86 (SD: 0.87) ($P < 0.001$) and from 0.94 (SD: 0.74) to 0.81 (SD: 0.75) ($P < 0.001$), respectively.
- Migraine-related medical visits, emergency department visits and other PPM outpatient services decreased statistically significantly ($P < 0.001$ for all), resulting in a reduction in mean total costs (MTC) of PPM medical care from $541 (SD: $858) to $490 (SD: $974) ($P = 0.003$).
- Patients showed high adherence and persistence rates, with a mean proportion of days covered of 0.71 (SD: 0.29), a medication possession ratio of 0.74 (SD: 0.31) and a persistence duration of 160.3 (SD: 33.2) days after six months of follow-upo.

CONCLUSIONS:

- In this analysis using real-world data, patients with migraine comorbidities, acute medication overuse and/or unsatisfactory prior preventive migraine response reduced migraine-related medication use, HCRU and costs after fremanezumab initiation.

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Medical innovations and labor savings in health care. An exploratory study

Tsiachristas A, Notemboom A, Goudriaan R, Groot W.

The Hague: Aarts De Jong Wilms Goudriaan Public Economics bv and Maastricht University; 2009

OBJECTIVE:

- To estimate the annual workforce savings generated by pharmaceutical innovation in three groups of chronic diseases prevalent in the Netherlands.

METHOD:

- **Country:** The Netherlands
- **Reference period:** 1995-2007.
- **Data source:** Literature review; Bureau of Statistics of the Netherlands; National Institute for Public Health and the Environment; Trimbos Institute.
- **Variables:** Drugs approved after 1995 in asthma (montelukast), COPD (tiotropium), heart failure (candesartan, rosuvastatin), coronary heart disease (atorvastatin, abciximab, clopidrogel), schizophrenia/bipolar disorder (olanzapine, paliperidone, quietapine). Hospital admissions in 2004 and 2007. Average length of stay in hospital in 2004 and 2007. Full-time staff (nurses and carers, specialist doctors, other medical staff, other staff) in 2007.
- **Analysis:** Hospital days saved calculated as the subtraction of hospital admissions after drug approval (weighted by average length of stay) and admissions before drug approval (weighted), all weighted by the fraction of patients consuming these medicines. Avoided inpatient days translate into staff savings. Projections to 2025 based on four scenarios of annual growth in the share of use of these ten medicines.

RESULTS:

- The ten pharmaceutical innovations in the three disease groups considered generate annual savings of 7,212 full-time patient care staff: 4,920 in general hospitals (3.6% of their current staff) and 2,292 in mental hospitals (7.4% of their current staff).
- By professional categories, there are savings of 2,359 nurses and carers, 784 specialised doctors, 1,825 other medical staff and 2,244 other staff.
- By disease group, the savings in asthma/ COPD were 2,722 persons, in cardiovascular diseases 2,198 and in mental diseases 2,292.
- In a scenario for the year 2025, it is considered that the total staff saved could amount to a range between 9,082 and 11,874 persons per year, depending on whether the share of use of these medicines grows at an annual rate of 0% or 1.5%.

CONCLUSIONS:

- Innovative medicines have a positive impact on labour supply per capita, improving workers' health and reducing absenteeism. Pharmaceutical innovation can be a catalyst for the sustainability of the healthcare system.

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Economic impact of patiromer use in chronic kidney disease or heart failure for the treatment of chronic hyperkalemia in Spain

de Sequera P, Bover R, Ivanova-Markova Y, Ivanova A, et al.

Nefrología (2023); 43(6): 721-30

OBJECTIVE:

- To estimate the economic impact of the use of patiromer in patients with chronic kidney disease (CKD) or heart failure (HF) and hyperkalaemia in Spain.

METHOD:

- **Country:** Spain
- **Period:** 2020.
- **Sample:** Patients with CKD or HF and hyperkalaemia, simulation.
- **Sources:** Decision tree where information has been obtained from the literature.
- **Variables:** direct health costs related to resource use (treatment with renin-angiotensin-aldosterone system inhibitors, progression of CKD, cardiovascular events and hospitalisation for hyperkalaemia); direct non-health costs (informal care: costs derived from the time spent by the patient's relatives); indirect costs (loss of work productivity), as well as an intangible cost (premature mortality).
- **Analysis:** Comparison of two scenarios (with social perspective) in patients with CKD or HF and hyperpothesaemia treated with patiromer and without patiromer. A deterministic sensitivity analysis was performed to validate the consistency of the study results.

RESULTS:

- The average annual cost per patient in the scenario without patiromer is €9,834.09 and €10,739.37 in CKD and HF, respectively.
- The use of patiromer would result in cost savings of more than 30% in both diseases. In the case of CKD, the greatest savings come from delaying the progression of CKD, while in HF, 80% of these savings come from reducing premature mortality.
- The sensitivity analyses carried out show the consistency of the results, with savings in all cases.

CONCLUSIONS:

- The addition of patiromer allows control of hyperkalaemia and, as a consequence, maintenance of treatment with renin-angiotensin-aldosterone system inhibitors in patients with CKD or HF, generating annual savings in Spain of 32% (€3,127 in CKD; €3,466 in HF). These results support the positive contribution that patiromer can make in both CKD and HF-only patients.

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Impact of medication adherence on hospitalization risk and healthcare cost

Sokol M, McGuigan K, Verbrugge R, Epstein R.

Medical Care (2005); 43(6): 521-530

OBJECTIVE:

- To assess the relationship between treatment adherence, medical utilisation and healthcare costs in the United States for four high-prevalence diseases in which prescription drugs play an important role.

METHOD:

- **Country:** United States.
- **Reference period:** 1997-1999.
- **Study population:** 137,277 people under 65 years of age covered by occupational health insurance.
- **Data source:** Medco Health, HMO, FFS and PPO administrative databases.
- **Variables:** Health care cost measured as the cost per medicine consumption for the indicated therapeutic areas, the cost of medical visits made, hospital admissions and emergency department visits. Adherence to treatment measured as the percentage of days during the period of analysis considered (12 months) when the patient had an offer of 1 or more maintenance medicines for the condition, divided into 5 categories.
- **Analysis:** Multiple linear regression to assess the association between adherence and costs, controlling for sex, age, comorbidities, disease subtype, employment status and type of health insurance. Logistic regression analysis to assess the association between adherence and risk of hospitalisation, controlling for the above variables.

RESULTS:

- For the 4 diseases considered, patients with 80% to 100% adherence over the period have a statistically lower risk of being hospitalised than patients with lower adherence. For example, compared to 40-59% adherence, 12 percentage points (pp) less in diabetes, 5 pp less in hypertension, 3 pp less in hypercholesterolaemia and 8 pp less in heart failure.
- In patients with diabetes, hypertension and hypercholesterolaemia, medical costs decrease linearly with decreasing adherence rates. In these 3 diseases, total health care costs tend to decrease the higher the patient's adherence to treatment, although the pharmaceutical cost rises with adherence. The differences in heart failure are not significant.
- Diabetes is the only one of the diseases considered where healthcare costs decrease monotonically as adherence decreases (five blocks). Healthcare costs for patients with 80-100% adherence are reduced by an average of 27% in the 60-79% adherence category, 30% in the 40-59% category, 36% in the 20-39% category and 48% in the 1-19% adherence category.

CONCLUSIONS:

- In some chronic diseases, increased exposure to pharmacological treatment can bring a positive net economic return by reducing hospitalisations, medical visits and emergencies.

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Does prescription drug adherence reduce hospitalizations and costs? The case of diabetes

Encinosa WE, Bernard D, Dor A.

Advances in Health Economics and Health Services Research (2010); 22: 151-73

OBJECTIVE:

- To estimate the direct impact of adherence to type 2 diabetes treatment on hospitalisations and emergency department visits.

METHOD:

- **Country:** United States.
- **Reference period:** 2001-2002.
- **Sample:** Patients with T2DM of working age who required oral antidiabetic medication (n=56,744).
- **Data source:** MarketScan Research Databases (private health insurer); Employer Benefit Plan Design.
- **Variables**: Non-adherence (% of days the patient did not control their diabetes medication); severity of disease; 27 chronic conditions; utilisation of emergency services and hospitalisations; savings from better control.
- **Analysis**: Regression analysis (probit, IV probit, GMM) to determine the effect of non-adherence on resource use and costs, controlling for unobservable disease severity.

RESULTS:

- Increasing the rate of adherence to anti-diabetic medication from 50% to 100% reduces the rate of hospitalisation from 15% to 11.5%, and the rate of emergency department visits from 17.3% to 9.3%.
- On the one hand, increasing the adherence rate would generate an additional $776 per patient per year in drug costs. On the other hand, increasing adherence would reduce hospital costs by $865 per patient per year ($2,097 - $1,232) and emergency department costs by $21 ($49 - $28) per patient.
- Thus, increasing adherence would generate an average net saving of $110 per patient per year ($886 - $776) or, in other words, a saving of $1.14 for every additional dollar spent on antidiabetics.
- Not controlling for disease severity would result in a considerable downward bias in average savings: instead of gaining 14% of costs, 45% would be lost.

CONCLUSIONS:

- Enhancing adherence to type 2 diabetes treatment is a net cost-saving strategy, achieving a net saving of $1.14 for every additional dollar spent on medication.

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Impact of initial medication non-adherence on use of healthcare services and sick leave: a longitudinal study in a large primary care cohort in Spain

Aznar-Lou L, Fernández A, Gil-Girbau M, Sabés-Figuera R, et al.

British Journal of General Practice (2017); 67(662): e614-e622

OBJECTIVE:

- To estimate the impact of initial non-adherence to medication (INAM) on the use of health services, days of absenteeism and costs, both globally and by specific groups of drugs.

METHOD:

- **Country:** Catalonia (Spain).
- **Reference period:** 2012-2014.
- **Study population:** Patients aged 14 years and older, who were prescribed a new medicine in primary care in one of 13 selected categories. Cohort of 1.7 million people.
- **Data source:** Information System for the Development of Research in Primary Care (SI-DIAP), Official Journal of the Generalitat of Catalonia (DOGC), Official State Bulletin (BOE), National Statistics Institute (INE).
- **Variables:** Utilisation and costs of health services, drugs, laboratory tests and clinical analyses. Estimates of work productivity losses. Initial adherence, measured through three categories (adherent, partially adherent, non-adherent), in the 2 months following the prescription date.
- **Analysis:** Longitudinal cohort study, based on 3-year records. Multivariate multilevel linear regression (patient, doctor and primary care centre), adjusted for costs incurred in the 12 months prior to prescription. Analysis of 3 subgroups: chronic medicines, analgesics and penicillins.

RESULTS:

- Initially adherent patients made greater use of drugs and some health services than initially non-adherent or only partially adherent patients. This resulted in increases in average medical costs of between 2 and 11 euros per patient, and between 15 and 23 euros in patient drug costs.
- In contrast, the productivity loss of initially adherent patients has been lower than the others. Each initially adherent patient shows average productivity gains of between 81 and 245 euros relative to partially adherent patients, and between 53 and 160 euros relative to non-adherent patients. Overall, there is an offsetting effect, generating net savings from society's perspective when initial adherence to treatment occurs.
- The differences in costs between adherent and non-adherent patients are most pronounced in the sub-groups of penicillins (230 euros) and analgesics (167 euros), compared to drugs for chronic diseases (11 euros).
- INAM to treatment is associated with an economic impact in Catalonia of between 8 and 89 million euros.

CONCLUSIONS:

- Overall, INAM translates into a greater short-term economic burden for the system, as it generates a greater loss of labour productivity. Interventions to improve initial adherence in primary care could reduce costs and improve health outcomes.

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The economic burden of depression in the United States: How did it change between 1990 and 2000?

Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, et al.

The Journal of Clinical Psychiatry (2003); 64(12), 1465–1475

OBJECTIVE:

- Update the estimate of the economic burden of depression in the United States.

METHOD:

- **Country:** United States.
- **Period analysed:** 1990-2020.
- **Data source:** Direct health costs from Mental Health database, National Nursing Home Survey, National Hospital Discharge Survey, National Ambulatory Medical Care Survey; suicide data from Centers for Disease Control; work losses from National Vital Statistics Report and Bureau of Labor Statistics.
- **Variables:** Direct health costs measured as the number of hospitalisations, medical and nursing visits, and pharmacological costs based on sales of antidepressants. Labour losses as a consequence of the morbidity of the illness, absenteeism (20% of the time if suffering from depression) and absenteeism from work. Cost of suicides caused by depression (anticipated mortality).
- **Analysis:** Econometric models.

RESULTS:

- In the period under review, the prevalence rate of depression fell by 1.4 percentage points to 8.7%, from 17.5 million people in 1990 to 18.1 million in 2000. In contrast, the treatment rate rose by 56% to 43.6%, from 4.9 million to 7.9 million people treated in 2000.
- The employment rate of these people rose from 59.2 per cent in 1990 to 63.3 per cent in 2000.
- Suicides among people with depression decreased by 4.5%.
- In homogeneous terms, the economic burden of the depression rose from $77.4 billion in 1990 to $83.08 billion in 2000 in the United States (an increase of 7.4%). Direct costs increased by 31.2% to 31.4% of the total, while labour losses decreased by 0.8% to 68.6% of the total.
- The cost per patient with depression fell from $9,721 in 1990 to $8,419 (a decrease of 13.4%). Direct costs fell by 18.7% (-$763) due to a reduction in the cost of hospitalisations (-$1,611; -58.8%) and doctor visits (-$86; -8.1%), as the cost of drug treatment increased by a factor of 2.5 over the period (+$934). Productivity losses were reduced by 9.8% (-$522), as the cost of absenteeism fell (-$641;-16.8%) and for early mortality (-$17; -5.3%), while presenteeism costs increased by $136 (+11.3%).

CONCLUSIONS:

- The increased pharmacological cost of treating depression has been more than offset by lower hospital costs and lower work productivity losses due to better control of the disease.

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Value in Hepatitis C Virus Treatment: A Patient-Centered Cost-Effectiveness Analysis

Mattingly TJ, Slejko JF, Onukwugha E, Perfetto EM, et al.

PharmacoEconomics (2020); 38(2): 233-42

OBJECTIVE:

- To evaluate the cost-effectiveness of hepatitis C virus (HCV) drug therapy using a patient-centred approach.

METHOD:

- **Country:** United States.
- **Period:** Time horizon of 10 and 20 years.
- **Sample:** Board of 11 stakeholder advisors (SABs): four HCV patients, three infectious disease specialists, one general practitioner, two pharmacists and one representative of a national patient advocacy organisation.
- **Sources:** The simulation model was studied with parameters from the literature and the model was corroborated by a stakeholder advisory board.
- **Variables:** Indirect costs are estimates based on self-reported productivity in a matched-control sample. For effectiveness, quality-adjusted life years (QALYs) were used. This study included two novel measures developed from the Delphi panel and SAB: life years infected and working days lost.
- **Analysis:** An individual Markov model was constructed using guidance from a SAB, a Delphi panel of patients and published literature to assess the impact of direct-acting antivirals (DAAs) compared to no treatment.

RESULTS:

- Health costs and QALY gain were higher in the treatment group ($25,078 and 0.63 at 10 years and $8,077 and 1.66 at 20 years).
- Total years of life with infection and work days lost were reduced in the treatment group for both models (-7.24 and -35.05 at 10 years and -13.11 and -63.85 at 20 years, respectively).
- From a societal perspective, where absenteeism, presenteeism and patient/caregiver time costs were included, the 10 and 20 year scenarios showed that treating patients with AAD reduced total costs by $18,921 and $54,261, respectively.
- Health sector outcomes were sensitive to drug costs and utility estimates for post sustained virological response (SVR) health states. Social outcomes were sensitive to estimates of presenteeism and drug costs.

CONCLUSIONS:

- The treatment was efficient from a health sector perspective and a dominant cost-saving strategy when non-health related costs such as patient/caregiver time and productivity were also considered.

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Return On Investment From Immunization Against 10 Pathogens In 94 Low- And Middle-Income Countries, 2011–30

Sim SY, Watts E, Constenla D, Brenzel L, et al.

Health Affairs (Millwood) (2020); 39(8): 1343-53

OBJECTIVE:

- To assess the relationship between treatment adherence, medical utilisation and healthcare costs in the United States for four high-prevalence diseases in which prescription drugs play an important rolee.

METHOD:

- **Countries:** 94 low- and middle-income countries
- **Period:** 2011-2030
- **Sample:** 10 pathogens (haemophilus influenzae type b, hepatitis B, human papillomavirus, Japanese encephalitis, measles, neisseria meningitidis serotype A, streptococcus pneumoniae, rotavirus, rubella and yellow fever).
- **Sources:** Gavi, UN, UNICEF, WHO, Pan-American Health Organization (PAHO), Vaccine Impact Modeling Consortium.
- **Variables:** Immunisation programme costs and economic benefit.
  - Immunisation programme costs: vaccines, freight transport and delivery of vaccines, and other capital and recurrent costs (such as administration).
  - Economic benefit: estimates of cases and deaths averted; treatment and transport costs averted, lost wages for carers and lost productivity due to disability and death averted.
- **Analysis:** Return on investment, using the cost-of-illness and statistical lifetime value approach, from a social perspective.

RESULTS:

- Total costs of immunisation programmes for ten pathogens increase from $25.2 billion in the first decade (2011-20) to $39.9 billion in the second decade (2021-30) for 94 low- and middle-income countries.
- Over the two decades, vaccine costs account for 53.6% of total immunisation programme costs in the 94 countries and 51.9% in Gavi countries.
- Using the cost-of-illness method, vaccines against 10 pathogens averted $681.9 billion of economic burden in the 94 countries and $639.1 billion in Gavi countries between 2011 and 2020. The return on investment per dollar invested in immunisation was $26.1 between 2011 and 2020 and is estimated at $19.8 between 2021 and 2030.
- Using the statistical lifetime value method, from 2011 to 2020, $1,311.6 billion of economic benefits accrued in the 94 countries and $1,204.0 billion in Gavi countries. The return on investment is estimated at $51.0 between 2011 and 2020 and $52.2 between 2021 and 2030.

CONCLUSIONS:

- The results demonstrate a continued high return on investment for immunisation programmes.

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Cost-benefit analysis of vaccination against four preventable diseases in older adults: Impact of an aging population

Carrico J, Talbird S, La E, Poston P, et al.

Vaccine (2021); 39(36): 5187-97

OBJECTIVE:

- To estimate the economic value of the current vaccination programme and increased coverage against four preventable diseases in older adults in the United States.

METHOD:

- **Country:** United States.
- **Period:** 30-year horizon.
- **Sample:** Vaccination against influenza, pertussis, herpes zoster and pneumococcal disease in adults over 50.
- **Sources:** Parameter values are from the literature.
- **Variables:** Vaccine coverage and costs, input parameters of disease incidence and vaccine efficacy and duration of protection.
- **Analysis:** Age- and population-adjusted economic model to perform a cost-benefit analysis (CBA) comparing current vaccination coverage versus no vaccination and comparing increased versus current coverage.

RESULTS:

- It is estimated that current adult vaccination coverage (versus non-vaccination) will result in almost 65 million cases of averted disease, $185 billion in averted case costs and $136 billion in incremental costs of vaccination over a 30-year period from a societal perspective (cost-benefit ratio of 1.4).
- Increased vaccination coverage (compared to current coverage) is associated with more than 33 million additional cases of averted disease, $96 billion in additional costs of averted cases and almost $83 billion in incremental costs of vaccination, resulting in a social CBR of 1.2 over 30 years.
- Deterministic sensitivity analyses showed that the results were more sensitive to disease incidence, vaccine efficacy and productivity costs in relation to the time required for vaccination.

CONCLUSIONS:

- The results highlight the economic value of vaccination programmes in older adults in the United States and indicate that efforts to further increase vaccination coverage may be economically justified.

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The economic impact of over-the-counter products in the UK

Frontier Economics

Report (2023)

OBJECTIVE:

- Assess the impacts of over-the-counter (OTC) products in the UK, focusing on current impacts and possible future impacts from their increased use.

METHOD:

- **Country:** United Kingdom.
- **Period:** Not defined, from 2021.
- **Sample:** UK purchasers of non-prescription medicines, devices and food supplements.
- **Sources:** Frontier Economics, Nielsen IQ and PAGB member data, Office National Statistics, Pureprofile survey data, National Healthcare Service (NHS).
- **Variables:** direct and indirect employment, exports, health outcomes, demand for NHS services, number of prescriptions
- **Analysis:** Literature review, descriptive analysis and economic impact.

RESULTS:

- 92% of people used medicines without a prescription and each user spent an average of £4.50 on 1.3 medicines each month.
- For every £1 consumers spend in the non-prescription market (a £3,300 billion market):
  - The sector contributes £1 to the economy in wages and exports;
  - The economy saves £5.40 in lost work days; and
  - The health department saves £1.90 on prescription and appointment costs..
- It is estimated that if people attending primary care and A&E used over-the-counter medicines for self-treatment, the NHS could save at least £1.7 billion a year in costs. Avoiding these medical visits could also save the economy an additional £350 million per year, as employees would not need to take time off work to do so.
- The use of these drugs saves the NHS £6.4 billion a year in prescription and appointment costs.

CONCLUSIONS:

- Non-prescription medicines are crucial to the UK economy, with significant contributions in wages, exports and reduced lost work days. An increase in their use would save the health department more than a billion.

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Transforming lives, raising productivity

Pricewaterhouse Coopers (PwC)

Report (2023)

OBJECTIVE:

- Understand the benefits of increased investment in clinically innovative and cost-effective medicines for patients, society and the UK economy.

METHOD:

- **Country:** United Kingdom.
- **Period:** 2015-2022.
- **Sources:** IQVIA, OECD, PwC, ABPI, IHE, NHS - National Healthcare Service, The King's Fund, Nuffield Trust, Cancer Research UK, PHE - Public Health England, EFPIA, Office of Health Economics.
- **Variables:** Productivity, taxation, patient health outcomes, pharmaceutical spending, innovation.
- **Analysis:** Literature review and the author conducts descriptive analysis, comparative analysis and interviews.

RESULTS:

- At net prices, for every £100 in GDP, the UK spends approximately 81 pence on pharmaceuticals. This compares with £2.35, £1.94 and £1.84 spent by the US, Germany and Japan, respectively.
- The adoption of four classes of innovative medicines (direct-acting oral anticoagulants, sodium-glucose cotransporter type 2 inhibitors, severe asthma biologics, and non-peptide vasopressin antagonists):
  - It would enable the adherence of 1.2 Million patients who are currently not receiving these treatments.
  - It would produce an estimated productivity gain of £17.9 Billion (wages, unpaid work productivity generated by the increase in patient qalys, including reduced absenteeism or presenteeism) in the following diseases: coagulation, type 2 diabetes, severe asthma and autosomal dominant polycystic dominant kidney disease.
  - Would generate 429,000 QALYs.
  - 5.5 Billion £ in taxes would flow back into the state coffers.

CONCLUSIONS:

- Pharmaceutical innovation has a positive impact on the economy, both directly and indirectly.

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Economic Evaluation of Use of Diphtheria, Tetanus, and Acellular Pertussis Vaccine or Diphtheria, Tetanus, and Whole-Cell Pertussis Vaccine in the United States, 1997

Ekwueme D, Strebel P, Hadler S, Meltzer M, et al.

Archives of Pediatrics and Adolescent Medicine (2000); 154(8): 797-803

OBJECTIVE:

- To compare the economic cost and benefits associated with the use of acellular diphtheria-tetanus-pertussis vaccine (DTaP) versus whole-cell diphtheria-tetanus-pertussis vaccine (DTwP).

METHOD:

- **Country:** United States.
- **Reference year:** 1997.
- **Data source:** Disease and adverse event data from the National Medical Expenditures Survey and Codman Research Group's 1990 hospital discharge database; vaccine prices and vaccination coverage rates from the Centers for Disease Control and Prevention.
- **Variables:** Costs of the vaccination programme; cost of cases of disease with and without vaccines, net savings generated by the programme, cost-benefit ratios. Discount rate of 3%.
- **Sample:** Dummy cohort of 4.1 million children from birth to 15 years.
- **Analysis:** Standard cost-benefit analysis from the perspective of the health funder and society as a whole.

RESULTS:

- Without the DTP vaccination programme, in the cohort analysed there would have been 2.87 million cases of pertussis (resulting in about 1,131 deaths), 277,000 cases of diphtheria (and 27,675 deaths) and 165 cases of tetanus (25 deaths).
- It is estimated that with DTP vaccines, cases of diphtheria, tetanus and pertussis would be reduced by 99 per cent, 93 per cent and 95 per cent, respectively.
- For the health system, the cost of DTPa vaccination would be $547m and DTPe $435m, respectively. These costs include the cost of the vaccine ($253m and $104m), the cost of administering the vaccine ($230.5m), the cost of transport to administer the vaccine ($54.7m) and the treatment of adverse effects ($9.7m and $45.5m). Socially, the cost of vaccination would be $866m for DTaP and $754m for DTwP, when including parental productivity losses. To these costs should be added the cost of treating the few cases of diphtheria/tetanus/pertussis that occurred: $100m for the health system and $187m for society.
- This results in total programme health costs of $647 million for DTaP vaccination and $535 million for DTwP, and total programme costs of $1,053 million for DTaP vaccination and $941 million for DTwP.
- For the health system, the total discounted net discounted savings generated by vaccines would be 4,108m under the DTPa programme and $4,221m under the DTPe programme. From a social perspective, the savings amount to $22,511m and $22,623m, respectively.
- From a health system perspective, the cost-benefit ratio of the vaccination programme is 9:1 for DTaP and 11:1 for DTwP. From a societal perspective, the cost-benefit ratio would be 27:1 for DTaP and 31:1 for DTwP.

CONCLUSIONS:

- The triple vaccine results in very significant discounted net savings, both from a health system and social perspective.

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Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study

Jit M, Brisson M, Portnoy A, Hutubessy R.

Lancet Global Health (2014); 2(7): 406-414

OBJECTIVE:

- Develop and validate a simple generic model to estimate the health and economic effects of human papillomavirus (HPV) vaccination in women in 179 countries.

METHOD:

- **Countries:** 179 countries, including Spain.
- **Reference period:** 2012-2013, with extrapolation of data to reflect lifetime effects.
- **Study population:** 12-year-old girls, cohort of 58 million people.
- **Data source:** Databases of WHO, World Bank, International Agency for Research on Cancer, United Nations, and scientific studies.
- **Variables:** Number of cases of cervical cancer, deaths and years lived with disability averted over a patient's lifetime, and cost-effectiveness of vaccination.
- **Analysis:** Development of a PRIME (Papillomavirus Rapid Interface for Modelling and Economics) model. Assumes no change in the method of diagnosis of cervical cancers, and that vaccines offer lifelong protection. Indirect effects (such as herd protection effect) are not considered. Validation through comparison of PRIME results with other cost-effectiveness models..

RESULTS:

- Vaccination of the tested sample would prevent 690,000 cases of cervical cancer and 420,000 deaths over time, at a net cost of $4 billion.
- Furthermore, it would be cost-effective in 87% of countries (156 out of 179), with a promised cost-effectiveness ratio of $13,563 per death averted (95% CI: $7,901 - $19,225), and $11,647 per disability life-year averted (95% CI: $7,393 - $15,901).
- Seventy per cent of cancers averted, and 75 per cent of deaths averted, would occur in low- and lower-middle-income countries.
- Introducing HPV vaccination in countries that do not currently have the vaccine would prevent 63% more cases of cervical cancer than in countries with such programmes (average 1,600 cases per 100,000 population, vs. 980).
- In Spain, universal coverage of the HPV vaccine (210,000 women under 12 years of age) would prevent 1,250 cases of cervical cancer and 426 deaths, at a cost of $86 million, cost-effective, with a cost-effectiveness ratio of $33,800 per death averted, and $31,800 per year of life lived with disability averted (threshold: $32,400 GDP per capita).

CONCLUSIONS:

- Universal HPV vaccination tends to be cost-effective in almost every country in the world, preventing a significant number of deaths, cervical cancer cases and years of life lived with disability. There are large disparities between countries, and the countries with the greatest potential to benefit are those that have not yet introduced the vaccination programme.

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From trivalent to quadrivalent influenza vaccines: Public health and economic burden for different immunization strategies in Spain

Crépey P, Redondo E, Díez-Domingo J, et al.

PLoS One. 2020 May 21;15(5):e0233526

OBJECTIVE:

- To analyse the health and economic impact of replacing the trivalent influenza vaccine (TIV) with the tetravalent influenza vaccine (QIV) in various scenarios in Spain.

METHOD:

- **Country:** Spain.
- **Period:** 8 influenza seasons (2011-2018).
- **Sample:** Scenario 1 compares the current vaccination strategy with TIV alone with an alternative strategy where the entire eligible population uses QIV. In scenario 2, QIV is considered for under-65s and TIV for over-65s. In scenario 3, TIV is used for under-65s and QIV for over-65s.
- **Sources:** Spanish National Health Survey, BotPlus 2.0 database, NHS hospital admissions register (ICD-9 487 and 488) and primary studies, among other sources.
- **Variables:** Health effects, vaccine efficacy and epidemiological model results (weekly incidence of symptomatic influenza, incidence by age group and season, number of influenza cases by subtype and lineage for all years of the study period).
- **Analysis:** A dynamic transmission model developed by Crépey et al. (2015), previously used in the United States, was adapted. Analyses were conducted from both the payer and societal perspectives.

RESULTS:

- Replacing TIV with QIV in Spain would have prevented 138,707 cases of influenza B per season, resulting in 10,748 fewer visits to outpatient centres, 3,179 fewer hospitalisations and 192 fewer deaths.
- 532,768 in outpatient visit costs, 13 million euros in hospitalisation costs and 3 million euros in costs for influenza-related deaths per year.
- From a societal perspective, a further 5 million euros per year could be saved in costs associated with avoided productivity losses.
- The budgetary impact of the change in vaccination would be 6.5 million euros from a societal perspective, with an incremental cost-effectiveness ratio (ICER) of 1,527 euros per quality-adjusted life year (QALY) gained.

CONCLUSIONS:

- Incorporating QIV would be an efficient intervention for the Spanish NHS, with important economic and public health benefits, especially in the population over 65 years of age.

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Economic and health impact of the use of MF59-adjuvanted influenza vaccine in the population over 65 years of age in Spain

Pérez-Rubio A & Eiros JM.

Revista Española de Quimioterapia (2018); 31(1): 43-52

OBJECTIVE:

- To assess the impact on both regional and national budgets of seasonal vaccination campaigns carried out in Spain using MF59 adjuvanted vaccine compared to a conventional vaccine in the population over 65 years of age.

METHOD:

- **Country:** Spain.
- **Reporting period:** 2016-2017.
- **Study population:** Total population over 65 years of age.
- **Data source:** National Institute of Statistics (population), Ministry of Health, Social Services and Equality (vaccination coverage, costs of complications by related diagnostic tender groups, vaccine prices), literature (influenza cases, medical consultations, associated complications, costs of medical consultations).
- **Variables:** Budgetary impact, influenza cases averted, complications and costs averted, economic performance of the vaccination programme.
- **Analysis:** Performance of two scenarios of a budget impact analysis, one with the supply of the vaccine without adjuvant and the other with the supply of the vaccine adjuvanted with MF59, both from the perspective of the health system. Univariate sensitivity analysis, varying vaccine coverage and costs considered.

RESULTS:

- The budgetary impact of using the influenza vaccine with MF59 in all those over 65 years of age amounts to 6,967,288 euros, avoiding a cost of more than 89 million euros for the country as a whole, which represents a potential saving of 82 million euros. In other words, almost 13 euros are saved for every euro invested.
- In addition, the use of MF59 adjuvanted vaccine would prevent 113,000 cases of influenza per year, of which 24,000 would require hospital admission and 1,384 would die.
- All sensitivity analyses result in net cost savings. Based on the simulation results of varying coverage rates (from 25% to 75%) compared to the base case (of 55.5%), there would be net savings of between 37 and 111 million euros, and a 25% reduction in healthcare costs, which would still generate savings, in this case of 60 million euros.

CONCLUSIONS:

- The use of the flu vaccine with the MF59 adjuvant in all those over 65 years of age would increase the efficiency of the vaccination programmes planned in all the autonomous communities and in Spain as a whole.

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Estimated economic impact of vaccinations in 73 low- and middle income countries, 2001–2020

Ozawa S, Clark S, Portnoy A, Grewal S, et al.

Bull World Health Organ (2017); 95: 629–638

OBJECTIVE:

- Estimate the economic impact of a vaccination on 10 vaccine-preventable diseases between 2001 and 2020.

METHOD:

- **Countries:** 73 low- and middle-income countries.
- **Period:** 2001-2020.
- **Sources:** WHO-CHOICE Project; United Nations.
- **Variables:** Compared to non-vaccination, costs of treatment avoided, transport costs, productivity losses due to disability and premature mortality were modelled.
- **Analysis:** Health impact modelling to estimate the economic impact of achieving expected vaccination coverage for Haemophilus influenzae type b, hepatitis B, human papillomavirus, Japanese encephalitis, measles, Neisseria meningitidis serogroup A, rotavirus, rubella, Streptococcus pneumoniae and yellow fever. Sensitivity analysis with Monte Carlo simulations.

RESULTS:

- Across all countries analysed, vaccination would prevent more than 20 million deaths, 500 million cases of illness, 9 million cases of long-term disability and 960 million disability-adjusted life years in the period 2001-2020.
- Vaccination in these 73 countries would save a total of $350 billion in disease costs (95%CI: $260-460 million).
- Over these two decades, the deaths and disability averted by the vaccines provided would translate into labour productivity gains estimated at $330 billion and $9 billion, respectively.
- Over the lifetime of the vaccinated cohorts, it is estimated that the same vaccinations would save $5 billion in treatment costs.
- The broader economic and social value of these vaccines is estimated at $820 billion (95% CI: $560-1,200 billion) in the period 2001-2020, and $600 billion (95% CI: $420-870 billion) in the period 2011-2020. About 97% of this value is determined by the value of averted mortality.

CONCLUSIONS:

- Immunisation through vaccines goes beyond health, preventing costs and potentially increasing economic productivity.

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The impact of access to prescription drugs on disability in eleven European countries

Lichtenberg FR.

Disability and Health Journal (2019); 12(3): 375-386

OBJECTIVE:

- To test the hypothesis that the greater the relative number of medicines launched for a disease during 1982-2015 in a country, the lower the relative disability in 2015 of patients with that disease in that country.

METHOD:

- **Countries:** 11 European countries (Germany, Italy, Austria, Spain, Denmark, Switzerland, Sweden, France, Belgium, Greece and Portugal).
- **Period:** 1982-2015.
- **Sample:** 31 pathologies.
- **Sources:** Disability data from Survey of Health, Ageing and Retirement in Europe (6th wave); drug marketing data from IMS Health New Product Focus; Thériaque base to obtain the indication for each drug.
- **Variables:** Number of medicines marketed, by country and pathology; disability measured in different alternative ways (number of limitations in daily activities, CASP index of quality of life and well-being, prevalence of people with any limitation).
- **Analysis:** Two-way fixed effects models (by country and pathology) for different measures of disability. We controlled for the average level of disability in each country analysed for each particular disease, as well as for the number of patients with the disease and their average age.

RESULTS:

- The larger the relative size of the market (number of diagnosed patients), the greater the relative number of medicines launched for a disease in a country.
- The marketing of drugs in the period 1982-2015 reduced by 27% the probability of having any limitation in 2015 and by 4.9 percentage points (from 21.8% to 16.9%) the probability of having a severe limitation in 2015.
- This implies that the drugs launched in the period reduced the average number of limitations in performing activities of daily living by 29% in 2015 for people with at least one medical condition.
- There was also a small increase in the quality of life and well-being index.

CONCLUSIONS:

- In general, the greater the number of medicines launched in a country for a disease during the period 1982-2015, the lower the average disability of patients with that disease in that country in 2015.

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The impact of pharmaceutical innovation on the burden of disease in Ireland, 2000–2015

Lichtenberg FR.

Journal of Public Health (2020); 42(4): 816–827

OBJECTIVE:

- To analyse the impact that pharmaceutical innovation has had on the burden of disease in Ireland.

METHOD:

- **Country:** Ireland.
- **Period:** 1983-2015.
- **Sources:** IQVIA MIDAS, OECD Health Statistics, Theriaque.
- **Variables:** Burden of disease, measured as the number of years of potential life lost before the age of 70, 75 and 80 years and as the number of disability-adjusted life years lost; pharmaceutical innovation measured as the number of new chemical entities marketed; incremental cost-effectiveness ratio.
- **Analysis:** Fixed effects regression models by pathology and year, controlling for economic and social factors (income, educational level, risk factors, etc.).

RESULTS:

- Medicines marketed between 1983 and 1997 are associated with a 7.6% reduction in the number of disability-adjusted life years lost among the Irish population aged 30-49 years, and a 30.7% reduction in the population aged 69 years and over.
- New molecular entities marketed between 1983 and 1997 in the country reduced the number of disability-adjusted life years by 235,000 in 2015.
- Investment in medicines launched in the period under review was USD 396 million.
- In 2015, the cost-effectiveness ratio associated with pharmaceutical expenditure for the period 1983-1997 is 1,137 euros per disability-adjusted life year gained.

CONCLUSIONS:

- Investment in pharmaceutical innovation in Ireland can be considered a cost-effective strategy in terms of disability-adjusted life years averted.

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Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies

Trickey A, May M, Vehreschild J, Obel N, et al.

Lancet HIV (2017); 4(8): 349-56

OBJECTIVE:

- To analyse changes in 1, 2, and 3 year survival and life expectancy of HIV patients who started combination antiretroviral therapy between 1996 and 2013.

METHOD:

- **Country:** United Kingdom.
- **Period:** 1996-2013.
- **Data source:** 18 databases, 12 European, 4 from the USA and 2 from Canada, which collect information on 88,504 HIV patients.
- **Variables:** Life expectancy, all-cause mortality, HIV-related mortality, viral load, CD4 cell count in the first, second and third year after initiation of combination therapy.
- **Analysis:** Cox modelling of 18 patient cohorts for risks affecting survival of antiretroviral-treated patients over 4 time periods: 1996-99, 2000-2003, 2004-2007, 2008-2010.

RESULTS:

- In 1996-99, most patients were started on a pro-ketoinositide inhibitor regimen, while after 2000, non-nucleoside reverse transcriptase inhibitor-based regimens were the most common.
- Patients who started treatment in 2008-2010 had lower all-cause mortality already in the first year of treatment than patients who started in 2000-2003 (HR 0.71, 95% CI 0.61-0.83). All-cause mortality was also lower in the second and third year of treatment (HR 0.57; 95% CI 0.49-0.67).
- Non-AIDS mortality rates were also lower in the most recent stage than in 2000-2003, both in the first year of treatment (HR 0.48; 95% CI 0.34-0.67) and in the second and third years (HR 0.29; 95% CI 0.21-0-40).
- Based on mortality rates in the first three years of antiretroviral treatment, the life expectancy of patients increased in both sexes during the period analysed. For an average 20-year-old patient starting antiretroviral treatment, the expected age of death increased from 54.4 years in 1996-1999 to 64.0 years in 2008-2010 in men and from 58 to 66.6 years in women, with an average increase per period of 3.3 and 2.8 years for men and women, respectively.
- Based on mortality rates in the second and third year of treatment, life expectancy increased further for this average patient type: it increased by 3.7 years in men and 2.9 years in women in each period, from 62.5 years in 1996-1999 to 73.1 years in 2008-10 in men and from 67.1 to 76.0 years in women.

CONCLUSIONS:

- Even in the latest antiretroviral era, survival during the first three years of treatment may continue to improve, probably due to the development of less toxic drugs, better adherence and prevention, and better management of co-morbidity.

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Clinical and economic benefit of 32 years of antiretroviral treatment for people living with HIV in Spain: Has it been an efficient intervention?

Perez-Elías MJ, Podzamczer D, Ventayol P, Jarrín I, et al.

Infectious Diseases and Clinical Microbiology (2022); 40: 550–556

OBJECTIVE:

- To estimate the clinical and economic benefit of antiretroviral treatment (ART) in Spain in the period between 1987 and 2018.

METHOD:

- **Country:** Spain.
- **Period:** 1987-2018.
- **Sources:** SINIVIH and UNAIDS registry. HIV and Risk Behaviour Surveillance Unit of the National Epidemiology Centre. National AIDS Plan.
- **Variables:** Clinical outcomes were derived based on the following assumptions: (i) viral suppression by ART eliminates HIV transmissibility and thus the occurrence of new HIV cases; (ii) preventing progression of HIV patients to AIDS would reduce new AIDS cases; and (iii) reducing new AIDS cases would reduce AIDS-associated deaths.
- **Analysis:** cost-benefit analysis using second-order Monte Carlo simulation (1,000 simulations), from the perspectives of society and the NHS.

RESULTS:

- In the 32-year period analysed, antiretroviral treatment averted an estimated 323,651 AIDS deaths, 500,129 AIDS cases and 161,417 HIV cases.
- The NHS invested 6,185 million euros in the period analysed, with an estimated benefit of 1,032 million euros for the NHS and 35,812 million euros for society.
- For every euro invested in ART, there was a return on investment of €1.16 for the NHS and €6.79 for society, implying that it is considered an efficient intervention.

CONCLUSIONS:

- ART has prevented a large number of deaths and AIDS cases, generating significant savings for the health system and society.

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Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

Bardia A, Hurvitz SA, Tolaney SM, Loirat D, et al.

The New England Journal of Medicine (2021); 384(16): 1529-41

OBJECTIVE:

- To evaluate the efficacy and safety of sacituzumab govitecan compared to chemotherapy in metastatic triple negative breast cancer.

METHOD:

- **Countries:** 7 countries in America and Europe, including Spain.
- **Period:** November 2017 to September 2019.
- **Type of study:** Phase 3, multicentre, randomised, blinded, multicentre trial (ASCENT study).
- **Sample:** 468 patients aged 27 years and older with metastatic triple-negative breast cancer who relapsed or were refractory to two or more prior standard chemotherapy regimens for unresectable, locally advanced or metastatic disease. Prior therapy had to include a taxane.
- **Variables:** progression-free survival (PFS) (primary endpoint), overall survival (OS), duration of response, objective response rate and safety.
- **Analysis:** PFS, OS and duration of response were analysed using the Kaplan-Meier method. Hazard ratios were estimated using a stratified Cox proportional hazards model.

RESULTS:

- Median PFS was 5.6 months (95% CI 4.3-6.3) with sacituzumab govitecan compared with 1.7 months (95% CI 1.5-2.6) with chemotherapy (HR 0.41 [95% CI 0.32-0.52]; p<0.001). PFS was consistent across all pre-defined subgroups.
- Median overall survival was 12.1 months (95% CI 10.7-14.0) with sacituzumab govitecan compared to 6.7 months (95% CI 5.8-7.7) with chemotherapy (HR 0.48 [95% CI 0.38-0.59]; p<0.001).
- The objective response rate was 35% with sacituzumab govitecan and 5% with chemotherapy.
- Grade 3 adverse events occurred in 45% and 32% with sacituzumab govitecan and chemotherapy, respectively. The most frequent treatment-related grade 3 or higher adverse events were neutropenia (51% with sacituzumab govitecan and 33% with chemotherapy), leukopenia (10% and 5%), diarrhoea (10% and <1%), anaemia (8% and 5%) and febrile neutropenia (6% and 2%).

CONCLUSIONS:

- PFS and OS were significantly longer with sacituzumab govitecan than with single-agent chemotherapy among patients with metastatic triple-negative breast cancer.

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Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions

Zhou C, Tang K-J, Cho BC, Liu B, et al.

The New England Journal of Medicine (2023); 389(22): 2039-51

OBJECTIVE:

- To compare the efficacy and safety of amivantamab in combination with chemotherapy versus chemotherapy alone in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) characterised by EGFR exon 20 mutations.

METHOD:

- **Countries:** 26 countries in the Americas, Europe (including Spain), Asia and Oceania.
- **Period:** December 2020 to November 2022.
- **Type of study:** Phase 3, multicentre, randomised, controlled trial with standard chemotherapy (PAPILLON study).
- **Sample:** 308 adult patients with EGFR exon 20 mutation without previous treatment.
- **Variables:** Progression-free survival (primary endpoint), objective response rate, overall survival, duration of response, time to subsequent treatment, progression-free survival after first subsequent treatment, symptomatic progression-free survival and safety.
- **Analysis:** Mantel-Cox survival test stratified by ECOG performance status and history of brain metastases.

RESULTS:

- Progression-free survival for amivantamab-chemotherapy was 11.4 months (95%CI: 9.8 months-13.7 months) vs. 6.7 months with the comparator (95%CI: 5.6 months-7.3 months). HR of 0.40 (95%CI 0.30-0.53, p<0.001).
- Objective response was recorded in 73% of amivantamab-chemotherapy patients versus 47% of chemotherapy patients (rate ratio 1.50, 95%CI 1.32-1.68, P<0.001).
- The median duration of response for amivantamab-chemotherapy was 9.7 months (95% CI: 8.2- 13.45) versus 4.4 months (95% CI: 4.1-5.6) for chemotherapy.
- At 18 months, progression-free survival was recorded in 31% of patients in the amivantamab-chemotherapy group and in 3% of those in the chemotherapy group.
- Grade 3 or higher adverse events were more frequent in the amivantamab-chemotherapy group than in the chemotherapy group (75% vs. 54%). In the amivantamab-chemotherapy group, the most frequent grade 3 or higher events were neutropenia (33%), leukopenia (11%) and rash (11%) while in the chemotherapy group they were neutropenia (23%), anaemia (12%) and thrombocytopenia (10%).

CONCLUSIONS:

- The amivantamab-chemotherapy combination showed superior efficacy to chemotherapy in the first-line treatment of advanced EGFR exon 20-mutated NSCLC.

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Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma

Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, et al.

The New England Journal of Medicine (2022); 386(1): 24-34

OBJECTIVE:

- To evaluate the efficacy and safety of relatlimab and nivolumab versus nivolumab in previously untreated advanced melanoma.

METHOD:

- **Countries:** 25 countries in the Americas, Europe (including Spain) and Oceania.
- **Period:** May 2018 to December 2020.
- **Type of study:** Phase 2-3, multicentre, randomised, double-blind, multicentre trial (RELATIVITY-047 study).
- **Sample:** 714 patients over 12 years of age with histologically confirmed, unresectable stage III or IV melanoma without prior treatment.
- **Variables:** Progression-free survival (PFS) according to RECIST as primary variable. PFS in pre-specified subgroups and health-related quality of life as secondary variables.
- **Analysis:** Cox stratified proportional hazards model. Comparison of PFS between treatment groups was performed with bilateral logit analysis. Quality of life analysis: analysis of covariance model and quality of life questionnaires EQ-5D-3L and functional assessment of cancer therapy-melanoma questionnaire (FACT-M).

RESULTS:

- Median PFS was 10.1 months (95% CI 6.4-15.7) with relatlimab-nivolumab compared to 4.6 months (95% CI 3.4-5.6) with nivolumab (HR 0.75 [95% CI 0.62-0.92], p=0.006).
- In both treatment groups, PFS was longer for patients with LAG-3 expression ≥1%. However, a benefit was observed with relatlimab-nivolumab over nivolumab regardless of LAG-3 expression.
- Treatment-related adverse events of grade 3 or 4 occurred in 18.9 versus 9.7%, respectively.
- With respect to quality of life, changes from baseline in the FACT-M and EQ-5D-3L total score were stable and did not exceed the minimum clinically significant differences.

CONCLUSIONS:

- The relatlimab-nivolumab combination improved progression-free survival in both the genomic and subgroup analyses. Inhibition of two immune checkpoints, LAG-3 and PD-1, provided greater benefit than PD-1 inhibition alone in patients with previously untreated metastatic or unresectable melanoma, while maintaining an acceptable level of safety compared to nivolumab monotherapy.

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Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors

Strosberg J, El-Haddad G, Wolin E, Hendifar A, et al.

The New England Journal of Medicine (2017); 376(2): 125-35

OBJECTIVE:

- To evaluate the efficacy and safety of lutetium 177 (177Lu-Dotatate) compared to octreotide in patients with advanced, progressive, soma-tostatin receptor-positive midgut neuroendocrine tumours.

METHOD:

- **Countries:** 8 countries in the Americas and Europe, including Spain.
- **Period:** September 2012 to January 2016.
- **Type of study:** Phase 3, multicentre, randomised, blinded, multicentre trial (NETTER-1 study).
- **Sample:** 229 patients aged 18 years and older with midgut neuroendocrine tumours that had metastasised or were locally advanced, inoperable and showed disease progression.
- **Variables:** Progression-free survival (PFS) (primary variable), overall survival (OS), objective response rate (ORR) and safety (secondary variables).
- **Analysis:** PFS and OS were analysed using the Kaplan-Meier method. ORR and corresponding 95% confidence intervals were calculated for each treatment group and compared using Fisher's exact test. Hazard ratios were estimated using a non-stratified Cox proportional hazards model.

RESULTS:

- PFS at month 20 was 65.2% (95% CI 50.0 to 76.8) in the 177Lu-Dotatate group and 10.8% (95% CI 3.5 to 23.0) in the control group. Median PFS was not achieved for the treatment group and was 8.4 months (95% CI 5.8 to 9.1) in the control group (HR 0.21 [95% CI 0.13 to 0.33]; p<0.001).
- A total of 14 deaths were observed in the treatment group versus 26 deaths in the control group (HR: 0.40 p= 0.004). The data were not mature enough to provide an estimate of median OS in either group.
- ORR was 18% with 177Lu-Dotatate and 3% in the control group (P<0.001).
- Ninety-five percent of patients in the treatment group and 86% in the control group reported at least one adverse event. The percentages of patients with grade 3 or higher adverse events were similar between the two study populations.

CONCLUSIONS:

- 177Lu-Dotatate treatment had a longer PFS and higher ORR than octreotide treatment in patients with advanced midgut neuroendocrine tumours.

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Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

Armitage J, Baigent C, Barnes E, Betteridge DJ, et al.

Lancet (2019); 393(10170): 407–415

OBJECTIVE:

- Develop a meta-analysis to compare the efficacy and safety of statin therapy in people of different age groups.

METHOD:

- **Country:** Global.
- **Reference period:** Studies published between 1996 and 2017.
- **Study population:** 186,854 persons, of whom 39,242 (21%) were aged 55 years or younger, and 14,483 (8%) over 75 years.
- **Data source:** Individual patient data from 28 clinical trials.
- **Variables:** Major vascular events (e.g. major coronary events, stroke, coronary revascularisations), cause-specific mortality, changes in LDL-cholesterol levels.
- **Analysis:** Meta-analysis of the 28 randomised, controlled clinical trials (23 versus placebo and 5 comparing different statin treatment intensities) with at least 1,000 participants and a 2-year follow-up period. Analysis of 6 age subgroups.

RESULTS:

- Overall, for every 1.0 mmol/L reduction in LDL cholesterol levels achieved by statin therapy, there are reductions in the risk of major vascular events (21%), major coronary events (24%), coronary revascularisations (25%) and stroke (16%).
- With advancing age, these effects are maintained, except for the reduction in risk of major coronary events, which is significantly lower in older people (18%-19% >70 years, compared to 23%-331% for those <70 years).
- Deaths from vascular causes are reduced by 12% for every 1.0 mmol/L reduction in LDL cholesterol in all age groups. Excluding patients on dialysis or who have had a myocardial infarction (for whom statins are only recommended in combination with other treatments), these effects are only maintained in the elderly.

CONCLUSIONS:

- Statin use reduces the risk of major vascular events, regardless of patient age. The evidence regarding the benefit of statin use in primary care for people over 75 years of age is less straightforward, especially in the absence of a high risk of occlusive vascular events.

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Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Chou R, Cantor A, Dana T, Wagner J, et al.

JAMA (2022); 328(8): 754–771

OBJECTIVE:

- Update the 2016 systematic review by the United States Preventive Services Task Force (USPSTF) on the use of statins for primary prevention of cardiovascular disease.

METHOD:

- **Country:** Results of studies conducted in any country, published in English.
- **Reference period:** Until May 2022.
- **Population:** Randomised clinical trials of statins versus placebo or no statin, and statin intentionality in adults aged 40 years or older, with no prior cardiovascular events; large cohort studies of adverse events.
- **Data source:** Ovid MEDLINE, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews; grey literature.
- **Variables:** All-cause and cardiovascular mortality, myocardial infarction, stroke, composite cardiovascular outcomes and adverse events.
- **Analysis:** One investigator extracted data; a second checked accuracy. Meta-analyses were performed comparing statins with placebo or no statin. Statistical heterogeneity was assessed with the I2 statistic. Funnel plots and Egger's test were used to detect small sample effects. Significance tests were two-way with P<0.05.

RESULTS:

- Twenty-six studies were included. Statins were significantly associated with a lower risk of: (i) all-cause mortality (risk ratio [RR]: 0.92 [95% CI, 0.87-0.98]; absolute risk difference [ARD]: -0.35% [95%CI, -0.57% to -0.14%]), (ii) stroke (RR: 0.78 [95%CI, 0.68-0.90]; ARD: -0.39% [95%CI, -0.54% to -0.25%]), (iii) myocardial infarction (RR: 0.67 [95%CI, 0.60-0.75]; ARD: -0.85% [95%CI, -1.22% to -0.47%]) and (iv) composite cardiovascular outcomes (RR, 0.72 [95%CI, 0.64- 0.81]; ARD: 1.28% [95% CI, -1.61% to -0.95%]);
- The association with cardiovascular mortality was not statistically significant (RR: 0.91 [95% CI, 0.81-1.02]; ARD: -0.13%).
- Statin therapy was not significantly associated with an increased risk of (i) serious adverse events (RR: 0.97 [95% CI, 0.93-1.01]), (ii) myalgias (RR: 0.98 [95% CI, 0.86-1.11]) or (iii) elevated alanine aminotransferase levels (RR: 0.94 [95% CI, 0.78-1.13]).
- Statin therapy was not significantly associated with an increased risk of diabetes overall (RR: 1.04 [95% CI, 0.92-1.19]), although one trial found that high-intensity statin therapy was significantly associated with an increased risk (RR: 1.25 [95% CI, 1.05-1.49]). In contrast, there were no clear differences in outcomes based on statin intensity.

CONCLUSIONS:

- In adults at increased risk of cardiovascular disease but without prior cardiovascular events, statin therapy for primary prevention of cardiovascular disease was associated with a reduced risk of all-cause mortality and cardiovascular events.

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Association Between Chlorthalidone Treatment of Systolic Hypertension and Long-term Survival

Kostis JB, Cabrera J, Cheng JQ, Cosgrove NM, et al.

JAMA (2011); 306(23): 2588–2593

OBJECTIVE:

- To study the increase in life expectancy of participants in the SHEP (Systolic Hypertension in the Elderly Programme) clinical trial 22 years later, distinguishing between the group that received chlorthalidone treatment and the group that received placebo.

METHOD:

- **Country:** United States.
- **Reference year:** 2006.
- **Background:** SHEP study, a randomised, placebo-controlled trial in patients aged 60 years and older with isolated systolic hypertension conducted over 4.5 years (1985-1990).
  - The period between the recruitment of participants for the SHEP study and the ascertainment of the deaths of its participants, according to the National Death Index, was on average 21 years and 10 months.
- **Variables:** Death due to cardiovascular event and death from any cause.
- **Analysis:** Comparison of Kaplan-Meier survival curves between treated group and placebo.

RESULTS:

- The increase in life expectancy was 105 days (95% CI, -39 to 242; p=0.07) for all causes of morbidity and 158 days (95% CI, 36-287; p=0.009) for death from cardiovascular events.
- Each month of active treatment was associated with an extension of approximately 1 day of life expectancy.
- The treated group had a longer survival free of death from cardiovascular events than the placebo group (HR: 0.89, 95% CI: 0.80-0.99, p=0.03), but survival was similar for all causes of death (HR: 0.97, 95% CI: 0.90-1.04, p=0.42).
- After 22 years, 59.9% of the treated group and 60.5% of the placebo group died (log-rank p=0.38, Wilcoxon p=0.24).
- Deaths from cardiovascular events were lower in the treated group than in the placebo group (28.3% vs. 31.0%; log-rank p=0.03, p=0.02 Wilcoxon).
- Survival time at the 70th percentile for cardiovascular event-free deaths was 1.41 years longer (95% CI 0.34 to 2.61; 17.81 vs. 16.39 years; p=0.01) in the treated group than in placebo and 0.56 years longer for all-cause mortality.

CONCLUSIONS:

- In the SHEP clinical trial, treatment of isolated systolic hypertension with chlorthalidone for 4.5 years was associated with increased life expectancy after 22 years of follow-up.

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Teplizumab: A Disease-Modifying Therapy for Type 1 Diabetes That Preserves β-Cell Function

Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, et al.

Diabetes Care (2023); 46(10): 1848–1856

OBJECTIVE:

- To investigate the consistency of the effect of teplizumab on beta-cell function as measured by C-peptide stimulated in stage 3 type 1 diabetes.

METHOD:

- **Countries:** More than 115 countries in Asia, Europe and North America.
- **Benchmark period:** The non-integrated results of the studies were published between 2005 and 2019.
- **Population:** Patients with stage 3 type 1 diabetes (n=Teplizumab: 375; control group: 234).
- **Data source:** Five clinical trials in total (two were randomised, open-label, versus usual care, conducted in patients aged 7.5-30 years; the remaining three trials were randomised, double-blind, placebo-controlled trials conducted in patients aged 8-35 years.
- **Variables:** The primary endpoint was the change from baseline in the area under the C-peptide curve (AUC). Secondary variables were daily exogenous insulin use and adverse events.
- **Analysis:** Integrated efficacy and safety analyses were performed, based on a single-stage integrated intention-to-treat (ITT) analysis using individual patient data. A second integrated analysis assessed daily exogenous insulin use (units/kg/day) in the same studies.

RESULTS:

- The primary outcome of the integrated analysis, the change from baseline in stimulated C-peptide, was significantly improved in years 1 (mean increase of 0.08 nmol/L; $P < 0.0001$) and 2 (mean increase of 0.12 nmol/L; $P < 0.0001$) after one or two cycles of teplizumab.
- Reductions of 0.08 ($P = 0.0001$) and 0.10 units/kg/day ($P < 0.0001$) in exogenous insulin use were observed in years 1 and 2, respectively.
- Almost all patients in either treatment group experienced an adverse event (te- plizumab: 99.5%; control group: 95.1%), most of which were Grade 1 or 2 in severity (Grade 1: 94.7% and 87.3%. Grade 2: 87.9% and 59.6%).
- Most adverse events resolved without intervention. Adverse events leading to permanent discontinuation of study drug were reported in 14.3% and 3.7% of patients in the teplizumab and control groups, respectively.

CONCLUSIONS:

- The consistency of teplizumab's effect in preserving beta-cell function, as measured by C-peptide, in stage 3 type 1 diabetes is confirmed in multiple clinical trials.

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The role of weight control in the management of type 2 diabetes mellitus: Perspectives on semaglutide

Kurtzhals P, Kreiner F, Bindra R.

Diabetes Research and Clinical Practice (2023); 203: 11088

OBJECTIVE:

- To provide a focused review of the effects of semaglutide in people with type 2 diabetes mellitus (T2DM), with emphasis on weight loss, cardiometabolic benefits, safety and tolerability.

METHOD:

- **Country:** United States.
- **Population:** A total of 388 adults with T2D (SUSTAIN 1), 1,201 adults with T2D (SUSTAIN 7), 961 adults with T2D on metformin (SUSTAIN FORTE), 703 adults with T2D (PIONEER 1), 1,606 adults with T2D (PIONEER PLUS), and 1,210 adults with overweight or obesity and T2D (STEP 2) were analysed.
- **Variables:** TD2 treatment-related variables, including changes in body weight, percentage of participants who experienced weight loss of at least 5% or 10%, changes in glycosylated haemoglobin (HbA1c) levels in percentage points and mmol/mol, and changes in systolic blood pressure from baseline in mmHg.
- **Analysis:** Summary of results from SUSTAIN-1 (monotherapy, 30 weeks, placebo comparator), SUSTAIN-7 (40 weeks, dulaglutide comparator), SUSTAIN FORTE (higher subcutaneous dose, 40 weeks, low dose comparator), PIONEER-1 (monotherapy, 26 weeks, placebo comparator), PIO- NEER PLUS (higher oral dose, 68 weeks, placebo comparator), and STEP 2 (obesity and DM2, 68 weeks, placebo comparator) studies.

RESULTS:

- Weight loss: In the SUSTAIN FORTE trial, a higher dose of 2.0 mg semaglutide subcutaneously once weekly resulted in a weight loss of 6.9 kg compared to 6.0 kg with 1.0 mg semaglutide subcutaneously once weekly. In the 68-week PIONEER PLUS trial with once-daily oral semaglutide, weight losses of up to 7.0 kg and 9.2 kg were observed with 25 mg and 50 mg doses, respectively, exceeding the weight loss observed with 14 mg oral semaglutide (4.5 kg).
- Glycaemic control: In the SUSTAIN trial, the 1.0 mg dose of semaglutide was shown to reduce HbA1c by up to 1.8%, with more than 80% of participants achieving the recommended target. In the 40-week SUSTAIN FORTE trial, the 2.0 mg dose showed a greater reduction in HbA1c than the 1.0 mg dose (-2.2% versus -1.9% [-23.7 mmol/mol versus 21.2 mmol/mol]), while maintaining a consistent effect across all participant characteristics.

CONCLUSIONS:

- GLP-1 receptor agonists in general and semaglutide in particular offer the opportunity to reduce body weight while correcting elevated blood glucose levels in people with T2D.

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Budesonide/Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Improves Exacerbation Outcomes in Patients with COPD without a Recent Exacerbation History: A Subgroup Analysis of KRONOS

Martinez FJ, Ferguson GT, Bourne E, Ballal S, et al.

International Journal of Chronic Obstructive Pulmonary Disease (2021); 16: 179–189

OBJECTIVE:

- To investigate whether the benefits observed in the KRONOS clinical trial were driven by patients with COPD and ≥1 exacerbation in the 12 months prior to the study.

METHOD:

- **Countries:** United States, Canada, China and Japan.
- **Reference period:** 2015 to 2018.
- **Population:** Patients aged 40-80 years with a smoking history of ≥10 pack-years (current or former smokers) and a confirmed diagnosis of moderate to very severe COPD.
- **Data source:** 24-week, randomised, phase 3, double-blind, parallel-group, double-blind clinical trial.
- **Variables:** Rate of moderate/severe and severe COPD exacerbations; time to first moderate/severe COPD exacerbation.
- **Analysis:** Post hoc analyses of lung function and exacerbation rates were performed in the KRONOS study in two subgroups: patients with and without exacerbation in the previous 12 months. Analyses were performed in the modified intention-to-treat (mITT) population using a negative binomial regression model, with time-at-risk as an offset variable.

RESULTS:

- Overall, 74% (1,411/1,896) of the mITT analysis population did not experience moderate/severe exacerbations in the 12 months prior to the study.
- BGF MDI reduced exacerbation rates compared to glycopyrrolate/ formoterol fumarate metered-dose inhaler (GFF MDI) in the subgroups with previous exacerbations (58%; unadjusted p=0.0003) and without previous exacerbations (48%; unadjusted p=0.0001).
- The magnitude of reduction in exacerbation rates was generally similar between subgroups for BGF MDI versus BFF MDI.
- Among patients who had experienced COPD exacerbations in the 12 months prior to the study, the risk of experiencing another exacerbation during treatment was 49% lower when using the BGF MDI compared to the GFF MDI (HR 0.51 (0.33, 0.79), p = 0.0022).

CONCLUSIONS:

- In patients with or without a history of exacerbations in the 12 months prior to the study, the BGF MDI reduced exacerbation rates compared to the GFF MDI, suggesting that the results observed in the general population were not driven by the small subgroup with a prior history of exacerbations.

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The association between asthma control, health care costs and quality of life in France and Spain

Doz M, Chouaid C, Com-Ruelle L, Calvo E, et al.

BMC Pulmonary Medicine (2013); 13: 15

OBJECTIVE:

- To describe the costs and quality of life of adult asthma patients according to their degree of asthma control (EUCOAST study).

METHOD:

- **Countries:** France and Spain.
- **Reference year:** 2010.
- **Data source:** Medical history, test and questionnaire. In Spain, recruitment was carried out at the Hospi- tal Clínico y Provincial de Barcelona.
- **Variables:** Resource consumption in the 3 months prior to the study visit, including loss of work productivity due to temporary disability; peak expiratory volume (FEV1), EuroQol-5D-3L quality of life questionnaire containing 5 questions and the Visual Analogue Scale (VAS).
- **Sample:** Adult patients with asthma diagnosed less than 1 year ago who have received treatment. Patients over 45 with a smoking history of more than 20 years or COPD were excluded. Sample of 1,517 patients in Spain and 1,154 in France.
- **Analysis:** Statistical tests (Pearson Chi2 and Fisher) to compare between the 3 subgroups of patients (controlled, partially controlled and uncontrolled). Societal perspective. Multivariate analysis to analyse the relationship between asthma control and cost and quality of life outcomes.

RESULTS:

- In Spain, the sample is divided into 29.9% controlled, 34.1% partially controlled and 34.1% uncontrolled. In France, the proportion of patients with well-controlled asthma is 40.6%.
- 74.4% of those not controlled had an exacerbation in the 3 months prior to the visit, compared to 41.3% of those partially controlled and 9.2% of those controlled.
- In Spain, the average cost of a poorly controlled patient is €556.8, compared to €241 for a partially controlled patient and €152.6 for a controlled patient. Poor control increases the average cost of medication from €88 to €158, hospitalisation from €0 to €55, and visits to the general practitioner from €35 to €143. Productivity losses increase from €4 in 3 months to €122, from 2.6% of the total cost to 22% of the total.
- In France, the average cost rises from €85 if there is good control to €314 if there is partial control and to €540 if asthma is not controlled. In other words, poor control generates higher additional costs in France than in Spain.
- Quality of life improves with disease control. In Spain, the average score on the EQ- 5D-3L is 0.89 if asthma is well controlled, 0.82 if there is partial control and 0.69 if there is no control (in France, 0.88, 0.78 and 0.63, respectively). In VAS, the average score reported by patients is reduced from 80 to 75.1 and 62.8 in Spain and from 77.3 to 70.3 and 57.4 in France.

CONCLUSIONS:

- Better asthma control is associated with improved patient quality of life and lower direct and indirect costs.

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Effect of asthma control on general health-related quality of life in patients diagnosed with adult-onset asthma

Ilmarinen P, Juboori H, Tuomisto LE, Niemelä O, et al.

Scientific Reports (2019); 9(1): 16107

OBJECTIVE:

- To assess the effect of different levels of asthma control on health-related quality of life (HRQoL) in patients with asthma diagnosed in adulthood.

METHOD:

- **Country:** Finland.
- **Reference period:** The original cohort (phase I) was collected between October 1999 and April 2002, while the follow-up visit (phase II) took place between December 2012 and October 2013.
- **Population:** A total of 203 patients (79% of the total Seinäjoki adult asthma study [SAAS] cohort), with a diagnosis of new-onset asthma in adulthood (≥15 years), who participated in the follow-up visit 12 years after diagnosis.
- **Data source:** The SAAS study.
- **Variables:** The 15 dimensions of the 15D questionnaire to assess HRQoL in asthma.
- **Analysis:** HRQoL (scale between 0 - being dead - and 1 - perfect health) is calculated from the health status description system, using a set of preference or utility weights based on population-based studies.

RESULTS:

- HRQoL was lower in patients with uncontrolled or partially controlled asthma than among patients with controlled asthma (mean score difference of -0.091 and -0.034, respectively).
- Uncontrolled patients showed a lower level of HRQoL compared to partially controlled patients, with the average difference in scores being 0.057.
- A lower 15D score at the follow-up visit correlated with the following factors: uncontrolled asthma (Tobi regression estimate: -0.0534; p<0.001), lower forced vital capacity in the first second post bronchodilator use (0.0007; p=0.028), female sex (-0.0353; p= 0.001), presence of depression (-0.0402; p=0.042), treatment for dyspepsia (-0.0566; p=0.009) and lower baseline 15D score (0.3260; p<0.001).
- There was a statistically significant difference between the controlled and uncontrolled groups in 10 of the 15 dimensions of the 15D, with mobility, breathing, sleep, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity being affected.

CONCLUSIONS:

- Uncontrolled asthma affects daily life in several ways, including previously unknown components such as sexual activity and vitality.

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Clinical and economic value of sofosbuvir-based regimens in the treatment of chronic hepatitis Cin Spain

Esteban R, Domínguez-Hernández R, Martín-Escudero V, Casado MA.

Plos ONE (2022); 17(12): e0278544

OBJECTIVE:

- To assess the efficacy and value of sofosbuvir (SOF)-based regimens compared to previous therapeutic strategies (peginterferon/ and ribavirin in double/triple therapy with telaprevir or boceprevir).

METHOD:

- **Country:** Spain.
- **Period:** 2015-2019.
- **Sample:** 85,959 patients with chronic hepatitis treated with sofosbuvir-based regimens (SOF regimens such as Harvoni, Epclusa, Vosevi and Sovaldi in combination with daclatasvir or simeprevir) in combination with previous therapeutic strategies (PEG-IFN and ribavirin in double or triple therapy with telaprevir or boceprevir).
- **Sources:** Ministry of Health and Gilead Sciences.
- **Variables:** Avoided hepatitis C virus (HCV)-related mortality and liver complications; total costs; quality-adjusted life years (QALYs).
- **Analysis:** A previously developed Markov model was adapted to simulate HCV progression. In SOF-based regimens, all patients were treated independently with a sustained virological response (SVR) of 93-98%, obtained from real-world data. In prior therapy, only patients ≥F2 were treated according to clinical practice (38%) with a median SVR of 61% obtained from published literature. An annual discount rate of 3% was applied.

RESULTS:

- Compared to previous therapy, SOF-based regimens reduced lifetime decompensated cirrhosis by 89%, hepatocellular carcinoma by 77% and liver transplantation by 84%. They also reduced liver-related mortality by 82%.
- The clinical improvement was associated with a decrease in the cost associated with the management of liver complications of 770 million euros.
- In addition, SOF-based regimens gained 310,765 QALYs, saving 274 million euros (taking into account drugs, monitoring and HCV management).

CONCLUSIONS:

- In Spain, SOF-based regimens are beneficial for HCV patients, reducing the burden of liver disease and generating significant cost savings for the healthcare system.

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Impact of direct-acting antivirals for HCV on mortality in a large population-based cohort study

Janjua N, Wong S, Abdia Y, Jeong D, et al.

Journal of Hepatology (2021); 75(5): 1049-1057

OBJECTIVE:

- To assess the effect of sustained viral response (SVR) induced by direct-acting antivirals (DAAs) on mortality in a Canadian population-based cohort.

METHOD:

- **Country:** Canada (British Columbia).
- **Period:** 1990-2019.
- **Sample:** 10,851 chronic hepatitis C patients
- **Sources:** British Columbia Hepatitis Tester Cohort (which includes 1.7 million people); British Columbia Vital Statistics Registry.
- **Variables:** SVR defined as undetectable serum hepatitis C virus (HCV) RNA after 10 weeks of treatment; all-cause mortality, liver-related deaths and drug-related deaths; comorbidities.
- **Analysis:** Propensity Score Matching, comparing treated individuals with similar individuals not treated with DAAs. Multivariate proportional hazards modelling to assess the effect of DAAs on morbidity.

RESULTS:

- During the reporting period, 74,095 people were diagnosed with HCV, of whom 40,419 were RNA-positive. In total, 20,712 received treatment and 12,311 were treated with DAAs, of whom 10,851 were eligible for this analysis.
- Of the cohort of people treated with DAAs, 95% achieved an SVR.
- The median follow-up time was 2.2 years.
- The all-cause mortality rate was 19.5/1,000 person-years (PY) in the SVR group (552 deaths), 86.5/1,000 PY in the no SVR group (96 deaths) and 99.2/1,000 PY in the no treatment group (2,133 deaths).
- In the multivariable model, SVR was associated with a significant reduction in all-cause mortality (HR of 0.19, 95%CI 0.17-0.21), liver mortality (HR of 0.22, 95%CI 0.18-0.27) and drug-related mortality (HR of 0.26, 95%CI 0.21-0.32) compared to no treatment.
- Older age and cirrhosis were associated with an increased risk of liver-related mortality, while younger age, injecting drug use, heavy alcohol use and HIV/HBV co-infection were associated with an increased risk of drug-related mortality.

CONCLUSIONS:

- AAD treatment is associated with a substantial reduction in mortality in the Canadian population with chronic hepatitis C.

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Agomelatine in Standard Medical Practice in Depressed Patients: Results of a 1-Year Multicentre Observational Study In France

Gorwood P, Benichou J, Moore N, Wattez M, et al.

Clinical Drug Investigation (2020); 40(11): 1009-20

OBJECTIVE:

- To assess the efficacy, safety and quality of life of patients with depression treated with agomelatine in routine medical practice.

METHOD:

- **Country:** France.
- **Period:** March 2012 to September 2015.
- **Type of study:** Prospective, observational, multicentre cohort.
- **Sample:** 1,517 patients over 18 years of age whose doctor decided to start antidepressant treatment with agomelatine.
- **Variables:** Hamilton Depression Rating Scale (HAM-D17), Clinical Global Impression of Severity of Illness Scale (CGI-S), Quality of Life in Depression Scale (QLDS) and Sheehan Disability Scale (SDS).
- **Analysis:** Descriptive non-inferential statistics.

RESULTS:

- Most patients (62.3%) were treated with agomelatine for at least 6 months and 28.8% were treated for at least 1 year.
- The mean total score on the HAM-D17 scale decreased by 13.6 points (± 8.1) from baseline to the last visit under agomelatine treatment. Mean scores on the CGI-S decreased by 2.1 points (± 1.5).
- 90.7% of patients responded to treatment, (i.e. had a decrease in HAM-D17 total score of at least 50%) and 56.0% remitted (HAM-D17 total score<7).
- After treatment withdrawal, the mean HAM-D17 total score decreased by 4.1 points (± 6.7), as did the mean CGI-S score (-1.0 ± 1.5) and the mean SDS total score (-3.3 ± 6.3).
- The mean total score on the QLDS decreased by 12.7 points (±10.7) from baseline to the last visit with agomelatine. At the end of the period, the mean score was 9.8 points (±9.5), indicating an improvement in patients' quality of life.
- The total score and sub-scores of the SDS decreased from the start of treatment until the last visit, showing an improvement in the functional status of patients in terms of work/daily activities, social life and family life.
- The percentage of patients reporting at least one adverse event during treatment was 30.7%. Adverse events were treatment-related in 6.3% of patients and led to treatment discontinuation in 8.7% of patients.

CONCLUSIONS:

- This study confirms the long-term efficacy, good tolerability and improved quality of life of patients with depression treated with agomelatine under real clinical practice conditions.

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Efficacy and Safety of a Combination of Olanzapine and Samidorphan in Adult Patients With an Acute Exacerbation of Schizophrenia: Outcomes From the Randomized, Phase 3 ENLIGHTEN-1 Study

Potkin SG, Kunovac J, Silverman BL, Simmons A, et al.

Journal Clinical Psychiatry (2020); 81(2): 19m12769

OBJECTIVE:

- To evaluate the antipsychotic efficacy and safety of a combination of olanzapine and samidorphan (OLZ/SAM) versus olanzapine alone and placebo treatment in patients with acute bouts of schizophrenia.

METHOD:

- **Countries:** Bulgaria, United States, Serbia and Ukraine.
- **Period:** December 2015 to June 2017.
- **Type of study:** Phase 3, randomised, double-blind, placebo- and olanzapine-controlled study (ENLIGHTEN-1 study over a 4-week follow-up period).
- **Sample:** 403 patients aged 18-70 years with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
- **Variables:** Changes in the Positive and Negative Schizophrenia Syndrome Scale (PANSS) as primary variable. Clinical Global Impression of Severity of Illness Scale (CGI-S), changes in PANSS subscales and proportion of responders as secondary variables.
- **Analysis:** Repeated measures mixed effect model (MMRM). The mean±SD least squares (OLS) change from baseline for each treatment group was used, as well as the mean ± SE difference of the OLS and 95% CI for the treatment groups versus placebo. Binary efficacy endpoints were analysed using a logistic regression model.

RESULTS:

- The mean difference versus placebo from baseline to week 4 in PANSS total score was -6.4 (±1.8, p<0.001) for the OLZ/SAM group and -5.3 (±1.8, p=0.004) for the olanzapine group.
- The mean difference versus placebo in the CGI-S score was -0.38 (±0.12, p=0.002) for the OLZ/SAM group and -0.44 (±0.12, p<0.001) for the olanzapine group.
- The proportion of patients responding to PANSS at week 4 was significantly higher for OLZ/SAM (59.8%; p<0.001) and olanzapine (53.8%; p= 0.015) compared to placebo (38.3%). Compared to placebo, the proportion of patients responding to CGI-I at week 4 was significantly higher for OLZ/SAM (57.6%; p<0.001) and olanzapine (50.8%; p=0.004).
- 54.5% of the OLZ/SAM group, 54.9% of olanzapine and 44.8% of placebo reported at least one adverse event. The percentage of patients who discontinued treatment due to an adverse event was 1.5%, 2.3% and 5.2% in the OLZ/SAM, olanzapine and placebo groups, respectively.

CONCLUSIONS:

- Treatment with OLZ/SAM produced statistically and clinically significant efficacy improvements over 4 weeks versus placebo in patients with acute schizophrenia.

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Long-term efficacy of opicapone in fluctuating Parkinson's disease patients: a pooled analysis of data from two phase 3 clinical trials and their open-label extensions

Ferreira J, Leesc A, Rochad J, Poewee W, et al.

European Journal of Neurology (2019); 26(7): 953-960

OBJECTIVE:

- To evaluate the efficacy of the catechol-O-methyltransferase inhibitor (opicapone) as adjunctive therapy to levodopa in a population of patients with Parkinson's disease who participated in two pivotal trials.

METHOD:

- **Country:** Portugal.
- **Reference period:** 2011-2013 (BIPARK-1) and 2011-2012 (BIPARK 2).
- **Study population:** 766 adult patients (30-83 years old) with Parkinson's disease for at least 3 years, with off periods of ≥ 1.5 hours per day, and levodopa treatment for at least 1 year.
- **Data source:** BIPARK-1 and BIPARK-2 clinical trials.
- **Variables:** Absolute reductions in off-period time, absolute increases in on-period time, and changes in parts II and III of the Unified Parkinson's Disease Rating Scale (UPDRS).
- **Analysis:** Pooled analysis of two randomised, double-blind, placebo-controlled, randomised, double-blind, phase 3 clinical trials, with extension of the follow-up period by an additional 1 year, using open-label methodology.

RESULTS:

- Treatment with opicapone combined with levodopa reduced the average off time by 35-58 minutes per day (for the 25mg and 50g doses, respectively), compared to placebo, from baseline off times of 6.1-6.6 hours per day (results 17% higher than placebo).
- In addition, the treatment increased average times in periods without episodes of pro- blematic dyskinesias by between 43 and 65 minutes per day, compared to placebo.
- The positive treatment effects were maintained in the protocol-initiated open-label phase after one year at the 25 mg dose. The group already treated in the double-blind phase with opicapone 25mg achieved further improvements in outcomes after one year of follow-up (-19 minutes off time). The group treated in the double-blind phase with placebo obtained 51 minutes of off-time reductions.

CONCLUSIONS:

- In this pooled analysis of two clinical studies, opicapone reduced the amount of time in off periods and increased the amount of time in on periods in patients with Parkinson's disease, without increasing the frequency of episodes of problematic dyskinesia.

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Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial

Soileau MJ, Aldred J, Budur K, Fissea N, et al.

Lancet Neurol. 2022;21(12):1099-109

OBJECTIVE:

- To assess the safety and efficacy of foslevodopa-foscarbidopa, a soluble levodopa-carbidopa prodrug formulation, in patients with advanced Parkinson's disease.

METHOD:

- **Countries:** United States and Australia (65 centres).
- **Period:** October 2020 - September 2021 (12 weeks).
- **Sample:** 270 participants were selected and 174 enrolled. 141 were randomised and received continuous subcutaneous infusion of foslevodopa-foscarbidopa plus oral placebo capsules (n=74) or immediate release oral encapsulated levodopa-carbidopa plus continuous subcutaneous infusion of placebo solution (n=67).
- **Variables:** The primary criterion for assessing efficacy was to measure the change in average daily hours without problematic dyskinesia ('on' period) from baseline to week 12 of treatment. As key secondary criteria, the change in average daily hours of downtime (off period) during the same period, as recorded in the Parkinson's disease diary, was also analysed.
- **Analysis:** Randomised, double-blind, double-dummy, active-controlled study.

RESULTS:

- Compared to levodopa-carbidopa, foslevodopa-foscarbidopa showed a significantly greater increase in time without problematic dyskinesia (mean [SD] based on the model 2.72 [0.52] vs. 0.97 [0.50] hours; difference 1.75 hours, 95%CI: 0.46 to 3.05; p=0.0083) and a significantly greater reduction in downtime (-2.75 [0.50] vs -0.96 [0.49] hours; difference -1.79 hours, -3.03 to -0.54; p=0.0054).
- Time without dyskinesia showed a 25% increase (3.96 [3.77] h) from baseline in the foslevodo-pa-phoscarbidopa group compared to a 7% increase (1.15 [3.63] h) in the oral levodopa-carbidopa group.

CONCLUSIONS:

- Foslevodopa-phoscarbidopa improved motor fluctuations, with benefits both in the "on" time without problematic dyskinesia and in the "off" time, and had a favourable benefit-risk profile.

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Real-world study of relapsing-remitting multiple sclerosis patients treated with Teriflunomide in Nordic countries: Quality-Of-Life, efficacy, safety and adherence outcomes

Hestvik ALK, Frederiksen JL, Nielsen HH, Torkildsen Ø, et al.

Mult Scler Relat Disord. 2022;63:103892

OBJECTIVE:

- To analyse the performance of teriflunomide on the quality of life (QoL) of people with multiple sclerosis in a real-world setting.

METHOD:

- **Countries:** Denmark, Norway and Sweden.
- **Period:** 2016-2019.
- **Sample:** 200 patients treated with oral teriflunomide.
- **Sources:** Own study.
- **Variables:** Quality of life as measured by the Short Form-36 (SF-36) questionnaire (primary variable), clinical efficacy (relapse activity and disease progression), fatigue, safety, treatment satisfaction (measured by the Treatment Satisfaction Questionnaire for Medication version 1.4 TSQM- 1.4), treatment adherence and health economic outcomes.
- **Analysis:** Prospective, open-label, non-interventional, observational, multicentre study, with follow-up at 24 months.

RESULTS:

- Changes in SF-36 scores from baseline to the last visit indicated stable quality of life during teriflunomide treatment up to 24 months.
- Relapse activity decreased during the study compared to the pre-initiation period ($p<0.001$), patient-reported disability increased marginally and no substantial changes in fatigue scores were observed.
- The mean TSQM domain scores increased nominally, but not significantly, from month 6 to month 24. The TSQM domains of convenience and side effects had the highest median scores, indicating the acceptability of teriflunomide in this cohort. This was reflected in generally high treatment adherence and lower health care utilisation during the study period.
- During the two-year study, a decrease in the percentage of patients who made medical visits in the last six months was observed, from 92.5% to 74.4%. In addition, the number of patients who were in a hospital setting was found to decrease from 24.5% at baseline to 1.7% at the end of the study, while the percentage of patients who visited the emergency department in the last six months decreased from 8.5% at baseline to 4.1% at the end of the study. In terms of employment, there was a slight decrease in the percentage of patients working full-time (from 45.1% to 41.8%) or not working (from 27.2% to 24.8%), and an increase in patients working part-time (from 27.7% to 33.3%).
- The results were consistent with previous clinical trials and real-world studies.

CONCLUSIONS:

- This study provides a timely overview of quality of life, efficacy, safety and health economic outcomes in people with relapsing MS treated with teriflunomide in routine clinical practice in the Nordic countries.

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Impact of natalizumab on quality of life in a real-world cohort of patients with multiple sclerosis: Results from MS PATHS

Hersh CM, Kieseier B, de Moor C, Miller DM, et al.

Multiple Sclerosis Journal – Experimental, Translational and Clinical (2021); 7(2): 20552173211004634

OBJECTIVE:

- To assess the impact of natalizumab on the quality of life of patients with multiple sclerosis.

METHOD:

- **Countries:** United States and Europe.
- **Period:** From the inception of MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions) until 2019.
- **Sample:** 164 patients treated with natalizumab. In a subgroup, 145 patients were compared with natalizumab and 520 with ocrelizumab.
- **Sources:** Database of routine patient visits in a large real-world MS cohort known as MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions).
- **Variables:** Quality of life measured by the Neuro-QoL questionnaire.
- **Analysis:** The annual change in T-scores and the probability of a 5-point improvement from baseline was calculated for each Neuro-QoL domain after initiation of natalizumab treatment.

RESULTS:

- Among the 164 natalizumab-treated patients, 8 out of 12 Neuro-QoL domains improved significantly, with the greatest improvement in patients with an abnormal baseline Neuro-QoL.
- In the subgroup of patients treated with natalizumab (n=145) and treated with ocrelizumab (n=520), there were significant improvements in 9 and 4 of the 12 domains, respectively.
- The between-group difference was statistically significant for positive and well-being affect ($p = 0.02$), sleep ($p = 0.003$) and satisfaction with social roles and activities (RAS) ($p = 0.03$) in the general population and for emotional and behavioral dyscontrol ($p = 0.01$), participation in RAS ($p = 0.0001$) and satisfaction with RAS ($p = 0.02$) in patients with an abnormal baseline Neuro-QoL.

CONCLUSIONS:

- Natalizumab can produce clinically significant improvements in the mental and social health of patients with multiple sclerosis.

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Siponimod vs placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study

Kappos L, Bar-Or A, Cree BAC, Fox RJ, et al.

The Lancet (2018); 391(10127): 1263-73

OBJECTIVE:

- To evaluate the effect of siponimod, a selective sphingosine 1-phosphate (S1P) 1,5 receptor modulator, on the progression of disability in patients with secondary progressive multiple sclerosis (SPMS).

METHOD:

- **Countries:** 31 countries (Argentina, Australia, Austria, Belgium, Bulgaria, Canada, China, Czech Republic, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States).
- **Period:** 2013-2015.
- **Sample:** 1,651 patients were randomly selected and, after applying inclusion criteria, 1,645 patients were studied (1,099 in the siponimod group and 546 in the placebo group).
- **Sources:** Phase 3, double-blind, event-driven, exposure-driven trial.
- **Variables:** Progression of confirmed disability (PCD), efficacy and safety.
- **Analysis:** With a 2:1 randomization of siponimod to placebo, observation of at least 374 PCD events over 3 months allowed detection of a 30% reduction in 3-month PCD risk, using a two-sided log-rank test at the 5% significance level.

RESULTS:

- 903 (82%) patients receiving siponimod and 424 (78%) patients receiving placebo completed the study.
- 288 (26%) of the 1,096 patients who received siponimod and 173 (32%) of the 545 patients who received placebo had a PCD at 3 months (hazard ratio 0.79, 95%CI 0.65-0.95; relative risk reduction 21%; p=0.013).
- Adverse events occurred in 975 (89%) of the 1,099 patients receiving siponimod vs 445 (82%) of the 546 patients receiving placebo. Serious adverse events were reported in 197 (18%) patients in the siponimod group vs. 83 (15%) in the placebo group.
- Lymphopenia, increased liver transaminase levels, bradycardia and bradyarrhythmia at baseline, macular oedema, hypertension, zoster reactivation and seizures occurred more frequently with siponimod than with placebo. Dose escalation mitigated the cardiac effects of the first dose.
- The frequencies of infections, malignancies and deaths did not differ between groups.

CONCLUSIONS:

- Siponimod reduced the risk of disability progression in patients with PMDS, with a similar follow-up profile to other S1P modulators.

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Effectiveness of Etanercept in Rheumatoid Arthritis: Real-World Data from the German Non-interventional Study ADEQUATE with Focus on Treat-to-Target and Patient-Reported Outcomes

Feist E, Baraliakos X, Behrens F, Diamant T, et al.

Rheumatology Therapy (2022); 9(2): 621–635

OBJECTIVE:

- To analyse in a real-world setting in Germany the proportion of patients with rheumatoid arthritis (RA) who benefit from treatment with etanercept, a tumour necrosis factor-alpha (TNF-α) inhibitor drug, beyond 12 weeks.

METHOD:

- **Country:** Germany.
- **Period:** 12 months.
- **Sample:** Prospective, multicentre, non-interventional study of 824 patients over 18 years of age with moderate to severe active RA who did not respond adequately to disease-modifying antirheumatic drugs (DMARDs), including methotrexate. Patients with severe, active, progressive RA who had not previously received methotrexate treatment were also included, although prior treatment with other biologics, excluding etanercept, was allowed.
- **Variables:** Treatment effectiveness defined as the proportions of patients who achieved remission or low disease activity targets, defined on the basis of the 28-joint disease activity score (DAS28). Patient-reported outcomes (PROs) included patient global assessment, depression (assessed using the Patient Health Questionnaire-2 - PHQ2) and fatigue and pain (both measured using the visual analogue scale).
- **Analysis:** Follow-up at 12, 24, 36 and 52 weeks of treatment, using a case report form. Logistic regression analysis was performed to identify any parameters associated with achieving remission (DAS28< 2.6) or low disease activity (DAS28≤ 3.2), as well as other parameters associated with high or very high disease activity.

RESULTS:

- After 12 weeks, 24% of RA patients achieved remission with etanercept (194/794). This figure increased progressively over time: 31% at week 24 (203/664), 31% at week 36 (173/561) and 37% at week 52 (187/502).
- At week 12, 39% of patients (313/794) reached low disease activity. At week 24, this figure increased to 45% (300/664). Prolonging treatment to 52 weeks was associated with a further increase to 54% (273/502) of patients with low disease activity.
- There was a significant reduction in pain throughout the study. In addition, fatigue and depression, as measured by the PHQ-2 score, also decreased steadily. The proportion of patients without depression increased from 10% (78/807) at baseline to 30% (140/463) at week 52.

CONCLUSIONS:

- A significant proportion of RA patients reached the goal of remission or low disease activity after 12 weeks of etanercept treatment. Even beyond that time, the proportion of patients reaching treatment goals continued to increase until week 52. In addition, patients reported marked improvement in PROs, including pain, depression and fatigue.

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Maintenance of Patient-Reported Outcomes in Baricitinib-Treated Patients with Moderate-toSevere Active Rheumatoid Arthritis: Post Hoc Analyses from Two Phase 3 Trials

Sholter D, Wu J, Jia B, Zhang H, et al.

Rheumatology Therapy (2022); 9(2): 541–553

OBJECTIVE:

- To analyse the maintenance of the minimal clinically important difference (MCID) in patient-reported outcomes (PROs) and time to substantial response for the same set of PROs in patients with rheumatoid arthritis (RA) treated with baricitinib.

METHOD:

- **Country:** United States.
- **Reference period:** 24 weeks.
- **Type of study:** Post hoc analysis using data from the PROs of RA patients who were randomised to placebo and baricitinib 2 mg in two clinical trials.
- **Sample:** Patients from the RA-BUILD (n=457) and RA-BEACON (n=350) studies, with inadequate response to conventional synthetic and biologic disease-modifying antirheumatic drugs, respectively.
- **Variables:** Pain measured with the Visual Analogue Scale (VAS), physical functioning assessed with the Health Assessment Questionnaire-Disability Index (HAQ-DI), fatigue measured with FACIT-Fatigue, health-related quality of life (HRQoL) assessed with the SF-36, and patient global assessment using the Patient Global Assessment of Disease Activity (PtGA).
- **Analysis:** The analysis included the proportion of patients who achieved DCMI for each PRO at weeks 4, 12 and 24, the number needed to treat (NNT) for PRO responders and the proportion of patients who maintained improvements in PROs greater than or equal to DCMI at week 24.

RESULTS:

- In both trials, significantly more baricitinib-treated patients maintained DCMI improvement in VAS pain (148 vs. 99), HAQ-DI physical functioning (147 vs. 95), SF-36 physical component (127 vs. 77) and PtGA patient global assessment (147 vs. 100) at week 24 than those on placebo ($p < 0.001$).
- In both trials, at week 12, the incremental NNT ranged from 4 to 7 for all PROs, with the exception of FACIT-Fatigua in RA-BUILD. At week 24, the incremental NNT ranged from 5 to 8 for all PROs in both trials.

CONCLUSIONS:

- RA patients refractory to previous treatments experienced improvements in clinical and reported outcomes when receiving baricitinib.

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Clinical, Patient-Reported, and Ultrasound Outcomes from an Open-Label, 12-week Observational Study of Certolizumab Pegol in Spanish Patients with Rheumatoid Arthritis with or without Prior Anti-TNF

Blanco FJ, Rubio-Romero E, Sanmartí R, Díaz-Torné C, et al.

Clinical Rheumatology (2018); 16(5): 345-52

OBJECTIVE:

- To evaluate the effectiveness and safety of certolizumab pegol, an anti-tumour necrosis factor-alpha (TNF-α) drug, in Spanish patients with rheumatoid arthritis (RA).

METHOD:

- **Country:** Spain
- **Period:** January 2012 to March 2014.
- **Type of study:** Post-marketing, multicentre, prospective, observational, open-label trial (SONAR study).
- **Sample:** 77 elderly patients with active RA of more than 3 months' duration.
- **Variables:** Change from baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) at week 12 was used as the primary variable. Secondary variables were the RA activity index (DAS28), the patient's arthritis pain assessment (PtAAP-VAS) and the quality of life index measured by the SF-36 questionnaire.
- **Analysis:** Paired t-test was used to measure mean changes in all study variables.

RESULTS:

- The mean reduction over 12 weeks from baseline was -0.6 points on the HAQ-DI and -2.2 on the DAS28.
- The PtAAP-VAS decreased from baseline by -36.8 points and improvements in the physical and mental components of the SF-36 were 7.7 and 12.8 points, respectively.
- Signal indices of synovial hypertrophy decreased from 19.3 points at baseline to 12.3 (95% CI 9.5 to 15.1) at week 12, while joint effusion decreased from 14.3 at baseline to 7.7 at week 12 (95% CI 5.2 to 10.2). Power Doppler signal decreased from 8.9 to 4.6 (95% CI 3.1 to 6.2) at the end of the study period.
- 13 patients (16.9% of the total) reported reactions to treatment, of which 8 had to discontinue treatment.

CONCLUSIONS:

- Spanish RA patients treated with certolizumab pegol for 12 weeks showed improvements in clinical and patient-reported outcomes.

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Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial

Gordon KB, Foley P, Krueger JG, Pinter A, et al.

Lancet (2021); 397(10273): 475–486

OBJECTIVE:

- To evaluate the efficacy and safety of bimekizumab in patients with moderate to severe plaque psoriasis, the effects of treatment interruption and two maintenance dosing schedules over 56 weeks.

METHOD:

- **Countries:** 77 centres in nine countries in Asia, Australia, Europe and North America.
- **Baseline period:** 2-5 week screening period, conducted between February, 2018 and January, 2020. Initial placebo-controlled treatment period: 16 weeks. Treatment withdrawal period of 40 weeks.
- **Population:** Adult patients aged 18 years and older with moderate to severe plaque psoriasis (n= 435 [bimekizumab: 349; placebo: 86).
- **Data source:** Phase 3, multicentre, randomised, double-blind, multicentre clinical trial.
- **Variables:** Primary: proportion of patients who achieved a 90% or greater improvement from baseline on the Psoriasis Area Severity Index (PASI90) and the proportion of patients who achieved a score of 0 or 1 on the five-point Investigator's Global Assessment (IGA) scale at week 16.
- **Analysis:** Efficacy analyses were performed in the intention-to-treat population; safety analysis included all patients who received at least one dose of study treatment. Multiplicity and type I error were controlled for variables and classified using a sequential testing procedure. P values less than 0.05 were considered statistically significant.

RESULTS:

- The primary endpoints were met. At week 16, 317 (91%) of the 349 patients receiving bimekizumab 320 mg every 4 weeks achieved PASI90, compared to 1 (1%) of the 86 patients receiving placebo (risk difference 89.8, 95% CI 86.1-93.4, p<0.0001).
- Over the same period, 323 (93%) of 349 patients receiving bimekizumab 320 mg every 4 weeks achieved an IGA score of 0 or 1 versus 1 (1%) of 86 patients receiving placebo (risk difference 91.5, 95% CI 88.0-94.9, p<0.0001).
- Responses were maintained until week 56 with bimekizumab 320 mg every 8 weeks and every 4 weeks.
- Total adverse events reported were: (i) in the initial treatment period (up to week 16): 213 (61%) out of 349 patients on bimekizumab and 35 (41%) out of 86 on placebo; (ii) weeks 16-56: 78 (74%) out of 106 patients on bimekizumab every 4 weeks, 77 (77%) out of 100 patients on bimekizumab every 8 weeks and 72 (69%) out of 105 patients on placebo.

CONCLUSIONS:

- Bimekizumab showed high levels of response, which were sustainable for 56 weeks, with both maintenance dosing schedules (every 4 weeks and every 8 weeks). In addition, bimekizumab was well tolerated, with no unexpected safety findings.

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Rapid and sustained improvements in Generalized Pustular Psoriasis Physician Global Assessment scores with spesolimab for treatment of generalized pustular psoriasis flares in the randomized, placebo-controlled Effisayil 1 study

Elewski BE, Lebwohl MG, Anadkat MJ, Barker J, et al.

Journal of the American Academy of Dermatology (2023); 89(1): 36–44

OBJECTIVE:

- To evaluate the efficacy of spesolimab in the management of generalised pustular psoriasis (PPG) flares during the Effisayil 1 study, and to investigate the determinants of the optimal dosage (one or two doses) required for each patient.

METHOD:

- **Countries:** 37 centres in 12 countries.
- **Baseline period:** 20 February 2019 to 5 January 2021. The duration of the trial, after recruitment, was 12 weeks per patient. First dose: day 1. Second dose (if outbreaks persisted): day 8.
- **Population:** Patients aged 18-75 years with a history of PPG consistent with the European Rare and Severe Psoriasis Expert Network diagnostic criteria (n=53; spesolimab: 35; placebo: 18).
- **Data source:** Phase 2, multicentre, randomised, double-blind, placebo-controlled, multicentre trial.
- **Variables:** Primary: Clinician's Global Pustular Generalised Pustular Psoriasis Assessment (GPPGA) pustulation indicator score of 0 (no visible pustules) to 4 (severe pustulation) at the end of week 1. Secondary: GPPGA total score of 0 or 1 (complete or near-complete skin clearing) at the end of week 1.
- **Analyses:** Analyses were conducted in the intention-to-treat population. Multiplicity and type I error were controlled for variables. P values less than 0.05 were considered statistically significants.

RESULTS:

- At the end of week 1, a total of 19 of the 35 patients (54%) assigned to the spesolimab group and 1 of the 18 patients (6%) assigned to the placebo group had a GPP- GA pustulation subscore of 0 (no visible pustules) (difference, 49%; 95%CI, 21%-67%; p<0.001).
- A total of 15 patients (43%) assigned to the spesolimab group and 2 patients (11%) assigned to the placebo group had a total GPPGA score of 0 or 1 (complete or almost complete skin clearance) (difference, 32%; 95%CI, 2%-53%; p=0.02).
- In patients initially assigned to the placebo group who subsequently received spesolimab on day 8, an increase in the proportion of individuals with a GPPGA pustulation subscore of 0 was observed, from 5.6% on day 8 to 83.3% at week 2.
- No predictors of response to spesolimab were identified in the demographic or clinical characteristics of the patients.

CONCLUSIONS:

- Rapid symptom control of the generalised pustular psoriasis flare with spesolimab was achieved and maintained for 12 weeks, reinforcing its potential use as a therapeutic option for patients.

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Real-World Effectiveness of Dupilumab in Adult and Adolescent Patients with Atopic Dermatitis: 2-Year Interim Data from the PROSE Registry

Simpson EL, Lockshin B, Lee LW, Chen Z, et al.

Dermatology and Therapy (2024); 14(1): 261–270

OBJECTIVE:

- To evaluate the 2-year effectiveness of dupilumab in adult and paediatric patients with moderate to severe atopic dermatitis (AD) enrolled in a longitudinal registry.

METHOD:

- **Countries:** United States and Canada.
- **Baseline period:** Baseline data (day of first dupilumab injection) were reported for patients enrolled from April 2018 to July 2019. Follow-up was conducted for 2 years.
- **Population:** 12 years and older with moderate to severe AD, with first administration of dupilumab at baseline.
- **Data source:** PROSE longitudinal register.
- **Variables:** Clinician-reported outcomes (CRO): % body area affected by AD (BSA), Dermatitis Area and Severity Index (EASI), and the Numerical Pruritus Scale (NRS). Patient-reported outcomes (PRO): Dermatology Life Quality Index (DLQI), Numeric Itch Score Scale (PNRS), Patient Oriented Eczema Measure (POEM), Patient Global Assessment of Disease Questionnaire (PGAD) score (PGAD).
- **Analysis:** Prospective, observational, multicentre study. Assessments at months 3, 6, and every 6 months thereafter until the final visit at year 5. All data analyses are descriptive. For continuous variables, descriptive statistics include means and standard deviations (SD) or medians with interquartile ranges. For categorical or ordinal data (such as PGAD results), frequencies and percentages are used.

RESULTS:

- Of the 764 patients enrolled in PROSE, 632 (83%) remained in the study at the time of this interim analysis.
- Improvements were observed at the first clinic visit after baseline (3 months) in clinician-assessed measures (%BSA: from ~35% to ~10%; mean EASI score: from 16.1 to 5.6; NRS: from ~7.5 to ~7.5; NRS: from ~7.5 to ~10%; mean EASI score: from 16.1 to 5.6). ~3,8). These improvements were maintained over the 2-year period covered in this study.
- Consistent and sustained improvements were also observed over the 2-year period in PROs (mean POEM: from ~20 to ~10; mean DLQI: from ~12 to ~2), as well as in the proportion of patients reporting "very good/ excellent" in response to the PGAD questionnaire question (from 12.7% to 68.9%).
- Dupilumab treatment was well tolerated, with safety findings consistent with those previously reported in studies of dupilumab for the treatment of AD (total adverse events: 19%; serious: 2.1%).

CONCLUSIONS:

- Based on data from routine clinical practice, patients with moderate to severe AD experienced sustained improvements up to 2 years after starting dupilumab treatment.

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Dupilumab in patients with prurigo nodularis: two randomized, double-blind, placebo-controlled phase 3 trials

Yosipovitch G, Mollanazar N, Ständer S, Kwatra S, et al.

Nature Medicine (2023); 29(5): 1180–1190

OBJECTIVE:

- To evaluate the efficacy and safety of dupilumab in adults with prurigo nodularis (NP) not previously controlled with topical therapies.

METHOD:

- **Countries:** PRIME: 58 centres in eight countries/regions. PRIME2: 55 centres in 11 countries/regions.
- **Reference period:** Recruitment. PRIME: 12 December 2019 to 11 May 2021. PRIME2: January 16, 2020 to February 24, 2021. Treatment period of 24 weeks and post-treatment period of 12 weeks.
- **Population:** PRIME: 151 patients (75 dupilumab; 76 placebo). PRIME2: 160 patients (78 dupilumab; 82 placebo). All aged 18 to 80 years, with a clinical diagnosis of NP.
- **Data source:** Two parallel phase 3, quadruple-blinded (Participant, Caregiver, Investigator, Outcome Evaluator) parallel trials LIBERTY-PN PRIME and PRIME2.
- **Variables:** Primary: proportion of patients with a reduction ≥4 points on the Worst Itch Numeric Rating Scale (WI-NRS) at week 24 (PRIME) or week 12 (PRIME2). Secondary (both trials): proportion of patients with a reduction in the number of skin lesions on the Investigator's Global Assessment (IGA PN-S) of 0 or 1 at week 24. Other variables: assessment of quality of life, skin pain, sleep and mental health.
- **Analysis:** A multiplicity procedure was used to control for the type I error rate in the variables analysed. P values of less than 0.05 were considered statistically significant.

RESULTS:

- Both trials met all pre-defined primary and secondary endpoints. A ≥4-point reduction in WI-NRS at week 24 in the dupilumab- and placebo-treated groups was achieved by 60.0% and 18.4% of patients, respectively, in PRIME (95% CI: 27.8-57.7, P<0.001) and at week 12 by 37.2% and 22.0% of patients, respectively, in PRIME2 (95% CI, 2.3-31.2; P=0.022).
- Significantly more dupilumab-treated patients achieved a PN-S IGA score of 0 or 1 in each trial at week 24. PRIME: 48.0% vs. 18.4% (95% CI: 13.4-43.2; P<0.001); PRIME2: 44.9% vs. 15.9% (95% CI: 16.4-45.2; P<0.001).
- Dupilumab-treated patients showed significant improvements in quality of life compared to placebo-treated patients, based on mean (±s.s.) changes in DLQI score from baseline to week 24: PRIME: -12.0 (1.0) vs. -5.8 (1.0); PRIME2: -13.2 (1.2) vs. -6.8 (1.2) (95% CI: -8.3 to -4.0 and -8.4 to -4.4, respectively; both P < 0.001).

CONCLUSIONS:

- Dupilumab demonstrated clinically and statistically significant improvements in itching and skin lesions compared to placebo in the treatment of NP. Safety was consistent with the known safety profile of dupilumab.

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Tofacitinib in Ulcerative Colitis: Real-world Evidence from the ENEIDA Registry

Chaparro M, Garre A, Mesonero F, Rodríguez C, et al.

Journal of Crohn's and Colitis (2021); 15(1): 35-42

OBJECTIVE:

- To evaluate the effectiveness and safety of tofacitinib in real-life ulcerative colitis in Spain.

METHOD:

- **Country:** Spain.
- **Period:** 2019.
- **Sample:** Observational, prospective, multicentre study conducted using data from the ENEIDA registry. Included were 113 patients aged 18 years or older, diagnosed with ulcerative colitis, who received at least one dose of tofacitinib due to active disease.
- **Sources:** ENEIDA Registry, promoted by the Spanish Crohn's and Ulcerative Colitis Working Group.
- **Variables:** Effectiveness at weeks 4, 8 and 16 of treatment, defined as disease activity (PMS index: Partial May Score); remission response; relapses.
- **Analysis:** Descriptive analysis of quantitative variables, calculating mean and standard deviation, or median and interquartile range. Univariate analysis to compare categorical variables using the chi-square test.

RESULTS:

- The response and remission rates at week 8 were 60% and 31%, respectively.
- In multivariate analysis, a higher PMS at week 4 was the only variable associated with a lower probability of achieving remission at week 8 (OR 0.2, 95% CI 0.1-0.4).
- Higher PMS at week 4 [OR 0.5, 95%CI 0.3-0.7] and higher PMS at week 8 [OR 0.2, 95%CI 0.1-0.5] were associated with a lower likelihood of achieving remission at week 16.
- A total of 45 patients [40%] stopped taking tofacitinib over time.
- Higher WHO at week 8 was the only factor associated with higher tofacitinib discontinuation [HR=1.5; 95%CI 1.3-1.6].
- A total of 34 patients were in remission at week 8, 65% of whom had relapsed 52 weeks after achieving remission.
- 17 patients experienced adverse events.

CONCLUSIONS:

- Tofacitinib is effective and safe in patients with ulcerative colitis in real-world practice, even in a highly refractory cohort.

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Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial

Feagan BG, Patel H, Colombel J-F, Rubin DT, et al.

Alimentary Pharmacology & Therapeutics (2017); 45(2): 264-75

OBJECTIVE:

- To assess the effects of vedolizumab on health-related quality of life (HRQoL) in patients with ulcerative colitis.

METHOD:

- **Countries:** USA and Canada.
- **Period:** January 2009 to March 2012.
- **Type of study:** Multicentre, phase 3, blinded, randomised, placebo-controlled trial.
- **Sample:** 373 elderly patients with moderate or severe ulcerative colitis.
- **Treatment:** Patients were randomised in a 1:1:1 ratio to three groups: placebo, vedolizumab 300mg every 6 weeks and vedolizumab 300mg every 8 weeks.
- **Variables:** Inflammatory Bowel Disease Questionnaire (IBDQ) and the quality of life questionnaires SF-36 and EQ-5D.
- **Analysis:** An analysis of covariance model was used to calculate mean differences between vedolizumab and placebo groups in changes from baseline to week 52 for the 3 HRQoL measurement instruments.

RESULTS:

- In the IBDQ-specific test, the vedolizumab every 8 weeks group showed a difference from baseline of 48.4 points (standard error 3.4), while for vedolizumab every 4 weeks and placebo the difference was 49.0 points (standard error 3.3) and 27.3 points (standard error 3.3), respectively.
- According to the overall EQ-5D VAS quality of life test, patients treated with vedolizumab every 8 weeks and every 4 weeks had differences versus placebo of 9.3 points (95% CI 4.6 to 14.0) and 9.7 points (95% CI 5.0 to 14.4), respectively.
- Overall, compared to patients in the placebo group, patients treated with vedolizumab had 152% to 201% greater improvements in IBDQ, EQ-5D visual analogue scale and EQ-5D utility scores.
- 70% of patients who showed remission on the IBDQ test demonstrated clinical remission.

CONCLUSIONS:

- Vedolizumab therapy was associated with significant improvements in HRQoL measures compared to placebo.

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Results of the treatment of patients with complex perianal fistulas in Crohn's disease with darvadstrocel (alofisel®) registered at Valtermed

Ministerio de Sanidad

Informe VALTERMED de resultados en salud (2022)

OBJECTIVE:

- To analyse the information available in the Therapeutic Value of Medicines Information System (VALTERMED) on patients with complex perianal fistulas in Crohn's disease treated with darvadstrocel, in order to make a long-term assessment of treatment outcome in real practice.

METHOD:

- **Country:** Spain.
- **Period:** 2019-2021.
- **Sample:** 78 patients with complex perianal fistulas in Crohn's disease treated with darvadstro-cell.
- **Sources:** VALTERMED.
- **Variables:** Effectiveness at 6 and 12 months (combined remission, defined as clinical closure of all treated fistulae and absence of abscesses larger than 2 cm); safety (suspected development of new anal fistula and/or anal abscesses or recurrence of treated fistula; transmission of bacterial, viral or fungal pathogens; other potentially treatment-related adverse events).
- **Analysis:** Descriptive analysis.

RESULTS:

- 47% of patients are male and 53% female. The average age is 41.9 years.
- 39% of the patients analysed came from Catalonia, 15% from the Valencian Community, 10% from the Basque Country and the rest from other Autonomous Communities.
- Treatment initiation has been recorded in 56 patients out of 78 (72%). All of them have received a dose of darvadstrocel.
- Follow-up at 6 months: results are available for 86% of patients who have started treatment, of which 67% (32) meet the criteria for combined remission (69% have achieved closure of all fistulae; 96% have no abscesses larger than 2 cm).
- Follow-up at 12 months: Limited data are available on effectiveness at 12 months of treatment (12 patients, only 21% of the sample). Of these, 9 (75%) maintain combined remission (100% maintain absence of abscesses and 75% maintain clinical closure of all fistulas). No 24-month follow-up data are available at this time.
- Safety: Adverse effects have been reported in 16% (9) of patients who have started treatment. A recurrence or new anal fistula or abscess developed in 33% (3 out of 9).

CONCLUSIONS:

- The use of darvadstrocel in patients with anal fistulas in Crohn's disease shows promising results, although further registration in all patients who have started treatment and longer-term outcomes are needed.

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The Effects of Ustekinumab on Health-related Quality of Life in Patients With Moderate to Severe Crohn's Disease

Sands BE, Han C, Gasink C, Jacobstein D, et al.

Journal of Crohn's and Colitis (2018); 12(8): 883-95

OBJECTIVE:

- To assess the effect of ustekinumab on health-related quality of life (HRQoL) in patients with moderate to severe Crohn's disease.

METHOD:

- **Countries:** 26 countries in the Americas, Asia, Europe (including Spain) and Oceania.
- **Type of study:** multicentre, randomised, double-blind, placebo-controlled Phase 3 trials (UNITI-1 and UNITI-2 studies).
- **Period:** June 2011 to August 2016 (UNITI-1 study) and June 2011 to January 2017 (UNITI-2 study).
- **Sample:** 1,368 elderly patients with moderate or severe Crohn's disease with inadequate response or intolerance to anti-TNF or standard treatment.
- **Treatment:** Patients were randomised in a 1:1:1 ratio to three groups: placebo, ustekinumab 130mg (subcutaneous) and ustekinumab 6mg/kg (intravenous).
- **Variables:** Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 quality of life questionnaire (physical component -PCS- and mental component -MCS) after 8, 20 and 44 weeks of treatment.
- **Analysis:** Analysis of covariance was performed on van der Waerden normal scores. The proportions of patients with dichotomous IBDQ, PCS and MCS scores were compared using a Cochran-Mantel-Haenszel $\chi 2$ test.

RESULTS:

- Considering the IBDQ questionnaire, a higher proportion of patients receiving ustekinumab 6mg/kg or 130mg had a clinically significant improvement (of 16 points or more) versus placebo (UNITI-1: 54.8% and 46.9% versus 36.5%, respectively; UNITI-2: 68.1% and 58.7% versus 41.1%, respectively) at 8 weeks of treatment.
- Using the SF-36 questionnaire in UNITI-2, the proportion of patients with a clinically significant improvement in PCS (5 points or more) at 8 weeks of treatment was significantly higher for the ustekinumab 6mg/kg and 130mg groups than for the placebo group (49.2% and 44.0%, respectively, vs. 31.2%). Similarly, there was a clinically significant improvement in the mental component in the ustekinumab 6mg/kg and 130mg groups (51.3% and 49.2% vs. 38.6% in the placebo group). In UNITI-1, scores were only significantly higher in the MCS component for the ustekinumab 6mg/kg group compared to the placebo group (42.4% versus 30.0%).
- The improvements were maintained at week 44 of treatment: the proportion of patients with clinical improvements in HRQoL was 67.9% and 61.3% for the intravenous and subcutaneous doses of ustekinumab, while it was 50.4% in the placebo group.

CONCLUSIONS:

- Treatment with ustekinumab improved the overall health status and inflammatory bowel disease-specific HRQoL of patients with moderate to severe active CD.

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Effect of preventive treatment on health-related quality of life in episodic migraine

Bordini C, da Silva HM, Garbelini HP, Teixeira SO, et al.

Journal of Headache Pain (2005); 6: 387-391

OBJECTIVE:

- To assess the impact of preventive pharmacological treatment on the quality of life of patients with episodic migraine.

METHOD:

- **Country:** Portugal.
- **Sample:** 35 adult patients with episodic migraine without aura seen in a tertiary health centre.
- **Treatment:** Six months of preventive migraine treatment with beta-adrenergic blockers and antidepressants (n=15), beta-adrenergic blockers and flunarizine (n=5), neuroleptics (n=3), flunarizine (n=3), antidepressants and verapamil (n=2), antidepressants and neuroleptics (n=2), verapamil (n=2), valproic acid (n=2) or valproic acid and neuroleptics (n=1).
- **Data source:** Batatais Headache Clinic.
- **Variables:** Quality of life as measured by the SF-36 instrument; frequency of migraine attacks.
- **Analysis:** Comparison of health-related quality of life before and after treatment with T-test and Wilcoxon test.

RESULTS:

- The mean frequency of migraine attacks before and after treatment was 9.16 (SD: 3.45, range 3-14) and 2.4 (SD: 2.5, range 0-14) per month, respectively ($p<0.05$).
- Preventive treatment resulted in statistically significant improvements ($p<0.05$) in six of the eight SF-36 quality of life measures: physical role 72.7 vs 53; bodily pain 56.3 vs 42; general health 79.9 vs 65.9; vitality 55.3 vs 47.6; social function 72.4 vs 61.4; mental health 66.2 vs 56.4.
- Improvements in physical function (83 vs. 80) and emotional role (62.6 vs. 54.4) before and after preventive treatment were statistically non-significant.

CONCLUSIONS:

- Preventive treatment of migraine not only reduces the frequency of attacks, but also improves the quality of life of patients.

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Long-term effectiveness of eptinezumab in patients with migraine and prior preventive treatment failures: extension of a randomized controlled trial

Ashina M, Tepper S, Gendolla A, Sperling B, et al.

The Journal of Headache and Pain (2023); 24: 155

OBJECTIVE:

- To evaluate the long-term efficacy of eptinezumab in a migraine patient population during the 48-week extension phase of the DELIVER trial.

METHOD:

- **Country:** United States.
- **Period:** June 2020-September 2022.
- **Sample:** 865 adults with migraine with documented evidence of 2-4 previous migraine preventive treatment failures and completion of the 24-week placebo-controlled period of the DELIVER trial. They received eptinezumab (100 or 300 mg) either by continuing their randomised dose or, if originally receiving placebo, were randomised 1:1 to a dose of eptinezumab (100 or 300 mg).
- **Variables:** Changes since baseline in the number of monthly migraine days (MMD), quality of life as measured by the HIT-6 Score, the Migraine-Specific Quality of Life questionnaire (MSQ), the EuroQol-5D and the migraine-adapted Work Productivity and Impairment Index (WPAI:M).
- **Analysis:** A repeated measures mixed model was used.

RESULTS:

- Eptinezumab was associated with early and sustained reductions in migraine frequency. The mean (standard error) change in MMD from baseline during the final dose interval (weeks 61-72) was -6.4 (0.50) for placebo/eptinezumab 100 mg, -7.3 (0.49) for placebo/eptinezumab 300 mg, -7.1 (0.39) for eptinezumab 100 mg and -7.0 (0.39) for eptinezumab 300 mg.
- During weeks 61-72, 63-70% of patients demonstrated a ≥ 50% reduction in MMD, and 36-45% demonstrated a ≥ 75% reduction.
- Reductions in headache severity and acute medication use were observed, as well as patient-reported improvements in most bothersome symptoms and disease status.
- At the end of the extension, mean total HIT-6 scores decreased to a similar extent in all groups (-11.0 to -14.0 points). Mean EQ-5D-5L scores had improved by 6 to 9 points.
- Adverse events were generally mild, transient and similar in frequency/type to previous eptinezumab trials.
- Working patients reported between 3.5 and 7.4 fewer days lost (WPAI:M), and reductions in WPAI:M sub-scores for presenteeism, loss of work productivity and activity impairment were consistent with an increased ability to function at work when present.

CONCLUSIONS:

- The long-term efficacy and safety of eptinezumab is demonstrated in patients with migraine and several previous preventive treatment failures.

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Once-daily oral atogepant for the long-term preventive treatment of migraine: Findings from a multicenter, randomized, open-label, phase 3 trial

Ashina M, Tepper S, Reuter U, Blumenfeld A, et al.

Headache (2023); 63(1): 79-88

OBJECTIVE:

- To assess the long-term safety, tolerability and efficacy of once-daily oral atogepant in adults with migraine.

METHOD:

- **Country:** United States (111 centres).
- **Period:** 2018-2020.
- **Sample:** Participants who had completed the initial trial or new participants with 4-14 days/month of migraine were included. They were randomised (5:2) to atogepant 60 mg once daily or to oral standard care (SC) migraine preventive medication.
- **Variables:** Safety and tolerability (treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs and Columbia-Suicide Severity Rating Scale scores); efficacy (change from baseline in mean monthly migraine days (MMD) and the proportion of participants with reductions from baseline of ≥50%, ≥75% and 100% in MMD).
- **Analysis:** Open-label, randomised, multicentre, 52-week, multicentre trial in adults (18-80 years) with migraine.

RESULTS:

- The trial included 744 participants randomised to atogepant 60 mg (n=546) or SC (n=198).
- TEAEs occurred in 67.0% (n=364/543) of atogepant-treated participants and in 78.6% (154/196) SC-treated patients. The most frequent adverse events (>5) in the treatment arm were upper respiratory tract infection (10.3%; 56/543), constipation (7.2%; 39/543), nausea (6.3%; 34/543) and urinary tract infection (5.2%; 28/543). Serious AEs were reported in 4.4% (24/543) for atogepant.
- The mean change (standard error) in MMD for atogepant was -3.8 (0.1) for the first 4 weeks of treatment and -5.2 (0.2) in weeks 49-52 from baseline.
- The proportion of atogepant-treated participants with ≥50%, ≥75% and 100% reductions in MMD increased from 60.4% (310/513), 37.2% (191/513) and 20.7% (106/513) at weeks 1-4 to 84.2% (282/335), 69.9% (234/335) and 48.4% (162/335) at weeks 49-52.

CONCLUSIONS:

- Daily use of oral atogepant for the preventive treatment of migraine during this 1-year open-label trial was safe, well tolerated and effective.

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The impact of new (orphan) drug approvals on premature mortality from rare diseases in the United States and France, 1999-2007

Lichtenberg, FR.

European Journal Health Economics (2013); 14: 41-56

OBJECTIVE:

- To analyse the impact of the introduction of new orphan drugs on premature mortality from rare diseases.

METHOD:

- **Countries:** United States and France.
- **Reference periods:** 1999-2006 (US) and 2000-2007 (France).
- **Data sources:** Orphanet, FirstDataBank, Federal Drug Administration, Centers for Disease Control, Agen- ce Francaise de Securite Sanitaire des Produits de Sante, Centre d'épidémiologie sur les causes médicales de décès.
- **Variables:** Premature mortality measured as the number of potential years of life lost before age 65 and 75; cumulative number of orphan drugs approved in previous years (delays between 0 and 5 years); various disease prevalence ranges (number of people at risk of death).
- **Analysis:** Weighted least squares, difference-in-differences econometric model to analyse the extent to which premature mortality for a given rare disease i in year t depends on the cumulative number of drugs (stock) approved for that disease in year t-k (lag of k years) and the prevalence of the disease at the beginning of year t, controlling for disease type and year. Subsequent analysis to compare the actual decline in premature mortality with that which would have occurred without the existence of the orphan drugs.

RESULTS:

- The three-year stock of approved orphan drugs has increased from 119 in 1999 to 204 in 2006.
- In the US, premature mortality for a given rare disease tends to decrease 3-4 years after the orphan drug has been approved to treat it, with an elasticity between -0.85 and -0.92. Prior to this, no significant changes are apparent. Changes in the prevalence rate of the disease or in the way premature mortality is measured do not change the results much.
- In France, more modest results on premature mortality are observed than in the US (elasticity between -0.15 and -0.22), and with a somewhat longer time lag (3-5 years). Changes in disease prevalence or in the way premature mortality is measured also have little effect on the results.
- The reduction in the growth rate of potential years of life lost before age 65 attributable to the stock of orphan drugs is 4.2% in the United States and 1.1% in France (-4.1% and -0.8% before age 75).

CONCLUSIONS:

- Approval of an orphan drug leads to a reduction in premature mortality associated with the targeted rare disease some 3-5 years later.

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Estimating Population Health Benefits Associated with Specialty and Traditional Drugs in the Year Following Product Approval

Chambers J, Thorat T, Wilkinson C, Salem M, et al.

Applied Health Economics Health Policy (2017); 15(2): 227-235

OBJECTIVE:

- Estimate the health outcomes associated with the use of specialised medicines, compared to traditional medicines, in the year following their approval.

METHOD:

- **Country:** United States.
- **Reference period:** 1999-2011.
- **Study population:** 279 drugs approved by the FDA in the reference period. Of these, publications have been found reporting quality-adjusted life years for 101 drugs (56 specialised) and life years gained for 50 drugs (34 specialised).
- **Data source:** Scientific publications (241 related to estimates of quality-adjusted life years, and 111 to estimates of life years gained), Centers for Disease Control and Prevention (CDC), Scientific Societies.
- **Variables:** Quality-adjusted life years (QALYs) and life years gained (YLGs).
- **Analysis:** Categorisation of speciality and traditional medicines. Weighting of health outcomes for each drug in the year after approval, multiplying the health gain by 10% of the identified prevalence. Mann-Whitney U tests to compare health gains for both groups of drugs.

RESULTS:

- On average, specialised medicines were prescribed for diseases of lower prevalence than traditional medicines (1.1 million vs. 14.3 million people per disease) ($p<0.0001$).
- Average estimated population-level QALY gains in the year following new drug approval were 4,200 for speciality drugs, 6 times higher than the figure for traditional drugs (694).
- Gains were estimated at 7,250 YLGs for specialised drugs, and 2,500 for traditional drugs.

CONCLUSIONS:

- Although often indicated for less prevalent diseases, speciality drugs tend to offer greater potential for health gains, especially in terms of QALYs.

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Limitations of standard cost-effectiveness methods for health technology assessment of treatments for rare, chronic diseases: a case study of treatment for cystic fibrosis

Rubin JL, Lopez A, Booth J, Gunther P, et al.

Journal of Medical Economics (2022); 25(1): 783-791

OBJECTIVE:

- Analyse alternative hypotheses for key variables that could affect the results of cost-effectiveness analysis (CEA), using the base case of cystic fibrosis treatment with elexacaftor/tezacaf- tor/ivacaftor (ELX/TEZ/IVA) as an example.

METHOD:

- **Country:** United States.
- **Period:** Throughout the patient's life.
- **Sample:** Two cohorts, each consisting of 2,000 patient profiles, all with identical baseline characteristics, for the purpose of comparing costs and clinical outcomes in patients treated with ELX/TEZ/IVA together with best supportive care and patients treated with best supportive care alone.
- **Sources:** Initial data are derived from a phase III clinical trial of ELX/TEZ/IVA in patients aged 12 years and older.
- **Variables:** Median survival, discounted life years, discounted quality-adjusted life years (QALYs), cost and utility parameters.
- **Analysis:** The incremental cost-effectiveness ratio (ICER) of ELX/TEZ/VAT was assessed using base case data and assumptions reflecting standard CEA methods. The scenario analysis included estimates of ICERs obtained by using the alternative assumptions for key variables: (1) applying a lower discount rate (1.5%) to health benefits than to costs (3%); (2) including a treatment-specific utility increment; (3) excluding disease management costs incurred during the period of prolonged survival attributable to ELX/TEZ/IVA treatment; and (4) decreasing the price of ELX/TEZ/IVA after loss of exclusivity.

RESULTS:

- ELX/TEZ/IVA, together with best supportive care, was projected to increase median survival in people with cystic fibrosis by 29.7 years compared to treatment with best supportive care alone (70.4 vs. 40.8 years).
- Over the patient's lifetime, treatment with ELX/TEZ/IVA was associated with 25.0 additional undiscounted life years, which was reduced to 9.1 discounted life years and 9.2 discounted QALYs.
- The base case ICER was £482,000 per QALY gained over the patients' lifetime time horizon.
- The joint modification of the assumptions resulted in the ICER decreasing by 75% from the base case, resulting in an ICER of £122,000 per QALY gained. The largest decrease in ICER (45%) occurred by modifying the pricing trajectory to allow generic entry, followed by applying a differential discount to health benefits and costs (36%), the use of a specific treatment utility increment (14%) and the exclusion of additional management costs (10%).

CONCLUSIONS:

- This study illustrates the impact that modifications to standard CEA methods can have on the perceived value of innovative interventions and how addressing these limitations can change the outcomes of cost-effectiveness measures for rare and chronic diseases.

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5-Year Follow-Up Supports Curative Potential of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma (ZUMA-1)

Neelapu SS, Jacobson CA, Ghobadi A, Miklos DB, et al.

Blood (2023); 141(19): 2307-15

OBJECTIVE:

- To report on the long-term efficacy and safety of axicabtagene ciloleucel (axi-cel) therapy in patients with ZUMA-1 phase 2 refractory diffuse large B-cell lymphoma (DLBCL) after 5 years of follow-up.

METHOD:

- **Countries:** USA and Israel.
- **Period:** May 2015 to March 2022.
- **Type of study:** Phase 2, multicentre, single-arm, multicentre trial (long-term follow-up of the ZUMA-1 study).
- **Sample:** 101 patients diagnosed with DLBCL infused with axi-cel.
- **Variables:** Objective response rate (ORR) (complete response (CR)+ partial response (PR)) as primary variable. Overall survival (OS), progression-free survival (PFS), event-free survival (EFS), duration of response and safety as secondary variables.
- **Analysis:** Bilateral 95% confidence intervals (CI) for response rates were assessed using the Clopper-Pearson method. Time outcomes were assessed using the Kaplan-Meier methodology.

RESULTS:

- ORR was 83% (95%CI 74%-90%) and 58% of patients achieved CR. The median CR duration was 62.2 months, while the median PR was 1.9 months.
- Among all treated patients, the median duration of response was 11.1 months (95% CI 4.2 months-51.3 months).
- The median OS was 25.8 months (95%CI: 12.8 months-not estimable) and the 5-year OS rate was 42.6% (95%CI: 32.8%-51.9%).
- The median PFS was 5.9 months (95%CI: 3.3 months-15.0 months) and the 5-year PFS rate was 31.8% (95%CI: 22.9%-41.1%).
- The median EFS was 5.7 months (95%CI: 3.1 months-13.9 months) and the 5-year EFS rate was 30.3% (95%CI: 21.5%-39.6%).
- Cytokine release syndrome occurred in 93% of patients, with grade 3 or higher in 11%. Neurological events occurred in 64% of patients, with 30% being grade 3 or higher events. No therapy-related secondary malignancies were found.

CONCLUSIONS:

- Five-year follow-up data from the ZUMA-1 trial demonstrates continued durability of treatment response and long-term survival in patients with refractory DLBCL treated with axi-cel, while maintaining a manageable safety profile.

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Tisagenlecleucel vs. historical standard of care in children and young adult patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia

Stackelberg A, Jäschke K, Jousseaume E, Templin C, et al.

Leukemia. 2023;37(12):2346-55

OBJECTIVE:

- To compare the efficacy and safety of tisagenlecleucel (tisa-cel) with standard of care (SOC) in paediatric and young patients up to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL).

METHOD:

- **Countries:** 11 countries in North America, Europe, Asia and Australia.
- **Period:** 2013 to 2020.
- **Type of study:** Retrospective non-randomised study comparing three studies (ELIANA, ENSIGN and CCTL019B2001X) versus three population-based registries (ALL-REZ BFM, GMALL and ALL-SCT BFM).
- **Sample:** 511 patients aged 3 to 25 years, of whom 209 were infused with tisa-cel and the rest with standard of care.
- **Primary endpoints:** Overall survival (OS), progression-free survival (PFS), relapse-free survival (RFS) and objective response rate (ORR).
- **Analysis:** Two sets of analyses were performed, one full (FAS) and one intention-to-treat (ITT). Estimated time to first event was estimated using Cox regression and Kaplan-Meier curves with log-rank tests. For ORR, probabilities were estimated by logistic regression and Wald Z-test.

RESULTS:

- By ITT, 2-year OS was 59.49% (95%CI: 52.08-66.13%) for tisa-cel versus 36.16% (95%CI: 30.38-41.95%) for SOC and 65.41% (95%CI: 58.02-71.82%) versus 36.83% (30.98-42.68%) in FAS for tisa-cel and SOC, respectively.
- The probability of SLR at 2 years was 59.60% (95%CI: 49.74-68.16%) for tisa-cel versus 54.57% (95%CI: 42.60-65.05%) for SOC.
- Treatment with tisagenlecleucel was associated with a significantly higher ORR, with a probability per ITT of 1.99 (1.33-2.97, p<0.001) and a probability per FAS of 3.34 (2.14-5.19, p<0.001) compared to SOC.

CONCLUSIONS:

- Comparison of tisa-cel treatment in different clinical trials against a history of actual clinical practice provided evidence for the superiority of this CAR-T therapy over standard treatment in patients with relapsed or refractory B-cell ALL.

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Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial

Strauss KA, Farrar MA, Muntoni F, Saito K, et al.

Nature Medicine (2022); 28(7): 1381-9

OBJECTIVE:

- To assess the efficacy and safety of onasemnogene abeparvovec among children with genetically confirmed spinal muscular atrophy (SMA) type 1 before clinical disease onset.

METHOD:

- **Countries:** Australia, Belgium, Canada, Japan, UK and USA.
- **Period:** April 2018 and July 2019.
- **Type of study:** Phase 3, multicentre, single-arm trial (SPR1NT study) versus two population-based registries (Pediatric Neuromuscular Clinical Research [PNCR] and NeuroNEXT).
- **Sample:** 14 presymptomatic patients with genetically confirmed SMA and two copies of the SMN2 gene.
- **Variables:** Ability to sit independently for 30 seconds, ability to walk independently according to the Baley Scales of Infant and Toddler Development (BSID) and the WHO Multicentre Growth Reference Study (WHO-MGRS) as primary variables. Ventilator-free survival and growth according to WHO infant growth standards and safety as secondary variables.
- **Analysis:** The one-sided binomial test was used for the ability to sit independently. Formal tests for primary and secondary efficacy endpoints were conducted using a hierarchical approach to protect against Type I error.

RESULTS:

- 100% (95%CI: 97.5%-100%) of patients were able to sit independently for at least 30 seconds at any visit until the end of follow-up (18 months) compared to 0% of the PNCR cohort ($p<0.0001$).
- 100% of the patients achieved motor milestones as defined by BSID and WHO-MGRS. 64% of patients walked independently according to BSID criteria at a mean age of 526 days (367- 564 days) and 36% did so within the normal developmental window of ≤534 days. Seventy-one per cent walked alone as defined by WHO-MGRS criteria at a mean age of 493 days (367-564 days).
- 100% of patients were alive and off permanent ventilation at 14 months of age, compared to 26% of the PNCR cohort ($p<0.0001$).
- 93% of patients maintained a weight at or above the 3rd percentile according to WHO child growth standards without the need for non-oral/mechanical feeding support at all visits up to 18 months of age.
- A total of 159 treatment-related adverse events (TRAEs) were observed. All children experienced at least one TRAE and 36% had an TRAE considered severe.

CONCLUSIONS:

- Onasemnogene abeparvovec was effective and well tolerated in patients expected to develop SMA type 1.

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Effectiveness of a Meningococcal Group B Vaccine (4CMenB) in Children

Castilla MJ, García MC, Abad R, Sánchez-Cambronero L, et al.

The New England Journal of Medicine (2023); 388(5): 427-38

OBJECTIVE:

- To analyse the effectiveness of the four-component, protein-based meningococcal serogroup B vaccine (4CMenB) in the prevention of invasive meningococcal disease in children in Spain.

METHOD:

- **Country:** Spain.
- **Period:** October 2015 - October 2017 or October 2017 - October 2019.
- **Sample:** 306 cases (243 [79.4%] with serogroup B disease) and 1,224 controls.
- **Sources:** Data on meningococcal immunisation (with 4CMenB, serogroup C conjugate or ACWY [serogroups A, C, W-135 and Y] vaccines) were from regional electronic immunisation registries.
- **Variables:** Effectiveness of vaccination, vaccination status (partial or complete vaccination, defined as receipt of at least 2 doses, administered according to manufacturer's recommendations), the meningococcal serogroup causing invasive disease (B or non-B), age group (<24 or ≥24 months) and study period.
- **Analysis:** National matched case-control study where clinical cases and their matched controls were compared for 4CMenB vaccination status using conditional logistic regression to obtain crude and adjusted (by sex and high-risk conditions) matched odds ratios with 95% confidence intervals.

RESULTS:

- The effectiveness of full vaccination with 4CMenB was 76% (95%CI 57-87) against invasive meningococcal disease caused by any serogroup, and partial vaccination was 54% (95%CI 18-74) effective.
- Full vaccination resulted in an effectiveness of 71% (95% CI 45-85) against serogroup B meningococcal disease.
- Vaccine effectiveness with at least one dose of 4CMenB was 64% (95% CI 41-78) against serogroup B disease and 82% (95% CI 21-96) against non-serogroup B disease.

CONCLUSIONS:

- Full vaccination with 4CMenB was shown to be effective in preventing invasive disease caused by both serogroup B meningococci and other serogroups in children under 5 years of age in Spain.

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Quadrivalent Human Papillomavirus Vaccine Effectiveness after 12 Years in Madrid (Spain)

Hernandez-Aguado JJ, Sánchez Torres DA, Martínez Lamela E, Aguión Gálvez G, et al.

Vaccines (2022); 10(3): 387

OBJECTIVE:

- To compare the prevalence of human papillomavirus (HPV) infection and cervical cytological abnormalities between women previously vaccinated with the tetravalent HPV vaccine and unvaccinated women in Spain.

METHOD:

- **Country:** Spain.
- **Period:** October 2018 - October 2019.
- **Sample:** 790 women aged 25-26 years living in Madrid in the study period who were vaccinated in the routine vaccination programme (girls aged 11-14 years) started in 2007, or in subsequent years.
- **Sources:** Data provided by the relevant Public Health Department (vaccination and census data) and contacts with women from hospital databases and the Regional Vaccination Register.
- **Variables:** Prevalence of HPV and cytological abnormalities, proportion of women vaccinated and unvaccinated against HPV.
- **Analysis:** The association of qualitative variables between the two study groups was compared using the chi-square test or Fisher's exact test. Quantitative variables were compared by Student's t-test or Mann-Whitney U-test according to the distribution

RESULTS:

- 48% (378/792) of participants were unvaccinated and 52% (414/792) were vaccinated against HPV.
- Women vaccinated at 14 years of age or earlier had a prevalence of high-risk HPV (HR-HPV) of 24.4% (81/332), while in women vaccinated at 15 years of age or older the prevalence was 45.1% (37/82) [OR 0.39 (95% CI 0.23-0.64) p = 0.0003].
- There was a significant reduction in the prevalence of HPV 6 (0% vs. 1.3%) and 16 (2.4% vs. 6.1%) among vaccinated vs. unvaccinated women.
- The odds ratio (OR) of having an HPV 16-related abnormal cytology according to vaccination status is 6.22 (95%CI: 1.06-36.21; p 0.04), meaning that the unvaccinated group is six times more likely to have an HPV 16-related abnormal cytology than the vaccinated group.
- Among HR-HPV-positive women, the rate of cytological abnormalities was 42.1% (96/228), compared to 12.4% (69/554) among HR-HPV-negative women [OR: 5.11 (95% CI: 3.55-7.35; p = 0.0001)].

CONCLUSIONS:

- HPV vaccination at an early age (11-14 years) in a cohort of Spanish girls was effective, decreasing the prevalence of high-risk vaccine genotypes, as well as reducing related cytological alterations.

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Safety and Efficacy of Spray Intranasal Live Attenuated Influenza Vaccine: Systematic Review and Meta-Analysis

Perego G, Vigezzi GP, Cocciolo G, Chiappa F, et al.

Vaccines (2021); 9(9): 998

OBJECTIVE:

- To examine the safety and efficacy of live attenuated influenza nasal spray vaccine (LAIV) in adults, including those with underlying clinical conditions, pregnant women and children under 24 months of age.

METHOD:

- **Countries:** United States, Republic of South Africa, Russia, Norway, Thailand, Finland, Netherlands and United Kingdom.
- **Period:** 1976 to 2020.
- **Sample:** 1,278 articles were identified, from which duplicates, non-original articles, those covering different topics and those published in other languages were excluded. After screening, 144 articles were reviewed in full, of which 22 were included in the systematic review.
- **Sources:** Two electronic databases (PubMed/Medline and Scopus).
- **Variables:** Efficacy was assessed by seroconversion rates, defined as a 4-fold increase in antibody, and all systemic and local adverse effects after immunisation were considered to assess safety.
- **Analysis:** The Preferred Reporting Items for Systematic Review and Meta-analyses 2020 (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed to guide the development and conduct of this systematic review with meta-analysis. The odds ratio (OR) and its 95% confidence interval were calculated for each study based on the number of events for both seroconversion and adverse events in the intervention and control groups, as well as the total sample size.

RESULTS:

- Of the 22 included studies, 18 evaluated the efficacy of LAIV (81.8%), while 16 studied its safety (72.7%).
- In the meta-analysis, LAIV showed an increased likelihood of seroconversion compared to baiting, specifically for serotype A/H1N1 among healthy adults. The pooled OR was 2.26 (95% CI= 1.12-4.54), with a p-value of 0.022, no statistical heterogeneity (Chi2 = 2.28, df = 4, I2 = 0.0%, p = 0.684), based on 488 participants.
- Healthy adults receiving LAIV did not show an increased risk of adverse events compared to those receiving placebo, except for local symptoms such as sore throat (OR= 1.74, p-value = 0.000), nasal congestion (OR= 2.33, p-value = 0.003) and rhinorrhoea (OR= 2.37, p-value = 0.000).

CONCLUSIONS:

- LAIV is safe and effective in terms of seroconversion in healthy adults, considering that it did not lead to an increased risk of adverse events.

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Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group

Lancet (2021); 397(10285): 1637–45

OBJECTIVE:

- To assess the effects of tocilizumab in adult patients hospitalised for COVID-19 with hypoxia and systemic inflammation.

METHOD:

- **Country:** United Kingdom.
- **Period:** April 2020 and January 2021.
- **Sample:** 4,116 adult patients hospitalised for COVID-19 with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein ≥75 mg/L) were eligible to be randomised in a 1:1 ratio to usual standard care alone versus usual standard care plus tocilizumab at a dose of 400 mg-800 mg (depending on weight) administered intravenously. A second dose could be given 12-24 hours later if the patient's condition had not improved.
- **Source:** Randomised, controlled, open-label clinical trial (Randomised Evaluation of COVID-19 Therapy - RECOVERY); evidence obtained from Medine, Embase and MedRxiv.
- **Variables:** all-cause mortality at 28 days; time to hospital discharge; use of invasive mechanical ventilation (IMV); time to effective cessation of IMV; use of renal dialysis.
- **Analysis:** intention-to-treat comparison of both treatment arms. Construction of Kaplan-Meier survival curves to show the evolution of primary and secondary outcome variables.

RESULTS:

- 2,022 patients were randomly assigned to tocilizumab and 2,094 to usual care.
- 621 (31%) of the patients assigned to the tocilizumab treatment group and 729 (35%) of those assigned to usual care died within 28 days (rate ratio 0.85; 95% CI: 0.76-0.94; p=0.0028). Consistent results were observed across all pre-specified patient subgroups, including those receiving systemic corticosteroids.
- Patients assigned to tocilizumab were more likely to be discharged from the hospital within 28 days (57% vs. 50%; rate ratio 1.22; 1.12-1.33; p<0.0001).
- Among those who were not receiving invasive mechanical ventilation at baseline, patients assigned to tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (35% vs. 42%; HR 0.84; 95% CI: 0.77-0.92; p<0.0001).

CONCLUSIONS:

- Tocilizumab improved survival and other clinical outcomes in hospitalized COVID-19 patients with hypoxia and systemic inflammation, regardless of the level of respiratory support received.

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Hospitalisations and Deaths Averted by COVID-19 Vaccination in Navarre, Spain, 2021–2022

Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, Egüés N, et al.

Vaccines (2024); 12(1): 58

OBJECTIVE:

- To evaluate the efficacy of dexamethasone in hospitalised patients with Covid-19, in relation to 28-day mortality.

METHOD:

- **Country:** Spain (Navarra).
- **Period:** January 2021-December 2022 (four semesters).
- **Sample:** Population of Navarra who tested positive for SARS-CoV-2 for the first time in the period analysed.
- **Sources:** COVID-19 vaccination register of Navarra.
- **Variables:** Hospitalisations; Intensive Care Unit (ICU) admissions; deaths.
- **Analysis:** Observational study that took into account sex, age, comorbidities, COVID-19 vaccination status and date of COVID-19 diagnosis. A counterfactual assessment was performed to compare observed outcomes with those that would have occurred in the same population, time period and conditions, assuming that no COVID-19 cases had previously been vaccinated against the disease.

RESULTS:

- By the end of 2021, 84% of the population had received some dose of COVID-19 vaccine, 81% were fully vaccinated and 35% had received a booster dose. By December 2022, coverage increased to 88 per cent, 86 per cent and 56 per cent, respectively, and 18 per cent had received a second booster dose.
- During 2021 and 2022, it was estimated that the vaccines administered prevented 10,767 hospitalisations, 1,375 ICU admissions and 2,232 deaths due to COVID-19. The averted events comprised 16.33 hospitalisations, 2.09 ICU admissions and 3.39 deaths per 1000 population, and 70.9%, 75.5% and 74.7% of the events that would have been expected to occur in the absence of vaccination, respectively.
- Patients with severe chronic diseases without immune compromise accounted for 77% of hospitalisations, 66% of ICU admissions and 68% of deaths prevented by COVID-19 vaccination.
- The majority of deaths averted (78%) were concentrated in the population aged 80 years and older. The percentage of hospitalisations averted was over 70% in people over 50 years of age and in patients with major chronic diseases without immune compromise.
- On average, for every 134, 1,046 and 644 doses of vaccine administered, one hospitalisation, one ICU admission and one COVID-19 death were prevented. That is, one hospitalisation for every 53 people vaccinated, one ICU admission for every 419 and one death from COVID-19 for every 258 people vaccinated were prevented.

CONCLUSIONS:

- The COVID-19 vaccine has had a high impact on reducing the risk of serious health outcomes from the disease.

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