Breakthroughs and Blockbusters:

A Comprehensive Analysis of New Drug Launches and Established Market Leaders

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Contents	

Introduction

The pharmaceutical industry is navigating a complex landscape of opportunities and challenges in 2024. Recent scientific breakthroughs are ushering in new treatment options, yet obstacles such as governmental regulations, soaring costs, substantial patient burden, and global tensions are dampening investor enthusiasm. This report delves into the analysis of promising drug candidates poised to reach significant milestones, distinguishing themselves as potential blockbusters or groundbreaking therapies. Additionally, we provide an in-depth examination of the projected timelines for upcoming drug launches and essential clinical trial particulars for the year ahead.

Our investigation further evaluates the anticipated market impact of a diverse range of novel medications across various therapeutic domains, including neuroscience, endocrinology, oncology, rare diseases, and chronic blood disorders slated for release in 2024. Leveraging the AdisInsight database, we scrutinize the market revenue forecasts for established comparator drugs and assess how the introduction of new treatments might influence market dynamics.

We identify key medications generating substantial market interest and analyze their potential effects on revenue generation and market dominance. Furthermore, we furnish insights into the regulatory milestones governing these drugs and their implications for market entry. Our analysis also encompasses an examination of corporate agreements, mergers/acquisitions, and strategic partnerships formed within the industry, shedding light on evolving collaboration and partnership strategies among pharmaceutical giants pertaining to these drugs.

Breakthrough Therapies

From new vaccines, new formulations for biologics and small molecules, to groundbreaking gene therapies for challenging disorders, the past few years have seen remarkable medical advancements. These innovations provide opportunities for people to protect themselves from infectious diseases and mitigate the effects of other disorders.

We have identified 9 breakthrough therapies for the past few years that have had a major impact on the pharmaceutical industry.

Aflibercept (EYLEA HD)

MoA: Placenta growth factor inhibitors; Vascular endothelial growth factor A inhibitors

Drug Class: Recombinant fusion proteins

Originator: Regeneron Pharmaceuticals

Licensed by: Bayer HealthCare Pharmaceuticals; Bayer Yakuhin; Sanofi; Santen Pharmaceutical

Aflibercept (EYLEA HD)

Age-related macular degeneration (AMD) and diabetic retinopathy (DR) are two of the leading causes of visual impairment worldwide. Although most of the treatments are effective in treating AMD and DR, they are not effective in reducing the patients' burden of retinal disease (for example- suboptimal compliance and a real risk of vision loss). Thus, there is an unmet need for an alternative treatment with an improved safety and efficacy profile.

Aflibercept (EYLEA HD) is a treatment for age-related macular degeneration (AMD) and diabetic retinopathy (DR) that aims to improve safety and efficacy profiles

Prevalence

As of October 2023, the occurrence of AMD is on the rise, with projections suggesting that there will be 288 million cases worldwide by 2040 due to the increasing rate of diagnosis of the disease. Therefore, there is a clear need for a more effective and less burdensome treatment for AMD.

The prevalence of AMD is expected to rise significantly by 2040, highlighting the need for more effective and less burdensome treatments.

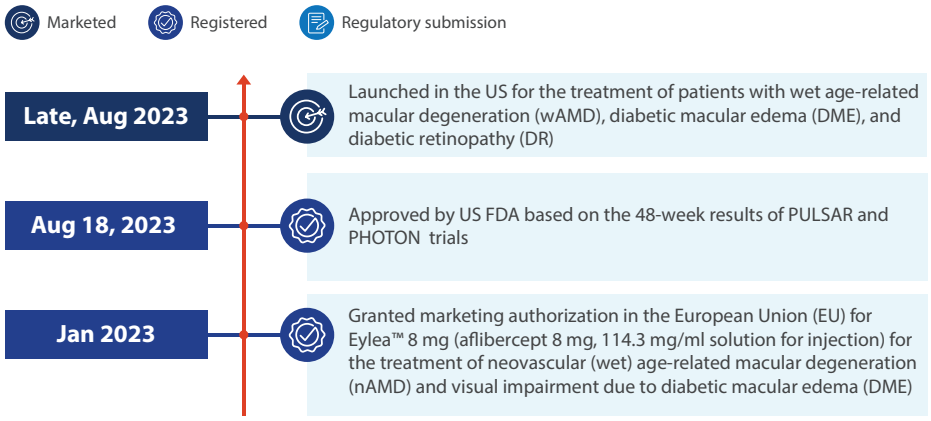
What is the need for Eylea HD

Regeneron Pharmaceuticals developed aflibercept for the treatment of glaucoma, diabetic retinopathy, retinopathy of prematurity, choroidal neovascularisation, diabetic macular oedema, wet age-related macular degeneration, branch retinal vein occlusion, eye disorders, central retinal vein occlusion, colorectal cancer, and retinal oedema.

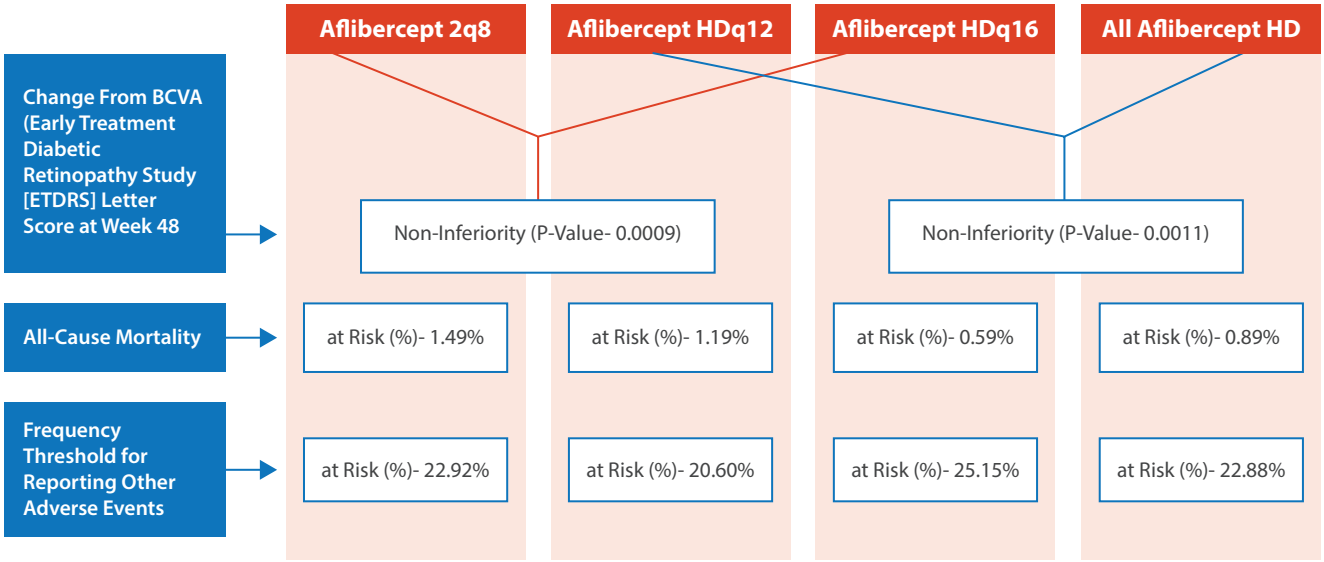
EYLEA HD, the high-dose, 8 mg formulation of aflibercept, can be administered in a single dose, simplifying patient lives and reducing the need for frequent visits

Initially, the market was dominated by the low-dose 2 mg formulation of Eylea, but over time patients needed more frequent doses and had to visit their eye care provider or retinal specialist for injections, which became a financial burden. In response, Regeneron created a high-dose 8 mg formulation of aflibercept (EYLEA HD) that can be administered in a single dose, eliminating the need for patients to visit their eye care provider, thereby simplifying their lives.

Regulatory Milestone

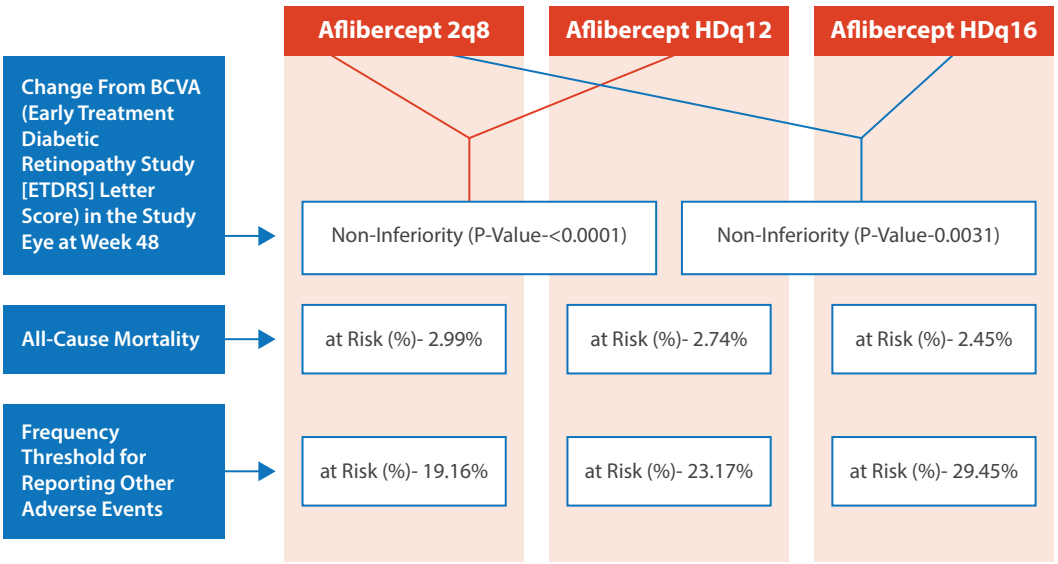


PULSAR for wAMD



*Aflibercept 2q8- aflibercept 2 mg administered every 8 weeks , Aflibercept HDq12- High dose (HD) aflibercept administered every 12 weeks, Aflibercept HDq16- high dose (HD) aflibercept administered every 16 weeks, All Aflibercept HD- participants from aflibercept HDq12 and aflibercept HDq16, BCVA- Baseline in Best Corrected Visual Acuity

PHOTON for DME



*Aflibercept 2q8- aflibercept 2 mg administered every 8 weeks, Aflibercept HDq12- High dose (HD) aflibercept administered every 12 weeks, Aflibercept HDq16- high dose (HD) aflibercept administered every 16 weeks, BCVA- Baseline in Best Corrected Visual Acuity

Influence on Eylea's market performance

Sales of Eylea have seen a steady increase over the past few years. The data indicates a positive trend in sales until 2022. However, the product experienced a downturn in the following year, with a decline in sales (as per fig 1). This decline could be attributed to various factors such as the launch of EYLEA® HD in August 2023. Sales of Eylea disappointed investors and related stocks went down. It will be interesting to see how the sales of Eylea evolve in the coming years and whether the drug will regain its popularity in the market.

Market revenue of Eylea (12 years) and post launch of EYLEA® HD (sales data for Eylea HD)

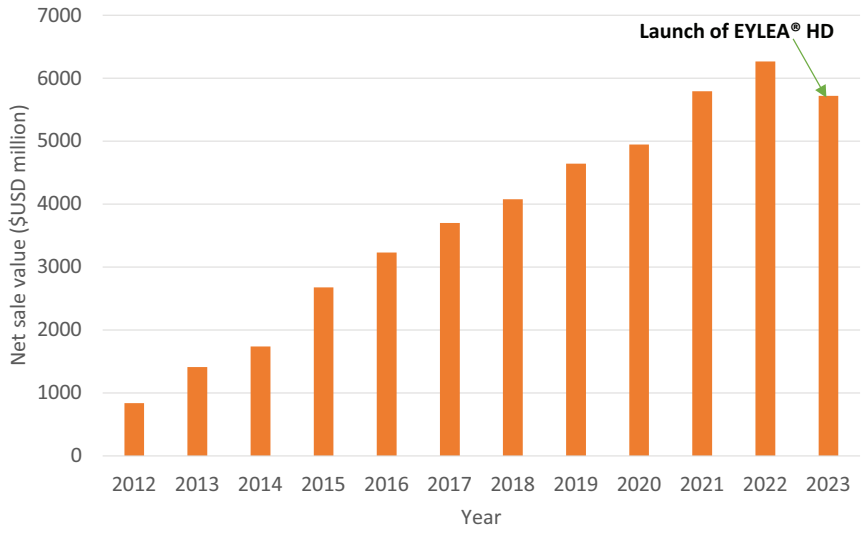


Fig 1: Change in market revenue of Eylea post launch of EYLEA HD

Sales comparison between Eylea and Eylea HD

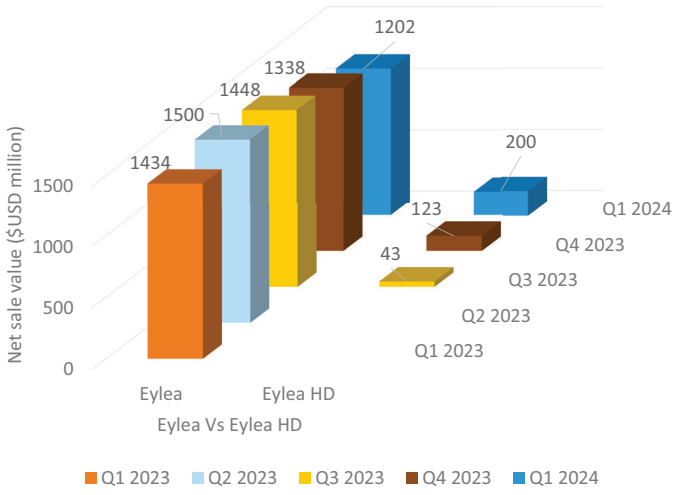


Fig 2: Market revenue of Eylea versus EYLEA HD

Budesonide controlled release (Kinpeygo/ Nefecon/TARPEYO)

MoA: Glucocorticoid receptor agonists

Drug Class: Corticosteroids; Small molecules

Originator: Uppsala University

Licensed by: Everest Medicines; STADA Arzneimittel; Viatris Inc

IgA nephropathy (IgAN) can lead to end-stage kidney disease (ESKD) if not controlled, and is associated with a higher risk of complications, emphasizing the need for effective treatment

Budesonide controlled release (Kinpeygo/ Nefecon/TARPEYO)

Globally, IgA nephropathy (IgAN) is the most common primary glomerulonephritis, which results in progression to end-stage kidney disease (ESKD) if not controlled. Also, IgA nephropathy is associated with an increased risk of complications like cardiovascular disease, infections, and kidney failure. Effective treatment is necessary to slow the progression of the disease, manage symptoms, and reduce the risk of complications.

Prevalence

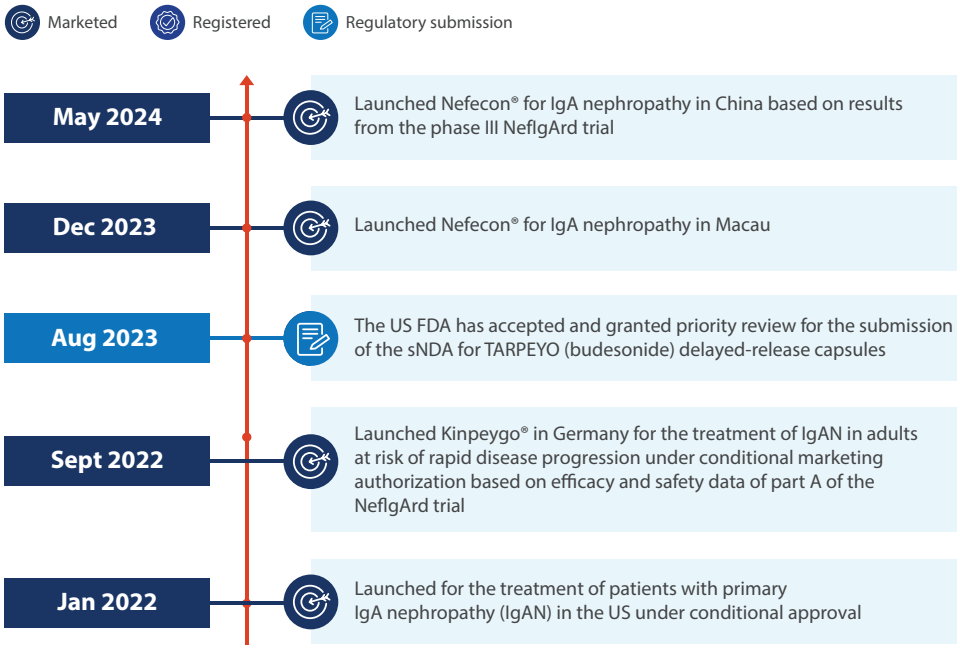
- As of December 2023, adult IgAN has the highest estimated incidence of at least 25 cases per million population yearly worldwide, surpassing other glomerular diseases such as membranous nephropathy (12 pmp/year), minimal change disease (8 pmp/year), focal segmental glomerulosclerosis (6 pmp/year), and membranoproliferative glomerulonephritis (2 pmp/year).
- The prevalence of IgAN greatly differs based on geographic location, with Asia having the highest frequency, followed by Europe and Africa having the lowest.

What is the need for budesonide controlled release

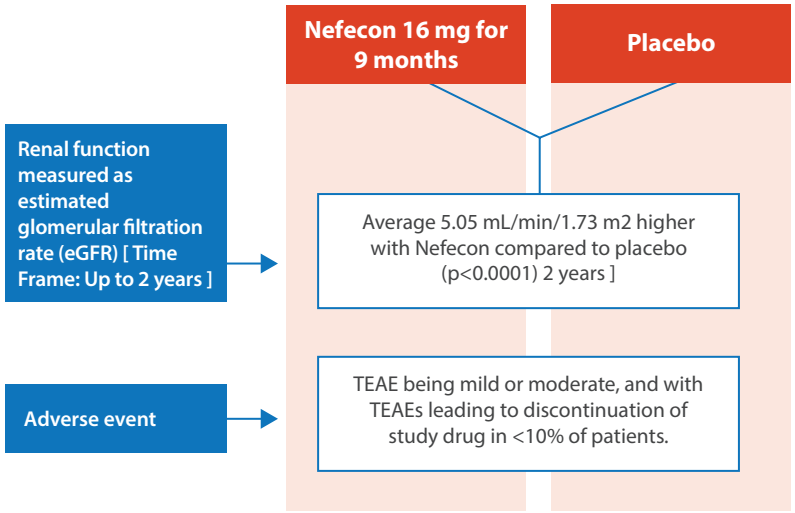
Previously, there were no direct treatments targeting IgA. Treatment for IgA nephropathy may involve medication for blood pressure control, inflammation reduction, and immune system suppression, along with lifestyle modifications like a healthy diet and weight management. A successful treatment plan is essential for enhancing the quality of life and long-term prognosis for individuals with IgA nephropathy. It can aid in preserving kidney function, delaying the need for dialysis or transplant, and minimizing the risk of disease-related complications. To effectively treat IgA nephropathy (IgAN) and improve the quality of life for patients, Calliditas Therapeutics (formerly Pharmalink) has developed an enteric-coated, controlled-release formulation of the corticosteroid budesonide which is the first and only FDA-approved treatment for IGA nephropathy to significantly reduce the loss of kidney function.

IgA nephropathy evidently needed direct treatments, as previous therapies were not designed for the disease, and a successful treatment plan is crucial for enhancing quality of life and long-term prognosis

Regulatory Milestones: Approvals and Future Prospects



NeflgArd trial for IgAN



*TEAE- Treatment-emergent adverse events

Driving Growth: Impact of budesonide controlled release revenue on company's profits

Calliditas Therapeutics AB is a specialty pharmaceutical company. It is focused on developing pharmaceutical products for patients with a significant unmet medical need.

Budesonide controlled release is the first and only FDA-approved treatment for IgA nephropathy that significantly reduces the loss of kidney function, offering a new hope for patients with the disease

After a noticeable decline in 2020 (due to the COVID pandemic), Calliditas Therapeutics has been gradually recovering and gearing up since. The launch of **budesonide controlled release (2022)** had a significant impact on the revenue of Calliditas Therapeutics. Budesonide controlled release's strong market presence and reputation for delivering high-quality and effective treatment have helped raise awareness for Calliditas Therapeutics' products among patients, healthcare providers, and payers. This has resulted in increased uptake and adoption of Calliditas Therapeutics' treatments, further boosting revenue for the company.

Effect of budesonide controlled release revenue on company's profit

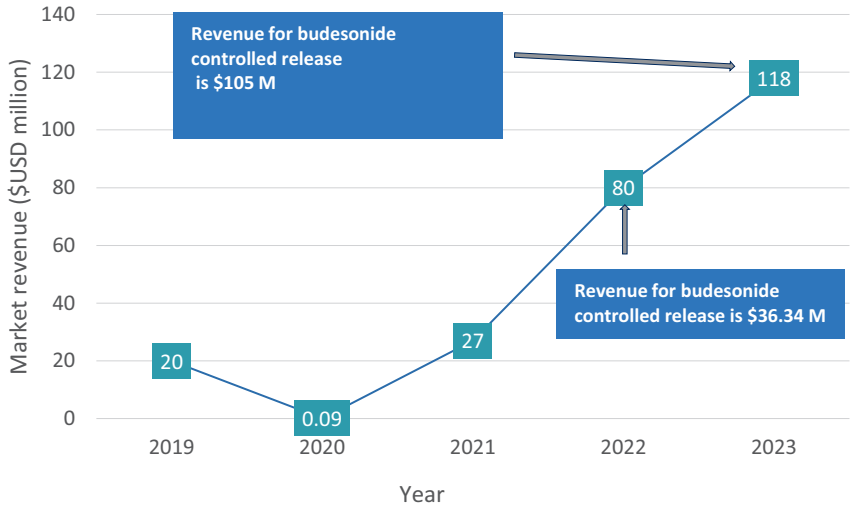


Fig 3 : Impact of budesonide controlled release revenue on company's revenue

Efanesoctocog alfa (Altuviiio/BIVV-001)

MoA: Factor VIII replacements

Drug Class: Blood coagulation factors; Recombinant fusion proteins

Originator: Amunix

Developer: Sanofi

Licensed by: Swedish Orphan Biovitrum

Efanesoctocog alfa (Altuviiio/BIVV-001)

Haemophilia A is a genetic bleeding disorder caused by a lack of factor VIII, resulting in prolonged and excessive bleeding either spontaneously or following injury. Von Willebrand disease is another bleeding disorder characterized by low levels of clotting protein in the blood. Various medications, such as Advate, Recombinate, Eloctate, and Hemlibra, are available for treating hemophilia A. However, a major challenge in treatment is the development of inhibitors, which prevent factor treatment from being effective in slowing or stopping bleeding episodes.

Hemophilia A and von Willebrand disease are bleeding disorders requiring effective treatment to manage symptoms and prevent complications

Prevalence

- According to the Centers for Disease Control and Prevention (October 2023), hemophilia A occurs in one out of 5000 males and accounts for 80% of hemophilia cases.
- More than 400,000 males worldwide are affected by hemophilia A, with a significant number going undiagnosed in developing countries.

Hemophilia A affects approximately 1 in 5000 males worldwide, with a significant number undiagnosed in developing countries

What is the need for Efanesoctocog alfa

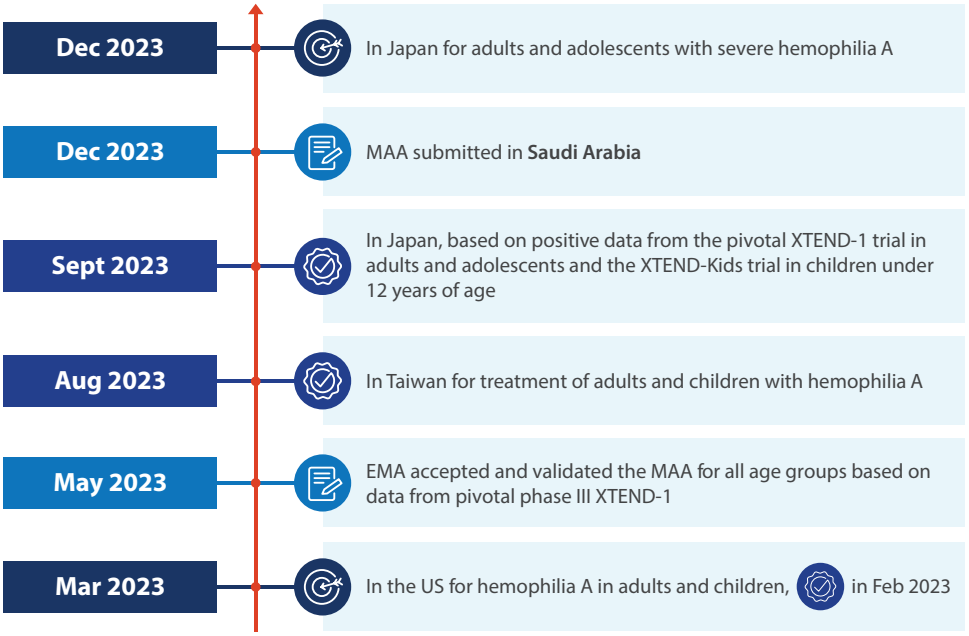
Efanesoctocog alfa (previously known as BIVV 001) is a fully recombinant antihemophilic factor, factor VIII therapy, developed by Bioverativ (a subsidiary of Sanofi) and Swedish Orphan Biovitrum, for the treatment and prevention of hemophilia A and treatment of von Willebrand's disease.

Efanesoctocog alfa is a fully recombinant antihemophilic factor therapy designed to overcome the von Willebrand factor ceiling and extend its time in circulation.

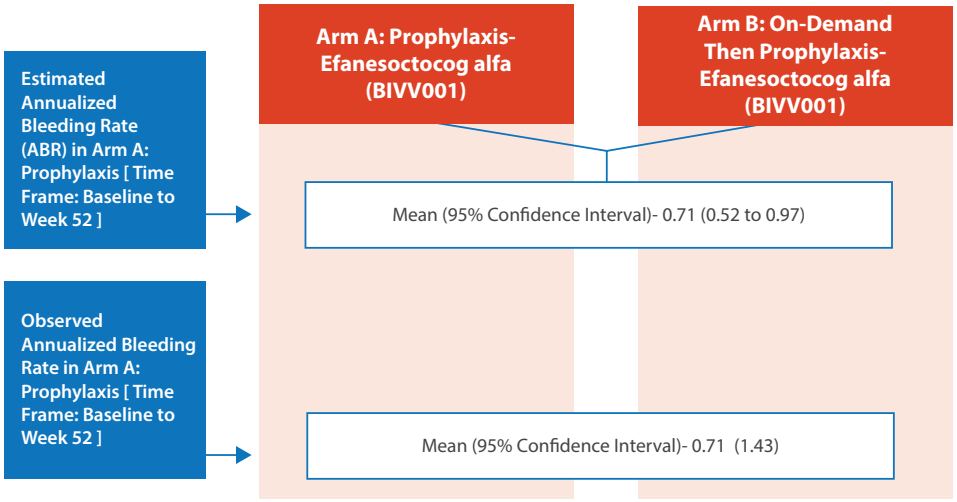
Efanesoctocog alfa fuses four different proteins to address the challenges of hemophilia A and builds on the company's existing Fc fusion technology by adding a region of von Willebrand factor (vWF) and XTEN polypeptides to potentially extend its time in circulation. It is the only investigational factor VIII therapy that is designed to overcome the vWF ceiling, which is believed to impose a half-life limitation on current factor VIII therapies. For patients unwilling to receive novel therapies, such as monoclonal antibodies or gene therapy, efanesoctocog alfa will likely be an interesting option.

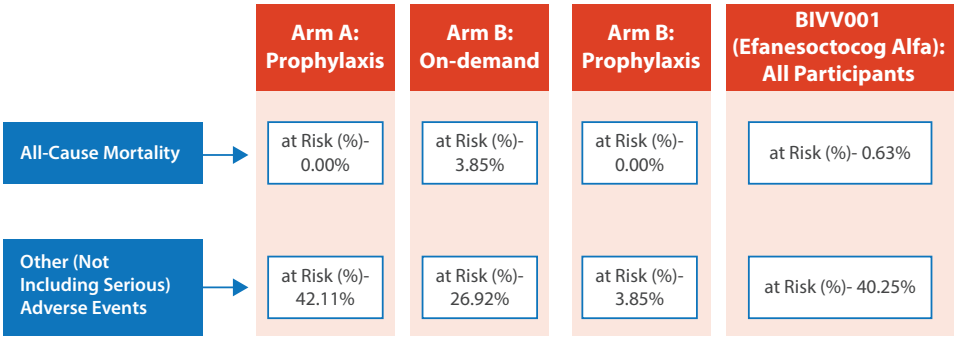
Regulatory Milestones

Marketed Registered Regulatory submission



XTEND-1 trial for haemophilia A





XTEND-Kids trial for haemophilia A

	BIVV001: Participants aged <6 Years	BIVV001: Participants aged 6 to <12 Years
Number of Participants With Neutralising Antibodies (Development of Inhibitors) Directed Against Factor VIII	Count of Participants (0.0%)	Count of Participants (0.0%)
All-Cause Mortality	At Risk (%)- 0.00%	At Risk (%)- 0.00%
Serious Adverse Events	At Risk (%)- 13.16%	At Risk (%)- 11.11%

Driving Growth: Impact of efanesoctocog alfa's revenue on Company's profit

Sanofi's revenue is driven by strong performance across its key business segments, including pharmaceuticals and consumer healthcare products. The company has also made strategic acquisitions and invested in research and development to drive innovation and expand its product portfolio.

Furthermore, Sanofi has successfully launched several new products in recent years, contributing to revenue growth and market share expansion. The company's robust pipeline of new drugs is expected to drive future growth and maintain its competitive position in the global healthcare market.

Overall, Sanofi's solid financial performance, innovative product portfolio, and strong market position indicate a promising outlook for continued revenue growth in the years ahead.

The revenue generated from Altuviiio drug sales has had a significant impact on Sanofi's overall revenue. As one of the company's top-selling drugs, Altuviiio has contributed substantially to Sanofi's financial performance and has played a key role in driving growth and profitability for the company in 2023. With strong sales and market demand for Altuviiio ($14.00M), Sanofi has been able to leverage its success to further expand its product portfolio and continue to drive innovation in the pharmaceutical industry. Recently launched and future pharma assets are expected to generate over €10 billion of annual sales by 2030, driven by late-stage pipeline assets and recently launched products including ALTUVIIIO®, Sarclisa®, and Tzield®

Analyzing the effect of Altuviiio's revenue on company profits

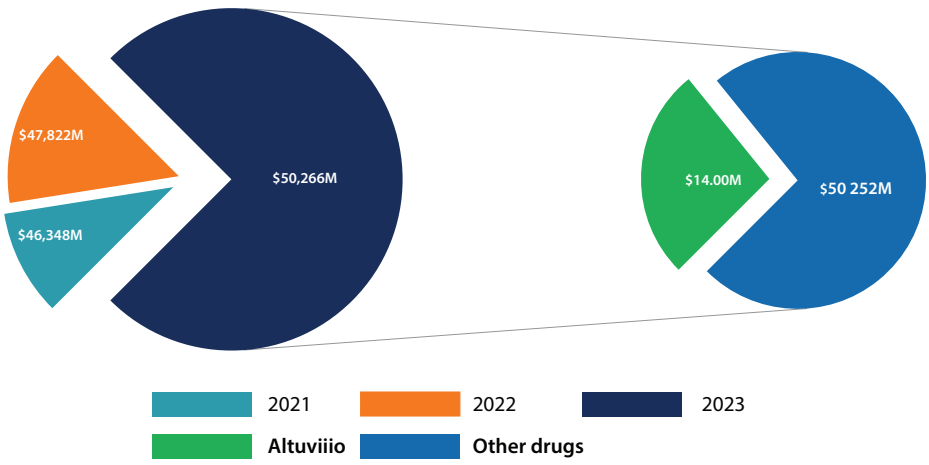


Fig 4: Impact of Altuviiio revenue on company's profits

Exagamglogene autotemcel (Exa-cel /CASGEVY™)

Blood disorders are a group of medical conditions that affect the blood's ability to function properly. There are various types of blood disorders, each with its own set of symptoms and complications. There are many types of blood disorders:

- Hemophilia is a blood disorder where the blood does not clot properly, leading to excessive bleeding and bruising
- Sickle cell anemia is another blood disorder that causes red blood cells to become malformed, leading to blockages in blood vessels and severe pain
- Thalassemia is a genetic disorder that affects the production of hemoglobin in the blood, leading to anaemia.

Exagamglogene autotemcel (Exa-cel / CASGEVY™)

MoA: Cell replacements; Fetal haemoglobin expression stimulants

Drug Class: Gene therapies; Haematopoietic stem cells therapies

Originator: CRISPR Therapeutics

Licensed by: Vertex Pharmaceuticals

Blood disorders affect the blood's ability to function properly, with various types including hemophilia, sickle cell anemia, and thalassemia

Prevalence

- The Centers for Disease Control and Prevention reported in July 2023 that sickle cell disease (SCD) impacts around 100,000 Americans. SCD occurs in approximately 1 out of every 365 Black or African-American births, about 1 out of every 16,300 Hispanic-American births, and approximately 1 in 13 Black or African-American infants are born with sickle cell trait
- As of December 2023, around 3% of the world's population are carriers of β-thalassaemia. The regions most affected include Africa, the Mediterranean basin, the Middle East, the Indian subcontinent, Southeast Asia, Melanesia, and the Pacific islands.

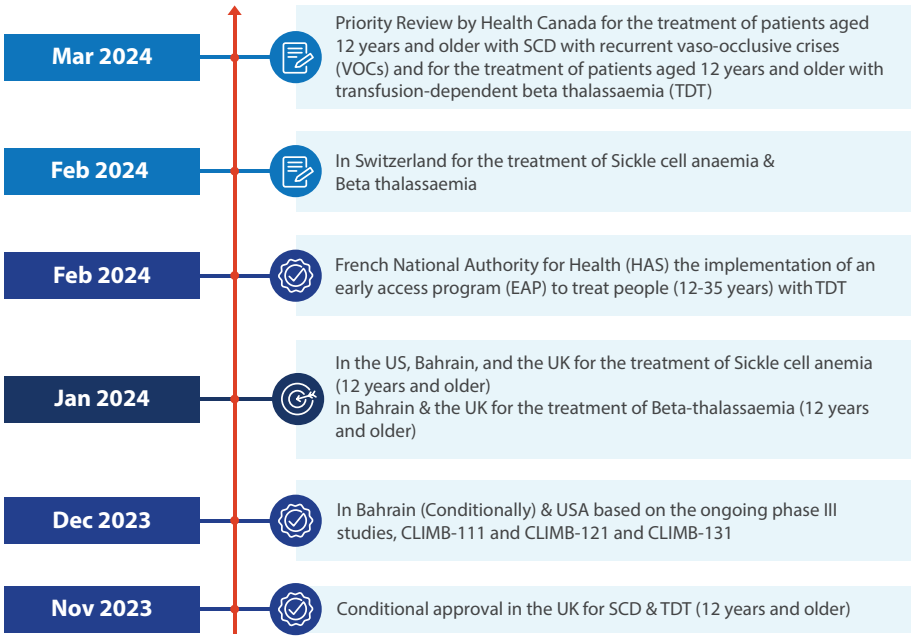
What is the need for CASGEVY

The management of sickle cell disease (SCD) and beta-thalassemia (TDT) poses a challenge due to the genetic nature of these blood disorders, which can greatly affect a patient's quality of life and may require frequent hospitalizations. Previously, a variety of treatments such as Xyndari, Oxbryta, Siklos, Droxia, Niprisan, and Reblozyl were introduced for the treatment of SCD and TDT. Exagamglogene autotemcel (exa-cel) is the first FDA-approved Crispr gene-editing drug developed using the CRISPR/Cas9 technology, by CRISPR Therapeutics, in collaboration with Vertex Pharmaceuticals (under the license from CRISPR Therapeutics), for the treatment of patients suffering from SCD. This stem cell therapy holds great promise for individuals suffering from debilitating, life-altering diseases that currently have limited treatment options . This innovative treatment has the potential to provide much-needed relief for patients who are facing symptoms with no curative treatments available.

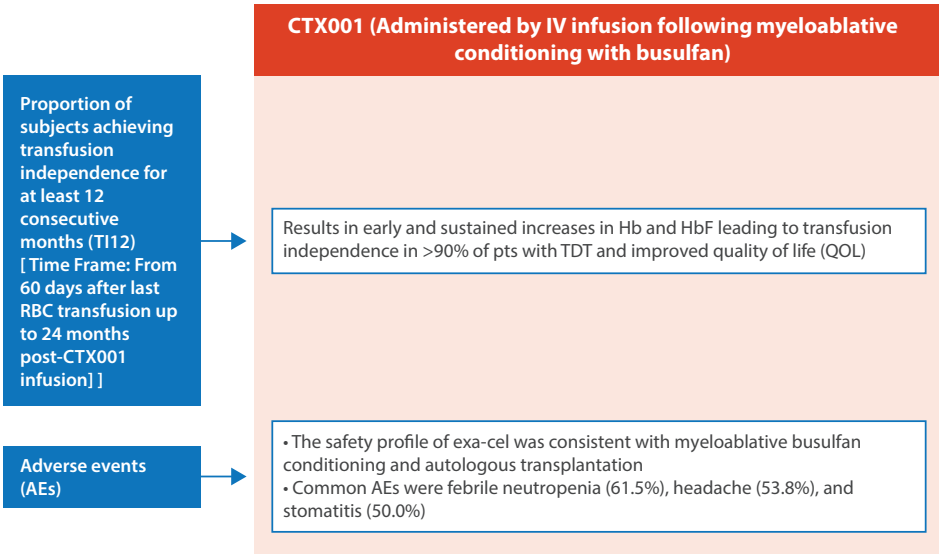
CASGEVY, a Crispr gene-editing drug, holds promise for treating sickle cell disease and beta-thalassemia, offering relief for patients with limited treatment options.

Regulatory Milestones

Marketed | Registered | Regulatory submission

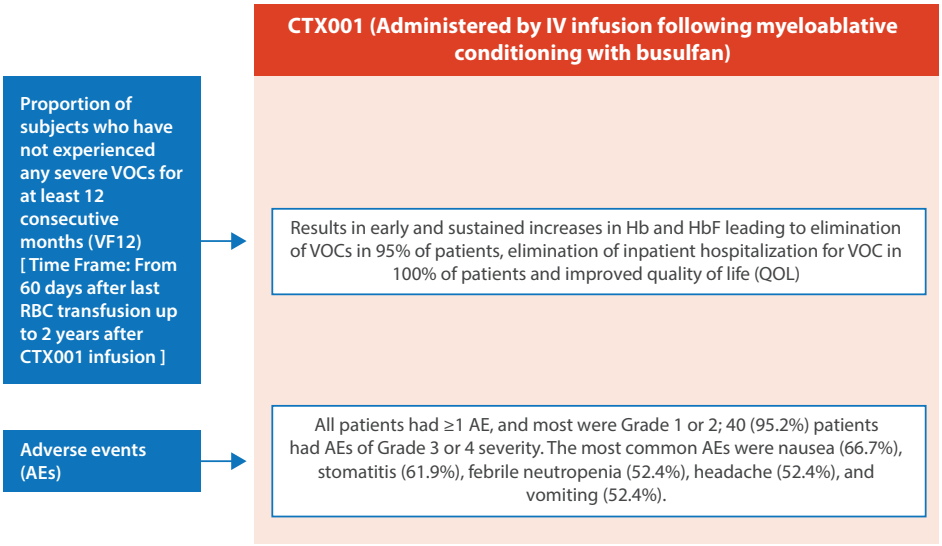


Climb-111 trial for beta-thalassaemia



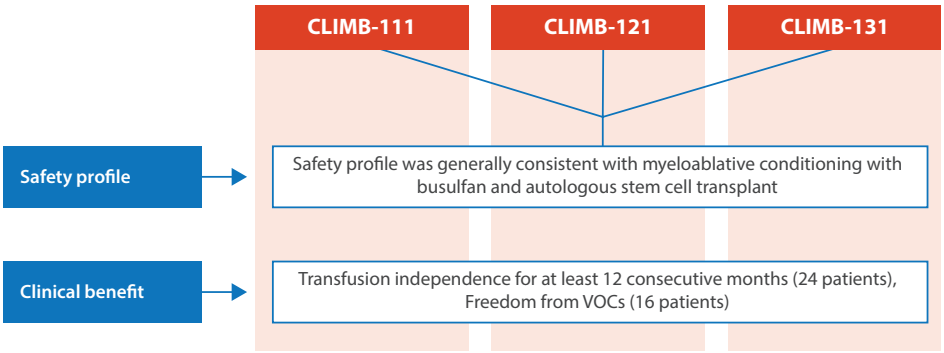
*HbF- Fetal hemoglobin, Hb- hemoglobin

Climb-121 trial for sickle cell anaemia



*HbF- Fetal hemoglobin, Hb- hemoglobin

Climb-131 trial for sickle cell anaemia and beta-thalassaemia



*VOCs - vaso-occlusive crises

Driving Growth: Impact of CASGEVY's revenue on company's profit

Over the past six years, analysis has shown that the revenue for CRISPR Therapeutics experienced a decline in 2020 due to the economic downturn caused by the COVID-19 pandemic. Additionally, in 2022, revenue further decreased as the company faced regulatory challenges common among gene editing companies.

However, despite these setbacks, the forecast for 2024 looks promising after the launch of CASGEVY. The innovative product has already generated a substantial revenue of $71.08 USD million to date (March 2024), indicating potential growth and success in the coming years. With the momentum gained from this new product, CRISPR Therapeutics is poised for a potentially lucrative year in 2024.

Market revenue of CRISPR therapeutics (6 years analysis)

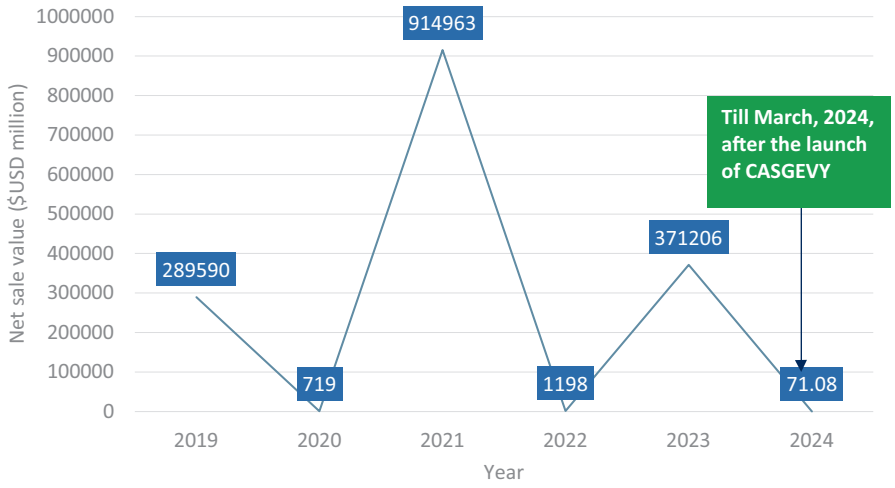


Fig 5: Effect on market revenue after the launch of CASGEVY

Betibeglogene autotemcel - bluebird bio (Lovo-cel / bb1111/LYFGENIA™/ Zynteglo)

Sickle cell disease and beta-thalassaemia significantly impact patients' quality of life, leading to frequent hospitalizations.

Inherited blood disorders such as sickle cell disease and beta-thalassaemia can cause severe pain, organ damage, and a shortened life span. Through a single administration, this gene therapy targets the underlying causes of SCD and transfusion-dependent beta-thalassaemia and aims to make patients transfusion-independent or free from VOC, leading to a significant improvement in quality of life and physical performance. The interest in gene therapies for these conditions stems not only from the potential for a cure, but also from concerns about the effectiveness, accessibility, and side effects of current treatments.

Betibeglogene autotemcel - bluebird bio (Lovo-cel / bb1111/LYFGENIA™/ Zynteglo)

MoA: Cell replacements

Drug Class: Gene therapies; Haematopoietic stem cells therapies

Originator: Genetix Pharmaceuticals, Bluebird bio

Gene therapies offer the potential for a cure and significant improvement in quality of life for patients with sickle cell disease and beta-thalassaemia

What is the need for Lovo-cel

According to a recent assessment by the Institute for Clinical and Economic Review (ICER), both **CASGEVY** and **Lovo-cel** have the potential to offer significant health benefits compared to standard care, given the severity of the diseases and the success rates of treatment, despite uncertainties surrounding long-term effectiveness and potential risks.

Lovo-cel and CASGEVY have the potential to offer significant health benefits compared to standard care for sickle cell disease and beta-thalassaemia

Lovo-cel is a β-globin gene therapy being developed by Bluebird Bio (formerly Genetix Pharmaceuticals), for the treatment of sickle cell anaemia and β-thalassaemia and is the first cell-based gene therapy for the treatment of sickle cell disease (SCD) in patients 12 years and older.

Regulatory Milestones

Marketed Registered Regulatory submission

2024	Expected commercial launch of LYFGENIA for Sickle cell anaemia in early 2024
Dec 2023	In USA for the treatment of Sickle cell disease in patients ages 12 and older
Apr 2023	BLA submitted to the US FDA for Sickle cell anaemia based on efficacy results from 36 patients in the HGB-206 Group C cohort with a median of 32 months of follow-up and two patients in the HGB-210 study
June 2022	Launched Zynteglo for Beta-thalassaemia in Denmark, Poland and Netherlands

HGB-206 and HGB- 210 trials for Sickle cell anaemia

Experimental: Group C (HGB-206)
bb1111 is administered by IV infusion following myeloablative conditioning with busulfan

Experimental: bb1111 (HGB-210)
Drug Product is administered by IV infusion following myeloablative conditioning with busulfan

Pooled analysis of HGB-206 Group C cohort and phase III HGB-210

All patients had stable production of anti-sickling adult hemoglobin after infusion through last follow-up (median >40% HbAT87Q), and VOEs and sVOEs were eliminated or significantly reduced in all patients

*VOEs- vaso-occlusive events, sVOEs- severe vaso-occlusive events

The launch of betibeglogene autotemcel: A failed attempt to boost company's revenue

Bluebird Bio saw an increase in market revenue in 2020 but experienced a decrease in 2021 and beyond. Despite receiving approval for their sickle cell gene therapy, LYFGENIA, the company did not receive a priority review voucher from the FDA as it was considered too similar to their existing therapy, Zynteglo (another brand for Betibeglogene autotemcel in the European Union). This lack of vouchers, along with laying off about 30% of its staff in 2021 as part of a restructuring plan, contributed to the continued decline in market revenue. Furthermore, competition from companies like Vertex Pharmaceuticals is expected to further hinder Bluebird Bio's market share growth.

Market revenue of Bluebird Bio (5 years analysis)

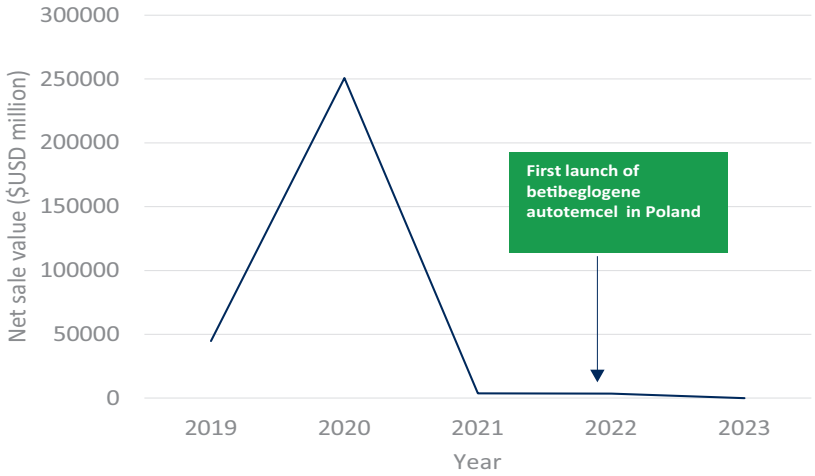


Fig 6: Effect on market revenue after the launch of betibeglogene autotemcel

Mirikizumab (Omvoh)

Mirikizumab (Omvoh)

MoA: Interleukin-23 subunit p19 inhibitors

Drug Class: Monoclonal antibodies

Originator: Eli Lilly and Company

Inflammatory bowel disease (IBD) refers to conditions involving chronic inflammation in the digestive tract. Two common types of IBD are ulcerative colitis, which causes inflammation and ulcers in the colon and rectum, and Crohn's disease, which involves inflammation in different layers of the digestive tract, typically affecting the small intestine. Some patients with IBD experience ongoing symptoms and disease activity despite treatment, leading to the designation of difficult-to-treat IBD. The lack of standardized definitions hinders research and comparison of data on conditions like chronic antibiotic-refractory pouchitis, complex perianal disease, and comorbid psychosocial complications that complicate disease management.

Inflammatory bowel disease (IBD) is a chronic condition characterized by inflammation in the digestive tract, with ulcerative colitis and Crohn's disease being two common types

Prevalence

- According to data published by Medscape in October 2023, approximately 1 million individuals in the United States suffer from ulcerative colitis (UC). The annual incidence of UC is 10.4-12 cases per 100,000 people, with a prevalence rate of 35-100 cases per 100,000 people. UC is three times more prevalent than Crohn's disease
- Ulcerative colitis is more commonly found in the Western and Northern hemispheres, with lower incidence rates in Asia and the Far East
- In Japan, there are over 160,000 patients diagnosed with ulcerative colitis, which equates to about 27 cases per 100,000 people. Unlike in Western nations, UC in Japan shows a male predominance.

What is the need for Omvoh

There are many treatment options available for the treatment of UC. But each of these has shown a certain degree of limitation:

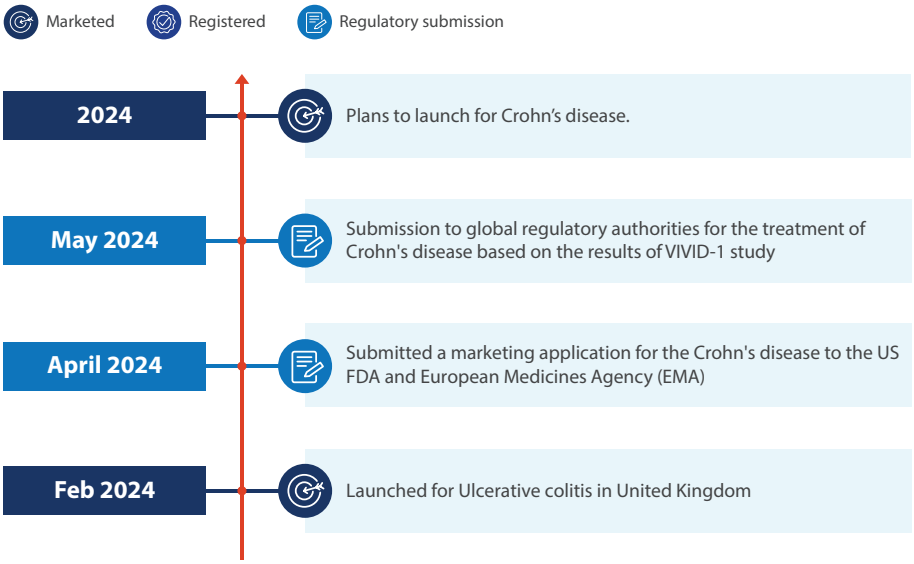
- In cases of severe inflammation, drugs like balsalazide, mesalamine, olsalazine, and sulfasalazine may not provide sufficient relief.
- Corticosteroids are beneficial for short-term use and should be taken at the lowest effective dose.
- Immune system-targeting medications can have harmful side effects such as liver damage, and increased risk of skin cancers, lymphoma, and infections.

Omvoh is a humanized IgG4 monoclonal antibody aiming to treat moderate to severe ulcerative colitis and potentially Crohn's disease

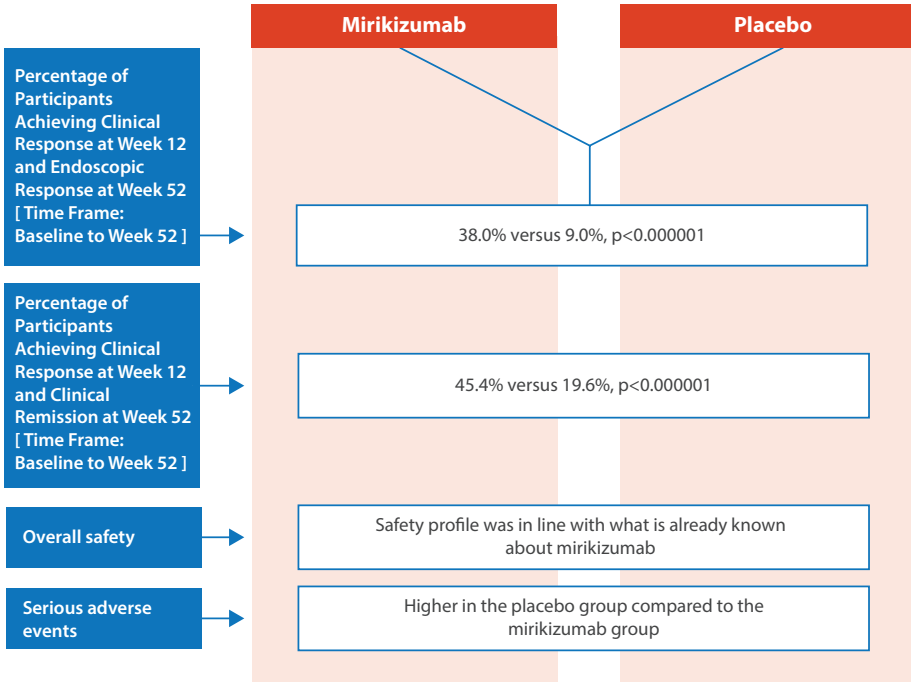
Mirikizumab (formerly LY 3074828) is a humanized IgG4 monoclonal antibody developed by Eli Lilly and Company, for the treatment of ulcerative colitis and Crohn's disease. This antibody binds and inhibits the p19 subunit of interleukin 23. The interleukin 23 (IL-23)/T-helper 17 (TH17) immune axis is the major immune pathway since IL-23 is important for maintaining TH17 responses. This drug is an antagonist of interleukin-23p19 (IL-23p19) designed for adults suffering from moderate to severe ulcerative colitis. This indicates the medication specifically aims at the p19 subunit of IL-23, which is responsible for the bowel inflammation associated with the disease. It took some time for the drug to demonstrate its efficacy to the FDA, primarily due to the results of phase 3 trials.

Omvoh celebrated a victory with the European Medicines Agency (EMA), but the multinational pharmaceutical company has bigger plans for the drug. Eli Lilly intends to use it to also treat Crohn's disease, another inflammatory condition. This medication is part of a group of new therapies that work in unique ways. It will help increase the market presence of these therapies and provide patients with potentially better and longer-lasting treatment options.

Regulatory Milestones



VIVID-1 study for crohn's disease



Analyzing Omvoh's revenue impact on company profits: a forecast for 2024

The company experienced a consistent increase in revenue over the past 5 years, with 2023 showing its highest revenue of $34.12 billion. In the fourth quarter of 2023, revenue saw a 28% increase, largely due to the growth of new products (Ebglyss, Jaypirca, Mounjaro, Omvoh and Zepbound) from $2.19 billion to $2.49 billion, driven by Mounjaro and Zepbound. Additionally, Growth Products revenue increased by 9% to $5.27 billion in Q4 2023, led by Verzenio and Jardiance. 2023 was a year of significant accomplishments for Lilly, as they provided life-changing medications to more patients than ever before, resulting in strong revenue growth. Marketing, selling, and administrative expenses also rose by 17% to $1.92 billion in Q4 2023, mainly due to costs associated with launching new products and higher incentive compensation expenses. The company anticipates 2024 revenue to fall within the range of $40.4 billion to $41.6 billion, with the growth primarily being driven by New Products in comparison to 2023.

Market forecast of Eli Lilly for 2024

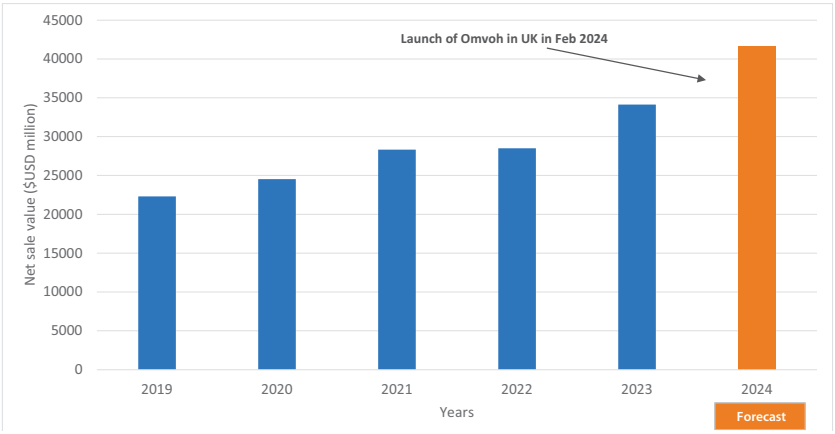


Fig 7: Effect of new product revenue on the market revenue

Abiraterone acetate/niraparib (AKEEGA)

Abiraterone acetate/niraparib (AKEEGA)

MoA: CYP17A1 protein inhibitors; Poly(ADP-ribose) polymerase 1 inhibitors; Poly(ADP-ribose) polymerase 2 inhibitors

Drug Class: Androstenols; Antiandrogens; Small molecules

Originator: Janssen

Prostate cancer ranks as the second most prevalent cancer among men in the United States, following skin cancer. Positioned just below the bladder in front of the rectum, the prostate is a gland that encircles the urethra - the passageway for urine and semen exiting the body - and secretes fluid essential for semen. Prostate cancer is often asymptomatic in the early stages and typically progresses slowly. Over half of prostate cancers stay in the prostate and are not considered life-threatening. Treatment options for localized prostate cancer include surgery or radiation, although in some cases no treatment may be necessary. Metastatic prostate cancer is typically managed with radiation or surgery, potentially in combination with hormone-blocking drugs. Androgen deprivation therapy (ADT) is a type of hormone therapy that blocks the action of androgens like testosterone. Chemotherapy is not typically the first line of treatment for hormone-sensitive metastatic prostate cancer but may be initiated once hormone therapy has become ineffective.

Prevalence

Prostate cancer is the second most prevalent cancer among men in the United States, with treatment options including surgery, radiation, and hormone-blocking drugs

According to the key statistics data published by American Cancer Society in 2024:

- The likelihood of being diagnosed with prostate cancer in a man's lifetime is approximately 1 in 8, with varying risk factors such as age, race/ethnicity, and other variables
- Prostate cancer is more common in older men, with around 6 in 10 cases found in men aged 65 or older, and it is uncommon in men under 40. The average age of diagnosis is around 67 years old
- African American and Caribbean men of African descent have a higher risk of developing prostate cancer compared to men of other racial backgrounds.

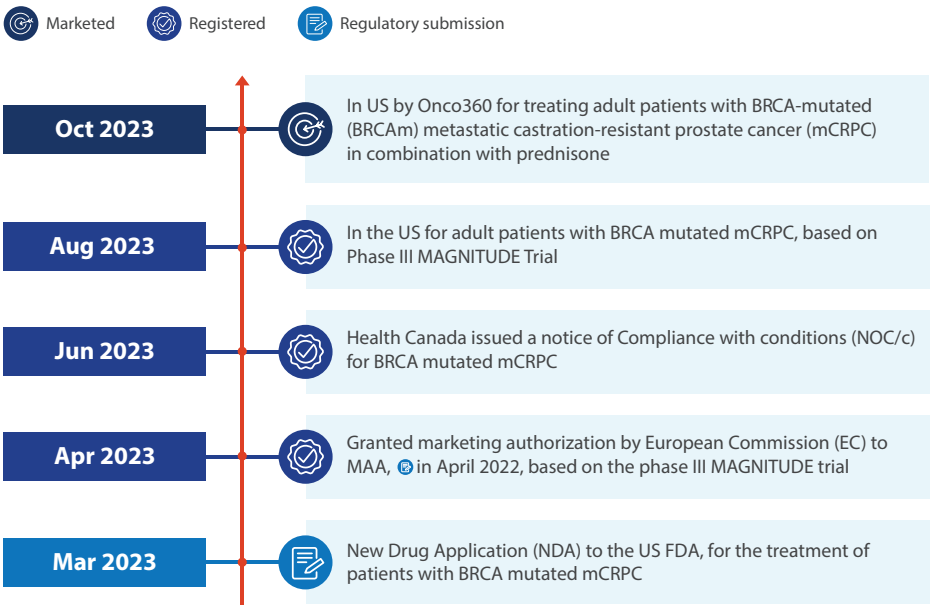
What is the need for AKEEGA

AKEEGA is a dual-action tablet that incorporates a PARP inhibitor and a next-generation hormonal therapy, offering a potential treatment for patients with metastatic castration-resistant prostate cancer

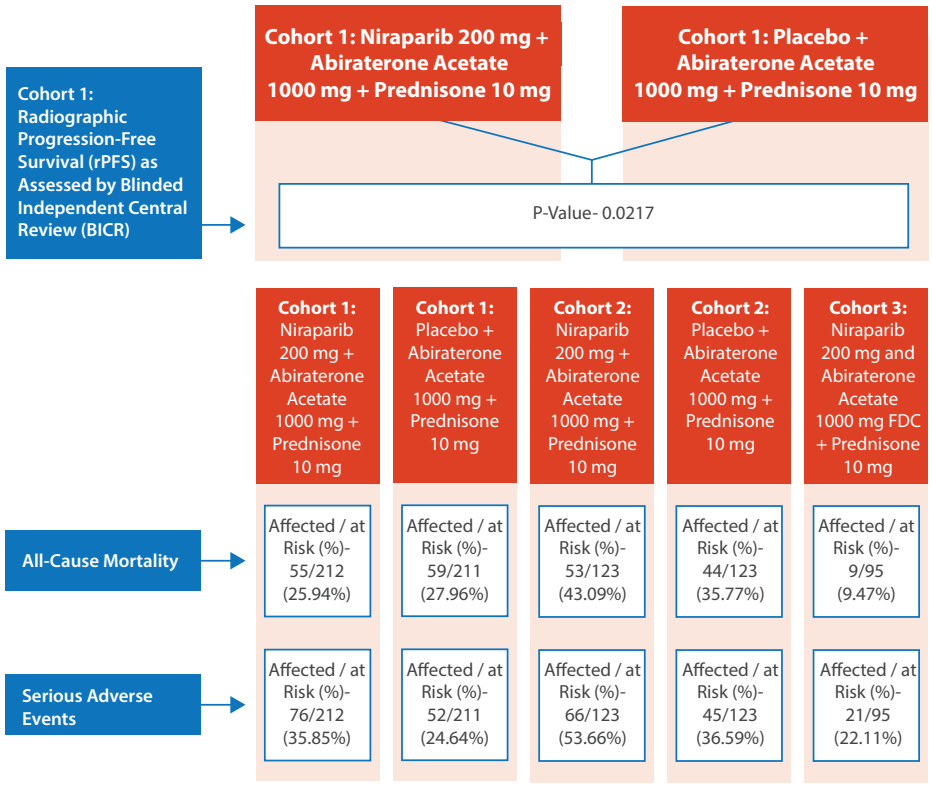
Numerous hormonal therapies such as apalutamide, darolutamide, and enzalutamide are widely available for treating prostate cancer. While these treatments may result in temporary side effects that typically resolve after treatment completion, individuals who have undergone an orchiectomy may experience prolonged effects. Common side effects include erectile dysfunction, decreased libido, hot flashes with sweating, development of breast tissue, depression, cognitive impairment, memory loss, cardiovascular issues, weight gain, muscle mass loss, as well as bone density issues like osteopenia or osteoporosis.

AKEEGA is developed by Janssen and is the pioneer in being the first and sole dual-action (or fixed-dose combination [FDC]) tablet that incorporates a PARP inhibitor (niraparib) and a next-generation hormonal therapy (abiraterone acetate). Its potential to effectively treat patients with suspected or confirmed deleterious BRCA-mutated, metastatic castration-resistant prostate cancer (mCRPC) is crucial in meeting the demand for more efficient treatments. The presence of BRCA gene mutations in approximately 10-15% of mCRPC patients indicates a more aggressive form of the disease.

Regulatory Milestones



MAGNITUDE study for prostate cancer



Driving Growth: Impact of AKEEGA revenue on company's profit

Janssen Pharmaceuticals experienced consistent growth in previous years but saw a decline in revenue in 2021 due to the global Covid-19 pandemic, resulting in a temporary pause in Johnson & Johnson's vaccine production. However, the company has been steadily increasing its revenue in subsequent years. The introduction of AKEEGA in October 2023 led to a significant rise in revenue, and it is anticipated that revenue will continue to increase in the future, as shown by the first quarter 2024 revenue data of 21383 USD million.

Market revenue for Janssen Pharmaceuticals

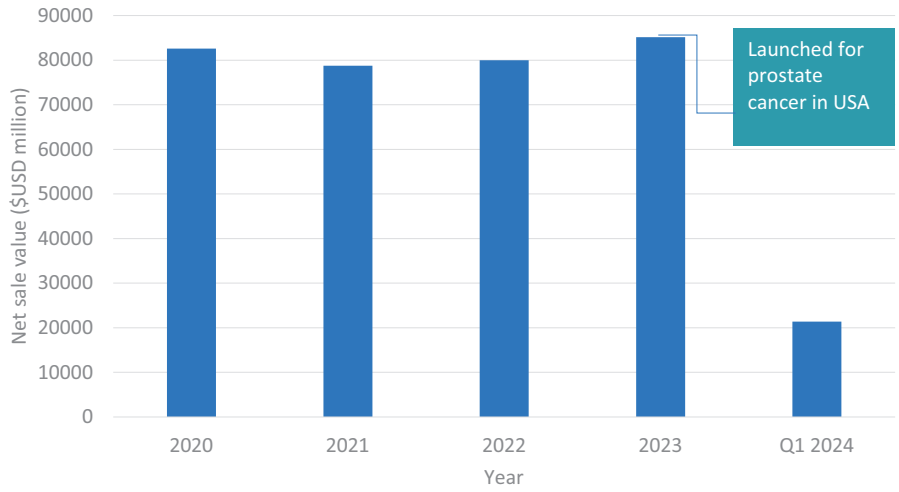


Fig 8: Effect on market revenue after the launch of AKEEGA

RSVpreF (Abrysvo)

RSVpreF (Abrysvo)
MoA: Immunostimulants
Drug Class: Subunit vaccines
Originator: Pfizer

Respiratory syncytial virus (RSV) infections remain a significant public health issue, especially for infants and individuals over the age of 65. This common upper respiratory infection can lead to hospitalizations in severe cases and typically occurs seasonally with symptoms resembling those of influenza and COVID-19. RSV is a primary reason for hospitalization in infants and young children with acute lower respiratory infections.

Prevalence

Respiratory syncytial virus (RSV) infections are a significant public health issue, especially for infants and individuals over the age of 65

The data published in Nature in 2024 reveals that the estimated incidence rates of RSV infection and illness (with at least one symptom) were 47.2 and 15.7 per 100 person-years, respectively, but varied depending on the site and year. The incidence of infection (regardless of symptoms) was highest among children under the age of one and between the ages of one and four years (72.6 and 79.1 per 100 person-years, respectively), and lowest among individuals aged 65 years and older (17.8 per 100 person-years).

What is the need for Abrysvo

Pfizer's Abrysvo demonstrated sustained high levels of protection against RSV infections for two consecutive seasons following a single dose and showed an efficacy rate of 77.8% in preventing RSV lower respiratory tract disease in adults aged 60 and above

The current option for prevention and treatment, Palivizumab, is only available to certain groups in well-resourced areas. However, several vaccine candidates are being tested on humans, which target young children, older adults, and pregnant women.

Abrysvo is a prophylactic vaccine, being developed by Pfizer, for the prevention of RSV infection and respiratory tract infections in infants through maternal immunization, and in adults and elderly through direct vaccination.

Abrysvo, a dual-acting vaccine, demonstrated sustained high levels of protection against both RSV A and RSV B infections for two consecutive seasons following a single dose. In adults aged 60 and above, Abrysvo showed an efficacy rate of 77.8% in preventing RSV lower respiratory tract disease with three or more symptoms during the second full RSV season.

US drugmaker Pfizer and British pharmaceutical company GSK are expected to face strong competition in the RSV vaccine market. GSK's innovative vaccine, Arexvy, received approval from the US FDA in May, making it the first RSV vaccine authorized for use in the US. Although Arexvy was the first to receive US approval, marking a historic milestone in RSV vaccine development, Pfizer's Abrysvo was also quickly approved by the FDA, allowing both vaccines to launch in the US around the same time this past fall, ahead of the winter RSV season. Both vaccines showed high effectiveness in key trials, but Pfizer's vaccine has a crucial advantage over Arexvy. Abrysvo is likely to be the first RSV vaccine approved to protect infants globally, potentially giving it a larger market share than its competitors. It is currently the only vaccine in advanced development that targets a wide range of patient populations.

Regulatory Milestones

Marketed Registered Regulatory submission

Mar 2024	In Australia for the prevention of RSV infection in infants (maternal immunization), and in adults and elderly (direct vaccination)
Mar 2024	In Japan for the prevention of RSV infection in adults aged 60 years and older
Jun 2024	In Canada for infection in infants (maternal immunization), and in adults and elderly
Aug 2023	In EU for infection in infants (maternal immunization), and in adults and elderly, based on evidence from phase III RENOIR and MATISSE trials
Aug 2023	In the US in infants (maternal immunization), and in adults and elderly (direct vaccination)
May 2023	In the US for the prevention of lower respiratory tract disease caused by RSV infections in infants (maternal immunization), and in adults and elderly (direct vaccination)

RENOIR study for Respiratory syncytial virus infections

	RSV vaccine (RSVpreF)
Efficacy against RSV-associated lower respiratory tract disease (LRTD) after disease surveillance following season one	88.9%
Efficacy against RSV-associated lower respiratory tract disease (LRTD) after disease surveillance following season two	77.8%
Adverse events	PF 06928316 showed a favorable safety profile in preventing LRTI-RSV

* LRTI-RSV- Lower Respiratory Tract Illness-Respiratory syncytial virus

MATISSE study for Respiratory syncytial virus infections

	RSV vaccine (RSVpreF)
Interim results of severe medically attended lower respiratory tract illness (severe MA-LRTI) first 90 days of life	81.8% (CI: 40.6%, 96.3%)
Safety	PF 06928316 is well-tolerated with no safety concerns for both the vaccinated individuals and their newborns

Driving Growth: Impact of Abrysvo revenue on company's profit

Pfizer experienced a consistent growth in revenue over the past five years, with the highest trend seen in 2021 and 2022. The introduction of vaccines played a significant role in boosting revenue during these years. In 2021, the company had a 92% increase in operational growth compared to 2020. However, in 2023, Pfizer saw a 42% decline in revenue from 2022, mainly due to decreased sales of Covid-19 products like Comirnaty and Paxlovid. On the other hand, the launch of Abrysvo in 2023 contributed $515 million to global revenues, largely driven by its introduction for older adults in the U.S.

Effect of Abrysvo revenue on company's profit

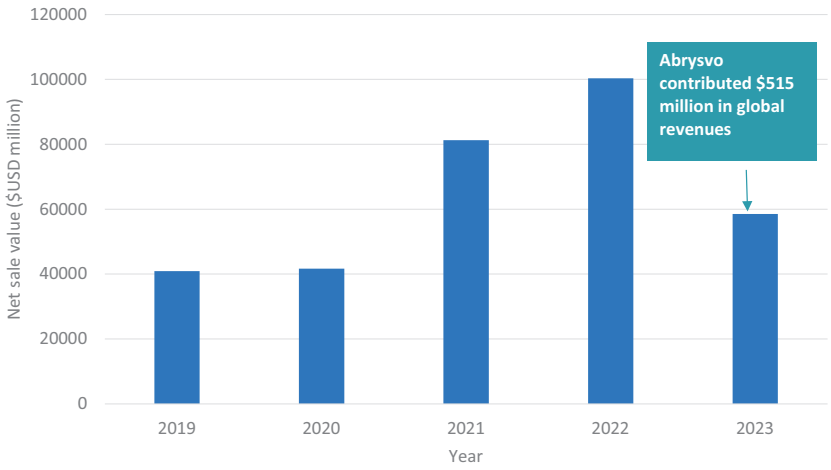


Fig 9: Effect on market revenue after the launch of Abrysvo

Below is a comparative analysis of the revenue generated by vaccines versus drugs. Vaccines play a major role in generating maximum revenues for Pfizer.

Pfizer's revenue generation for drugs versus vaccines (3 years)

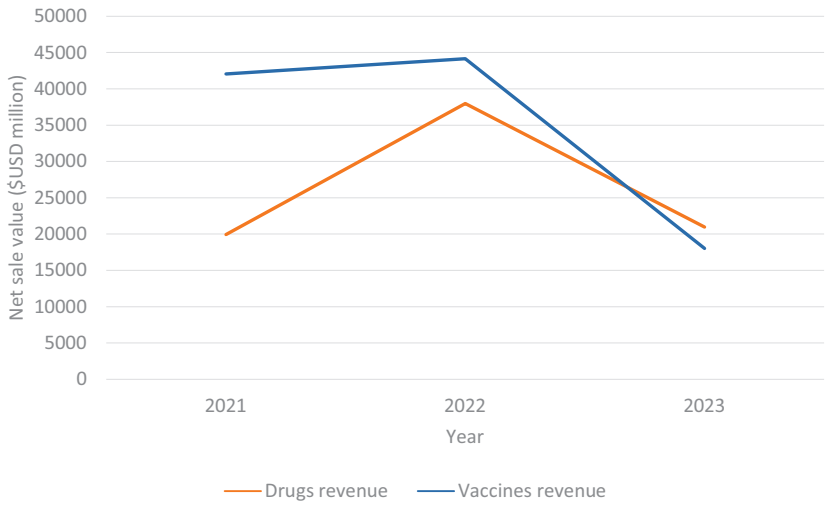


Fig 10 : Effect on market revenue for drugs versus vaccines

RSVpreF3 (Arexvy)

Respiratory syncytial virus (RSV) infections RSV is a leading cause of hospitalization for infants and young children with acute lower respiratory infections. The current need is for a vaccine that offers improved efficacy in preventing RSV infections.

RSVpreF3 (Arexvy)

MoA: Immunostimulants

Drug Class: Subunit vaccines; Synthetic vaccines

Originator: GlaxoSmithKline

What is the need for Arexvy

Currently, palivizumab, the monoclonal antibody used for prevention and treatment, is limited to specific groups in more affluent regions. Nevertheless, various vaccine candidates designed for young children, older adults, and pregnant women are undergoing human trials.

Arexvy is a vaccine developed by GSK for preventing respiratory syncytial virus (RSV) infections, which is currently undergoing human trials

GSK (formerly GlaxoSmithKline) has developed an adjuvanted vaccine called Arexvy for preventing respiratory syncytial virus (RSV) infections. The company is currently evaluating different versions of the vaccine that are given through intramuscular injections. Arexvy includes a recombinant subunit pre-fusion RSV antigen (RSVPreF3) to trigger an immune response and is boosted by GSK's AS01 adjuvant, which includes the QS-21 StimulonTM adjuvant from Agenus.

Regulatory Milestone

Marketed | Registered | Regulatory submission

Jun 2024	In US, PDUFA date (7th June 2024) for RSV infections (Prevention) in adults (50-59 yrs) at increased risk
Feb 2024	In US (Priority review) & Canada for RSV infections (Prevention) in adults (50-59 yrs) at increased risk
Jan 2024	In Australia for RSV infections (Prevention) in adults (60 yrs and older)
Jan 2024	In EU for RSV infections (Prevention) in adults (50-59 yrs) at increased risk
Dec 2023	In Japan for RSV infections (Prevention) in adults (50-59 yrs) at increased risk
2H 2023	RSV infections (Prevention) in adults (60 yrs and older) Sept: Japan; Aug: Canada; July: UK, June: EU,
Aug 2023	In the US for RSV infections (Prevention) in adults (60 yrs and older)
May 2023	In the US for RSV infections (Prevention) in adults (60 yrs and older)

Phase III study for Respiratory syncytial virus infections

	RSVPreF3 OA vaccine	Placebo
Number of Participants With First Episode of RT-PCR Confirmed RSV A and/or B Associated Lower Respiratory Tract Disease (LRTD) During the First Season Following a Single Dose of the RSVPreF3 OA Vaccine	57.89 to 94.08	
All-Cause Mortality	At Risk (%)- 0.39%	At Risk (%)- 0.46%
Serious Adverse Events	At Risk (%)- 4.88%	At Risk (%)- 4.86%

Driving Growth: Impact of Arexvy revenue on Company's Profit

GSK's revenue has been steadily increasing in recent years, reaching its peak in 2021 due to strong operational performance and successful commercial execution. However, in 2022, GSK experienced a decline in revenue following Russia's invasion of Ukraine. In 2023, GSK began to see an increase in revenue with the introduction of its respiratory syncytial virus vaccine, Arexvy. Despite facing tough competition from Pfizer's RSV vaccine, GSK reported a revenue of $1559.44 million for Arexvy, which was approved in multiple countries including the US, the EU, Japan, the UK, and Canada in 2023. Arexvy, the world's first approved RSV vaccine, received US FDA approval in May, preceding Pfizer Inc's Abrysvo approval.

Effect of Arexvy revenue on company's profits

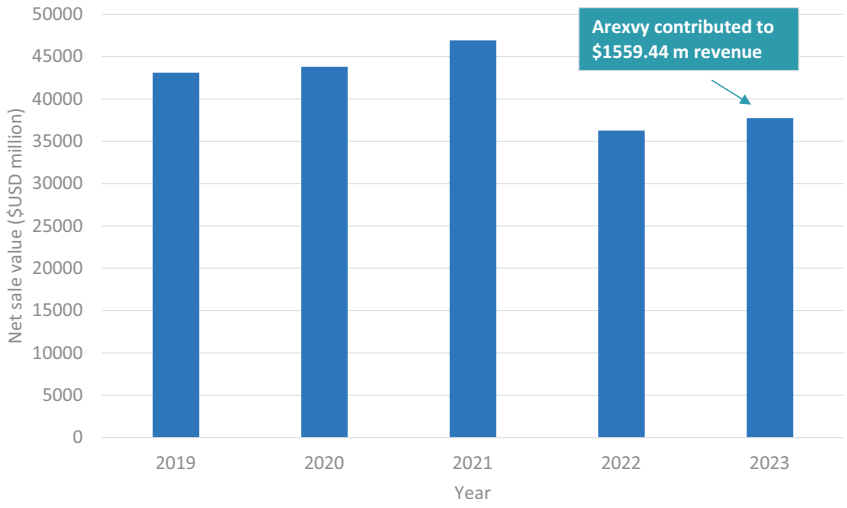


Fig 11: Effect on market revenue after the launch of Arexvy

Innovative and potential blockbuster drug launches on the horizon

A blockbuster drug is an extremely popular drug that generates annual sales of at least $1 billion for the marketing authorization holder. Examples of established blockbuster drugs include Vioxx, Lipitor, and Zoloft. Blockbuster drugs are commonly used to treat common medical problems like high cholesterol, diabetes, high blood pressure, asthma, and cancer.

Notable blockbuster drugs such as Keytruda and Humira have amassed sales of $25,011 and $14,404 million USD, respectively in 2023. Keytruda continues to harness its potential by expanding regulatory approvals for additional indications and broadening its usage in earlier stages of treatment and heightening global demand. Similarly, despite encountering increased competition from biosimilars, after losing exclusivity in the U.S., Humira has successfully maintained its position as a leading medication.

In this report, we have identified 12 innovative drugs with the potential to become blockbusters following their launch in 2024.

Donanemab

Alzheimer's disease (AD) is a progressive neurological condition that harms nerve cells in the brain. The neurons responsible for memory, language, and thinking are impacted by this disease, leading to memory loss and cognitive issues like language difficulties and trouble with navigation. The brain changes seen in Alzheimer's, such as the build-up of abnormal proteins named beta-amyloid and phosphorylated tau, along with neuronal degeneration, can affect basic functions like thinking, walking, mood, and behavior. Deposits of these

Donanemab

Indication: Alzheimer's disease

Route: Intravenous/ Subcutaneous

Owner: Eli Lilly & Co

Drug class: Antidementia, Monoclonal antibodies

MoA: Immunomodulators

PDUFA date: Approval delayed

Alzheimer's disease affects nerve cells critical for memory, language, and thinking. Beta-amyloid and tau proteins accumulate in Alzheimer's, leading to brain tissue loss and inflammation

proteins can also trigger inflammation in the brain and lead to tissue loss. In some rare cases, a genetic mutation can cause dominantly inherited Alzheimer's disease (DIAD). While symptoms of the disease may only appear later in life, the underlying brain changes may have started years earlier. Numerous hypotheses are being considered as potential causes of Alzheimer's disease:

- **Cholinergic hypothesis:** Inadequate amount of choline acetyltransferase and acetylcholine (ACh) led to AD
- **Amyloid hypothesis:** The mutation in the amyloid-ß precursor protein (APP) gene is one of the reasons for familial AD
- **Tau hypothesis:** The accumulation of neurofibrillary tangles (NFTs) because of increased phosphorylation of Tau protein in Alzheimer's disease.

Prevalence

By 2030, 82 million people are projected to have Alzheimer's disease

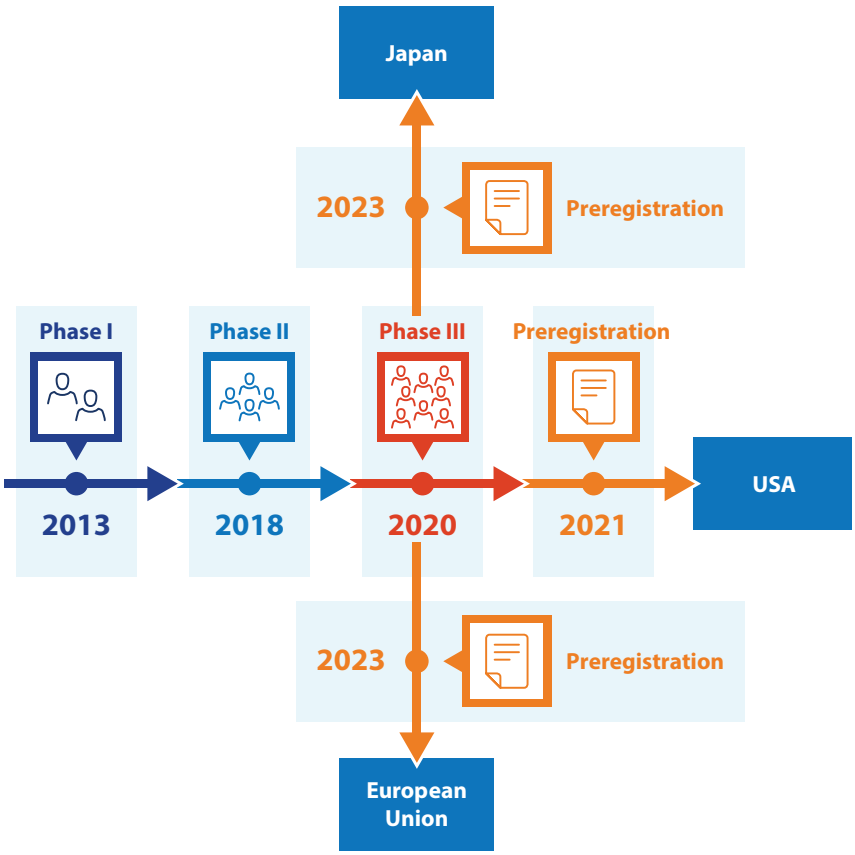
Being a progressive disease, AD's prevalence gets dreadful with time. Alzheimer's disease is rapidly increasing worldwide with a projection of 82 million by 2030 . Age, genetics, and family history are major risk factors for Alzheimer's disease.

What is the need for Donanemab

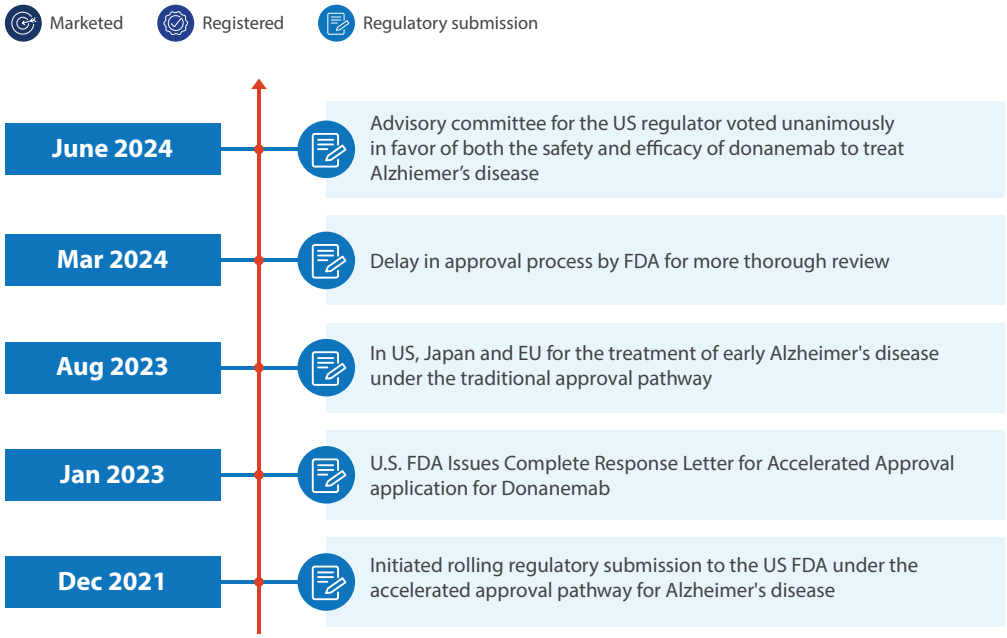
Donanemab is a promising anti-amyloid immunotherapy in late-stage development, expected to receive FDA approval in 2024

Cholinesterase Inhibitors like donepezil, rivastigmine, and galantamine, as well as the NMDA Receptor Antagonist Memantine, are commonly used to manage mild to moderate Alzheimer's symptoms. The current approach focuses on inhibiting Aβ aggregation and promoting Aβ clearance to slow symptom progression. Many potential therapies have failed late-stage trials, underscoring the need for accurate diagnostics and biomarkers. Promising drugs like Aducanumab and Lecanemab target Alzheimer's biology by removing beta-amyloid and slowing decline in early-stage disease. Lecanemab was the first amyloid beta-directed antibody approved in the USA and Japan in 2023, while Aducanumab received accelerated approval in 2021 for early Alzheimer's treatment. Donanemab, an anti-amyloid immunotherapy targeting N3pG beta amyloid, has shown promising results in slowing cognitive decline in early symptomatic Alzheimer's patients. It is currently in late-stage development with FDA approval expected in 2024.

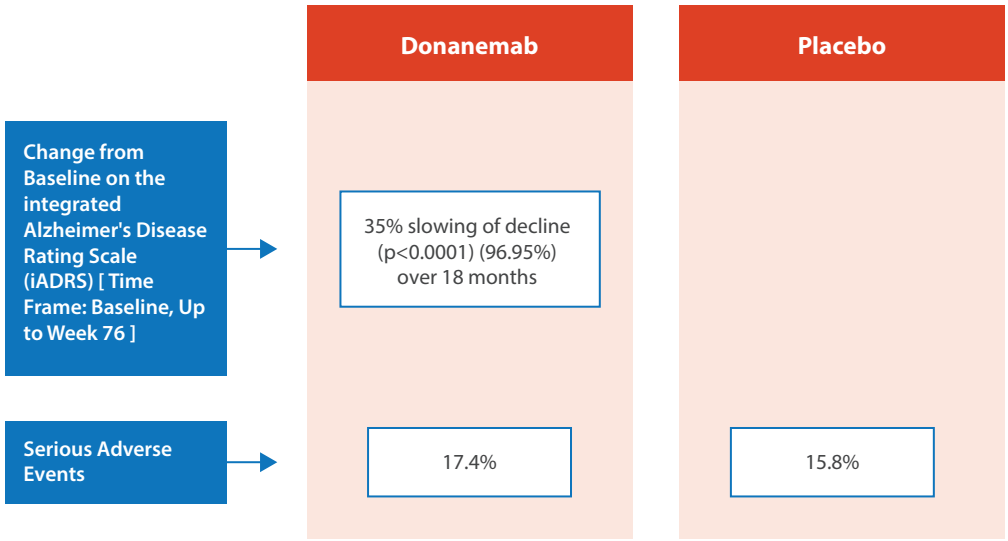
Development Timeline of Donanemab



Regulatory Milestones



TRAILBLAZER-ALZ 2 study for AD



Projected market trends for donepezil for AD

Over the years, the market revenue for donepezil, an established drug, has been decreasing as it only offers symptom relief for AD without treating the root cause. It is also estimated that the revenue for this drug will continue to decline or show steady sales in the coming years. Eli Lilly is hopeful that the expected sales of donanemab will boost company revenue in **2025 by $837 million**, representing approximately 1.8% of total revenue.

Market trends and forecast for donepezil

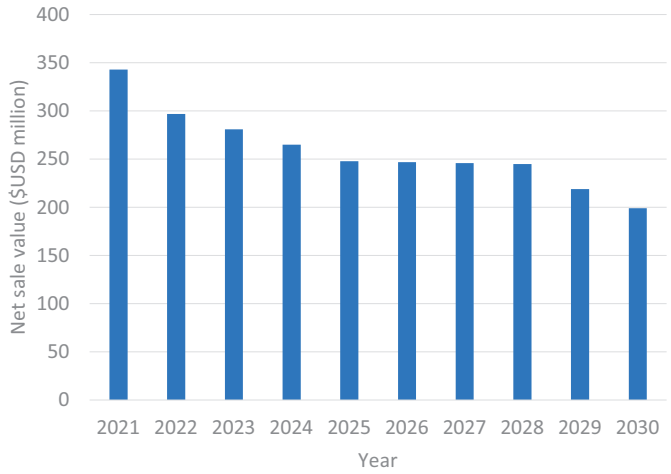
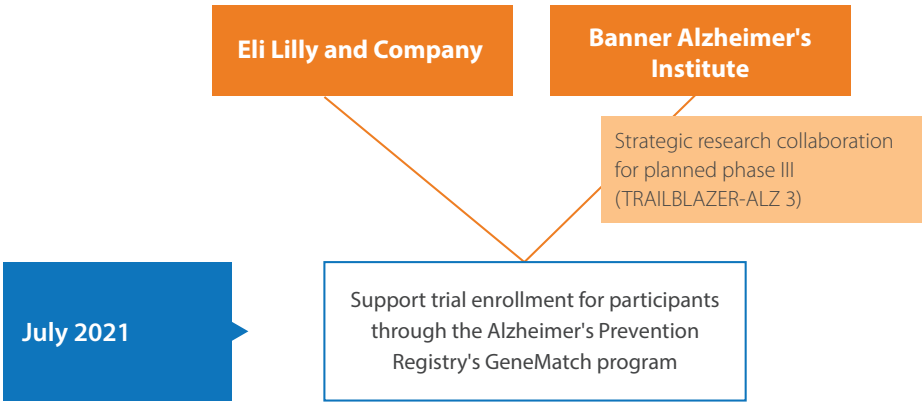


Fig 12: Market forecast for donepezil

Partnership between Eli Lilly and other institutes



Trospium chloride/xanomeline (KarXT)

Indication: Schizophrenia

Route: Oral

Owner: Karuna Therapeutics

Drug class: Small mlecules

MoA: Muscarinic M1 receptor agonists; Muscarinic M4 receptor agonists; Muscarinic receptor antagonists

PDUFA date: September 26, 2024

Schizophrenia affects thinking, emotions, and relationships, making it one of the most disabling mental illnesses. It affects 24 million people worldwide

Trospium chloride/xanomeline (KarXT)

Schizophrenia is a rare but chronic mental illness that affects thinking, emotions, perception, and relationships. Although less prevalent than other major mental illnesses, affecting less than 1% of adults in the United States, schizophrenia can be one of the most persistent and disabling conditions. Treatment involves medication, therapy, and community support. There is no specific cause for Schizophrenia: its treatment, involving antipsychotic drugs, focuses primarily on reducing the symptoms of the disease, which in turn improves the quality of life.

Prevalence

The prevalence of schizophrenia varies by country and data source worldwide, but the World Health Organization estimates that approximately 24 million people (1 in every 300) are affected globally. In the United States, the prevalence is estimated to range between 0.6% and 1.9%.

What is the need for KarXT

Currently, available treatment options have proven to be ineffective in addressing the negative and cognitive symptoms of the disease. Existing drugs, such as typical antipsychotics (such as chlorpromazine, haloperidol, thiothixene) and atypical antipsychotics (such as aripiprazole, asenapine, olanzapine, ziprasidone, quetiapine) have numerous shortcomings in terms of both efficacy and side effects. While some progress has been made with newer drugs, a more fundamental approach is needed to gain a better understanding of the underlying mechanisms and causes of the disorder that are still not fully understood.

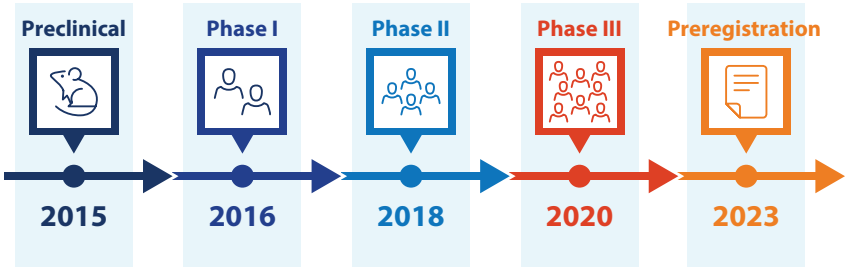
Current antipsychotic drugs often fail to effectively treat the negative and cognitive symptoms of schizophrenia: KarXT targets brain receptors without affecting dopamine or serotonin pathways

KarXT is a novel oral medication being developed for the management of psychiatric and neurological disorders such as schizophrenia and psychosis in Alzheimer's disease. It is a unique combination of the muscarinic agonist xanomeline and the muscarinic antagonist trospium. Unlike traditional antipsychotic medications, KarXT offers a groundbreaking dual mechanism of action that specifically targets muscarinic acetylcholine receptors in the brain without affecting the dopaminergic or serotonergic pathways, providing a new approach to treating severe mental illnesses.

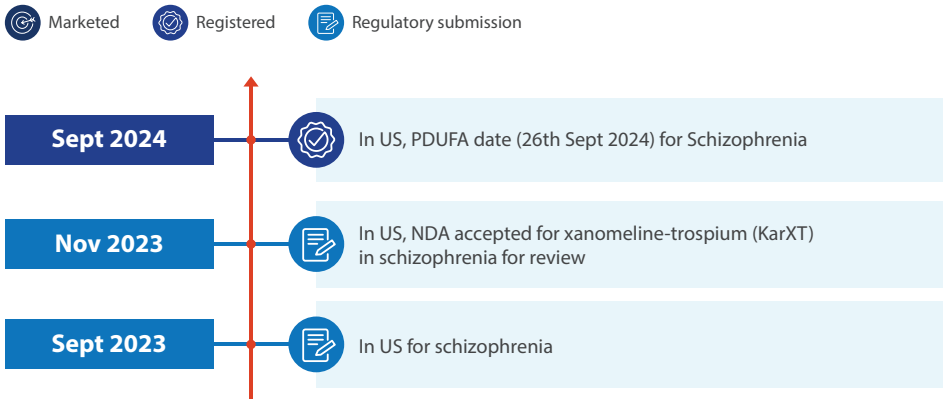
Quest for KarXT

The journey of KarXT began with the drug xanomeline, originally developed by Novo Nordisk and licensed to Eli Lilly for the treatment of Alzheimer's disease. Despite its promising efficacy, the development of xanomeline was halted due to severe cholinergic side effects such as nausea, vomiting, diarrhea, excessive sweating, and increased salivary production. In May 2012, an agreement was reached to license xanomeline to Karuna Therapeutics (a subsidiary of Bristol-Myers Squibb). To capitalize on the cognitive benefits of xanomeline, the company began searching for a compound that could alleviate its side effects while maintaining its effectiveness. This search led to the discovery of KarXT, a combination of xanomeline and trospium. Trospium acts by blocking peripheral muscarinic receptors and reducing the procholinergic side effects of xanomeline.

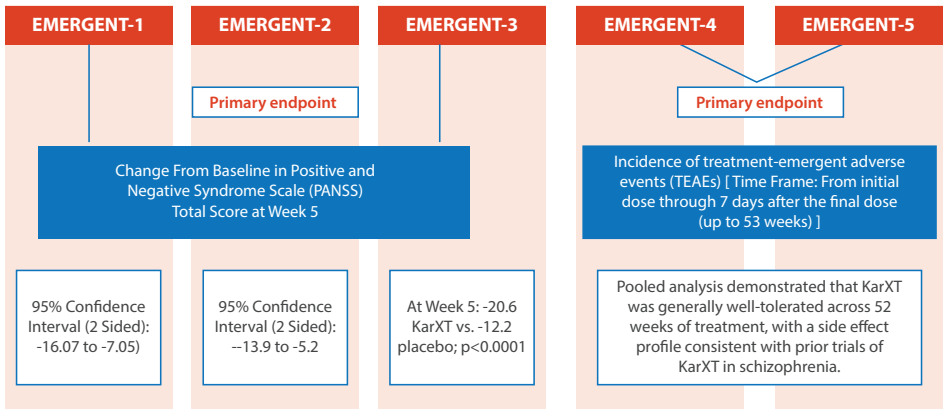
Development Timeline



Regulatory Milestones



EMERGENT trials for Schizophrenia



Projected market trends for quetiapine for Schizophrenia

The market revenue for quetiapine, a well-known drug, has been declining over time due to its association with severe side effects such as uncontrollable twitching or jerking movements in the face, tongue, or other body parts, as well as various infections and potential signs of blood clots. It is forecasted that the sales will continue to decline in the coming years. Bristol Myers Squibb sees KarXT as a promising opportunity for significant revenue growth.

Market trends and forecast for quetiapine

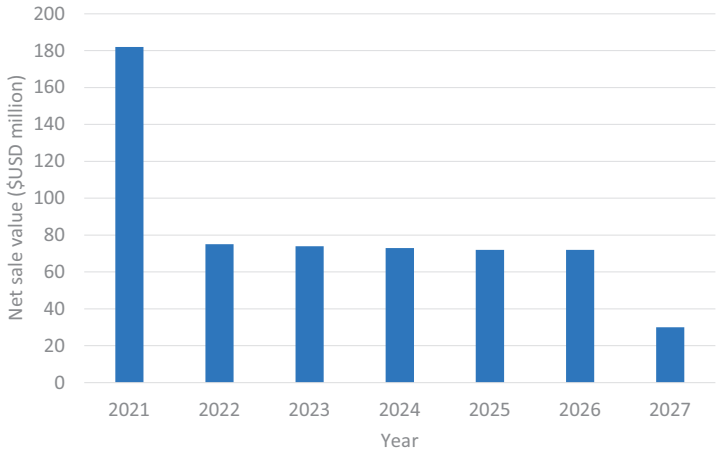


Fig 13: Market forecast for quetiapine

Partnership between Karuna Therapeutics, Inc. and Bristol Myers Squibb

An undisclosed company offered a cash proposal to buy Karuna's shares at a significant premium to its October 10 closing price of $175.94 per share.

March 31, 2024

Bristol Myers Squibb acquired Karuna for $330.00 per share in cash, for a total equity value of $14.0 billion, or $12.7 billion net of estimated cash acquired.

November 8, 2021

Karuna Therapeutics, Inc. and Zai Lab entered into an exclusive license agreement for the development, manufacturing, and commercialization of KarXT in Greater China, including mainland China, Hong Kong, Macau, and Taiwan.

Resmetirom (Rezdiffra)

Indication: Metabolic dysfunction-associated steatohepatitis (MASH)

Route: Oral

Owner: Madrigal Pharmaceuticals

Drug class: Antihyperlipidemic, Hepatoprotections Small molecules

MoA: Thyroid hormone receptor beta agonists

Marketed: Commercially available in USA as 'Rezdiffra' from Apr 2024

NASH, a severe liver condition, affects up to 6% of the U.S. population and is a leading cause of liver transplants

Resmetirom (Rezdiffra)

Non-alcoholic steatohepatitis (NASH) is a form of non-alcoholic fatty liver disease (NAFLD) where excess fat builds up in the liver, leading to inflammation and fibrosis. It affects approximately 3-6% of the US population and its prevalence is increasing . NAFLD can range from simple fatty liver to NASH, NASH with fibrosis, and NASH with cirrhosis. Some patients may progress to end-stage liver disease and liver cancer. NASH is becoming a leading cause of liver transplants in the US and is associated with a higher risk of heart attack, stroke, and death. In 2023, global liver disease organizations renamed NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD) and NASH to metabolic dysfunction-associated steatohepatitis (MASH). Genetic factors, diet, lack of physical activity, obesity, insulin resistance, and type 2 diabetes are major risk factors for developing NASH.

Prevalence

The findings reported in the Journal of Physiology and Biochemistry in March 2023 suggest that the global prevalence of NAFLD within the general population, as defined by imaging criteria, is approximately 25%. However, there is significant variability in different geographic regions, with rates reaching as high as 31.8% in the Middle East, 30.4% in South

America, and 13.5% in Africa. Incidence of NAFLD has been infrequently measured. The global Nonalcoholic Steatohepatitis (NASH) market is forecasted to grow significantly, reaching a value of USD 46230 million by 2028, up from USD 3064.2 million in 2021, with a projected CAGR of 46.7% during 2022-2028.

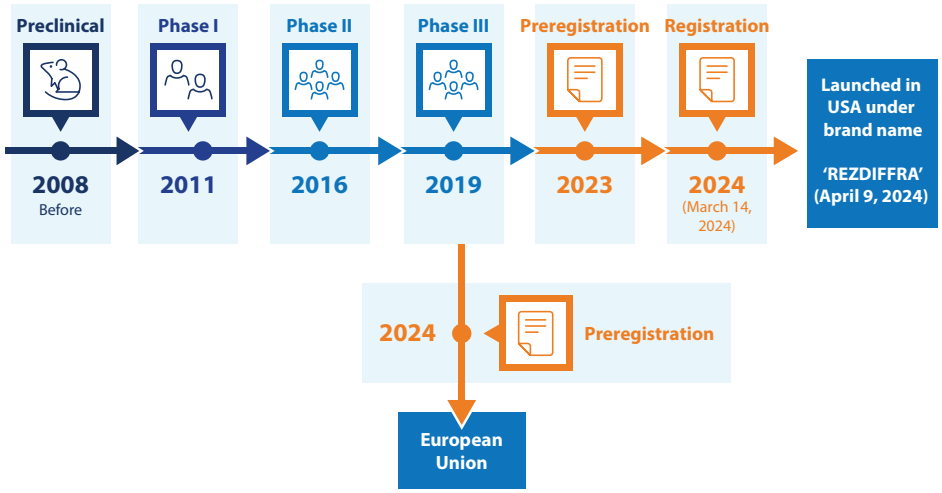
What is the need for Rezdiffra

The primary approach to treating Non-alcoholic steatohepatitis involves making lifestyle changes and incorporating nutritional interventions. Due to the complex nature of the disease's pathophysiology and the influence of various genetic and environmental factors on its development, there is a need for a diverse range of molecules with different biological targets in comparison to the traditional drugs used to tackle NASH. While medications such as vitamin E and pioglitazone are commonly used to manage metabolic associated fatty liver disease (MAFLD) and associated conditions, newer molecules like obeticholic acid, liraglutide, semaglutide, tirzepatide, canagliflozin, and empagliflozin have shown promise in the treatment of NAFLD and MAFLD. Approximately 25% of the US population with NAFLD also have NASH. Emerging therapies like MGL-3196, semaglutide, vonafexor, HPG1860, VK2809, BIO89-100, and LPCN 1144 are expected to drive growth in the NASH market. Developing a safe and effective novel therapeutic agent for MAFLD/MASH treatment is a major focus of biomedical research. The long-awaited solution for MASH treatment has finally arrived with the introduction of 'Resmetirom' by Madrigal Pharmaceuticals.

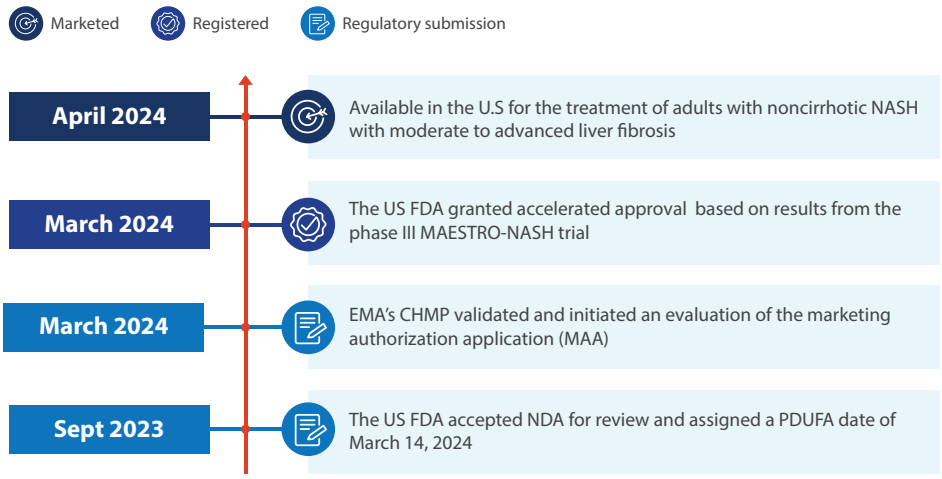
Resmetirom, a thyroid hormone receptor-beta (THR-beta) agonist, was developed in combination with diet and exercise for treating non-cirrhotic non-alcoholic steatohepatitis (NASH) in adults with moderate to advanced liver fibrosis (equivalent to stages F2 to F3 fibrosis). The drug functions by activating hepatic thyroid hormone receptor β (THR-β), leading to reductions in lipid levels, increased bile acid production, decreased intrahepatic triglycerides, and enhanced fat oxidation. Resmetirom exhibits a particular affinity for liver receptors involved in metabolic processes and cholesterol regulation, which helps to minimize the occurrence of extrahepatic side effects associated with thyroid hormone receptor activation.

Resmetirom, a thyroid hormone receptor agonist, targets liver fat and fibrosis in NASH treatment

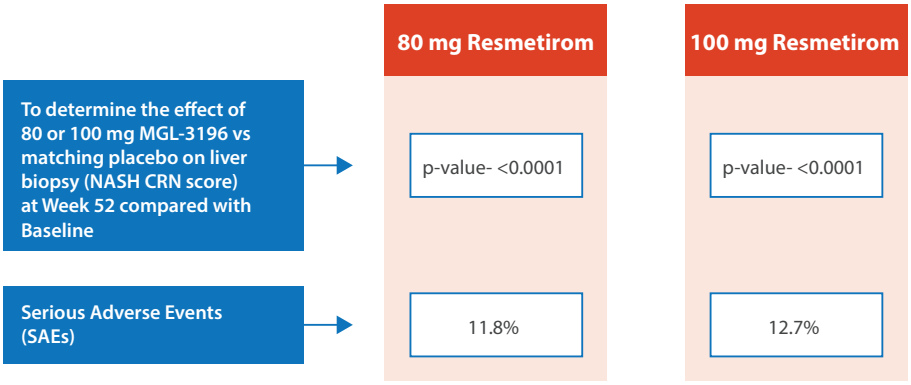
Development Timeline



Regulatory Milestones



MAESTRO-NASH for NASH



Projected market trends for pioglitazone for MASH

The market revenue for pioglitazone, an established drug used for treating MAFLD-associated conditions, remained consistent in 2022 and 2023. Projections indicate that the revenue will continue to be stable in the future, with minimal impact on revenue generation. According to data in Nature (March 2024), Resmetirom's annual sales could exceed US$3.5 billion by 2028. This potential increase in revenue would greatly benefit Madrigal, as it currently does not have any other approved drugs.

Market trends and forecast for pioglitazone

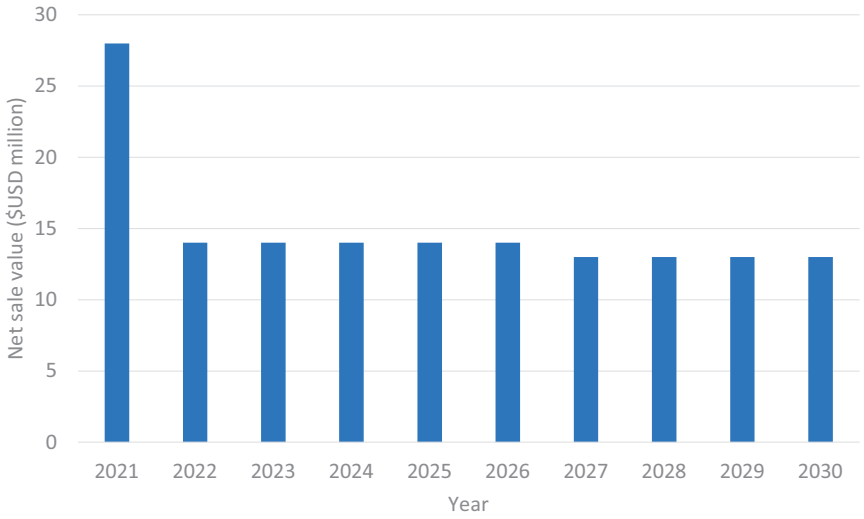


Fig 14: Market forecast for pioglitazone

Licensing agreement

Roche + VIA Pharmaceuticals

On 18 December 2008, **Roche** entered an exclusive worldwide license agreement providing **VIA Pharmaceuticals** with control of all development and commercialization of resmetirom for all potential indications. The agreement provides for milestone payments for development and royalties upon commercialization.

VIA Pharmaceuticals + Madrigal Pharmaceuticals

In September 2011, Madrigal Pharmaceuticals assumed all of VIA Pharmaceuticals rights and obligations under, the Roche agreement pursuant to an asset purchase agreement. Assumed control of all development and commercialization of resmetirom and will hold exclusive worldwide rights for all potential indications. Roche exclusively licensed certain patent rights and know-how relating to resmetirom in exchange for consideration consisting of an upfront payment, milestone payments, the remainder of which total $US8 million and are tied to regulatory approval in the US and Europe of resmetirom or any derivative product, and single-digit royalty payments based on net sales of resmetirom and any derivative products, subject to certain reductions.

Sotatercept (Winrevair)

Pulmonary arterial hypertension (PAH) is a rare and progressive condition characterized by elevated blood pressure and changes in the pulmonary arterioles. If left untreated, PAH can lead to right ventricular failure and even death. The European Society of Cardiology and the European Respiratory Society have updated the definition of PAH to include specific criteria such as a resting mean pulmonary arterial pressure of 20 mmHg, a pulmonary artery wedge pressure of 15 mmHg or lower, and a pulmonary vascular resistance (PVR) of 3 Wood units or higher. The World Health Organization (WHO) classifies PAH into five different groups based on factors such as underlying pathophysiology, causes, and response to treatment, including: PAH, pulmonary hypertension due to heart disease, pulmonary hypertension caused by lung disease or hypoxia, pulmonary hypertension due to pulmonary artery obstruction, and pulmonary hypertension with unclear or multiple contributing factors.

Prevalence

As per the American Lung Association, PAH is a rare and progressive condition without a known cause. It predominantly affects women aged 30-60 and is categorized as Group 1: PAH within the five types of pulmonary hypertension. While there is no cure for PAH, treatments exist to manage symptoms and enhance quality of life. Approximately 500-1000 new cases of PAH are diagnosed annually in the United States.

What is the need for Winerevair

Currently, available treatments for PAH primarily target well-known pathways such as the endothelin pathway, the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, and the prostacyclin pathway. However, these medications do not provide a cure for the disease but rather improve prognosis and help manage symptoms. Additionally, existing PAH drugs may have potential adverse effects and interactions with other medications. Treatment of PAH typically involves medications like calcium channel blockers (e.g. amlodipine, nifedipine), endothelin receptor antagonists (e.g. ambrisentan, macitentan), PDE-5 inhibitors (e.g. sildenafil, tadalafil), and prostacyclin analogs (e.g. epoprostenol). Due to the rarity of PAH, clinical trials are limited by patient eligibility criteria. New therapeutic targets are being developed to address the complex nature of the disease and improve long-term outcomes.

Sotatercept (Winrevair)

Indication: Pulmonary arterial hypertension (PAH)

Route: Subcutaneous

Owner: Merck & Co

Drug class: Antihypertensives, Immunoglobulin-Fc-fragments, Recombinant fusion proteins

MoA: Activin inhibitors; Transforming growth factor beta inhibitors

PDUFA date: March 26, 2024

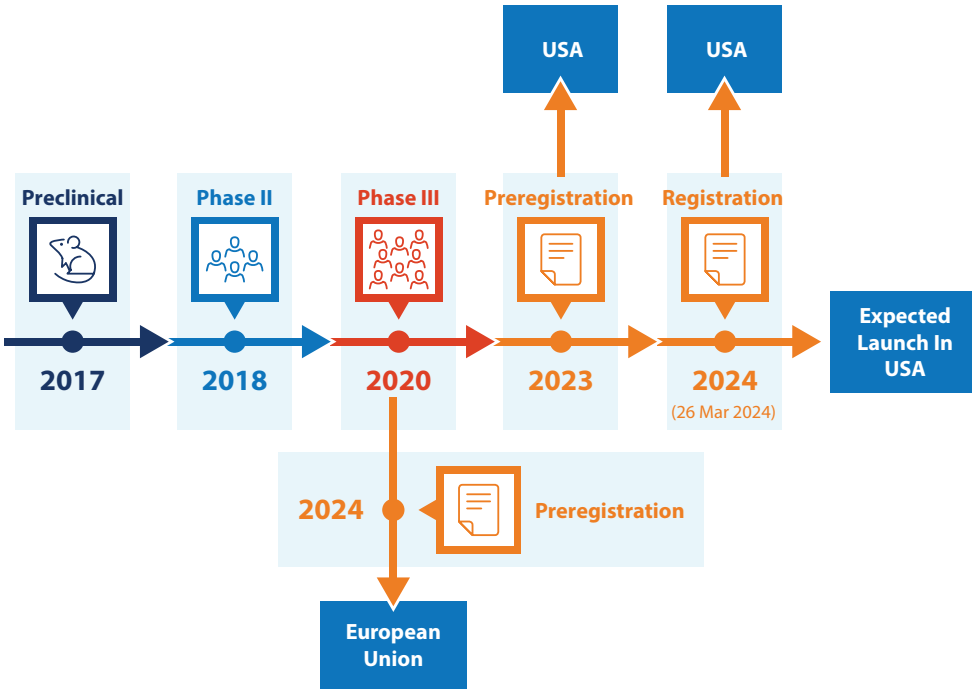
PAH is a rare, progressive disease characterized by elevated pulmonary blood pressure and changes in the pulmonary arterioles. If untreated, it can lead to right ventricular failure and death

PAH is rare, progressive, with no known cause, and mostly affects women aged 30-60. Current treatments focus on symptom management and quality of life improvement

Sotatercept focuses on the activin signaling pathway to treat PAH. Monthly subcutaneous injections could make it a promising treatment

One promising candidate is sotatercept, a first-of-its-kind activin signaling inhibitor being investigated for the treatment of PAH (WHO Group 1). By binding to activins and growth differentiation factors (GDFs), sotatercept helps restore the balance between pro-proliferative and anti-proliferative Bone Morphogenetic Protein (BMP) signaling pathways. Acting on the underlying cause of the disease, sotatercept is administered via monthly subcutaneous injections, making it a potential treatment option for PAH.

Development of Sotatercept

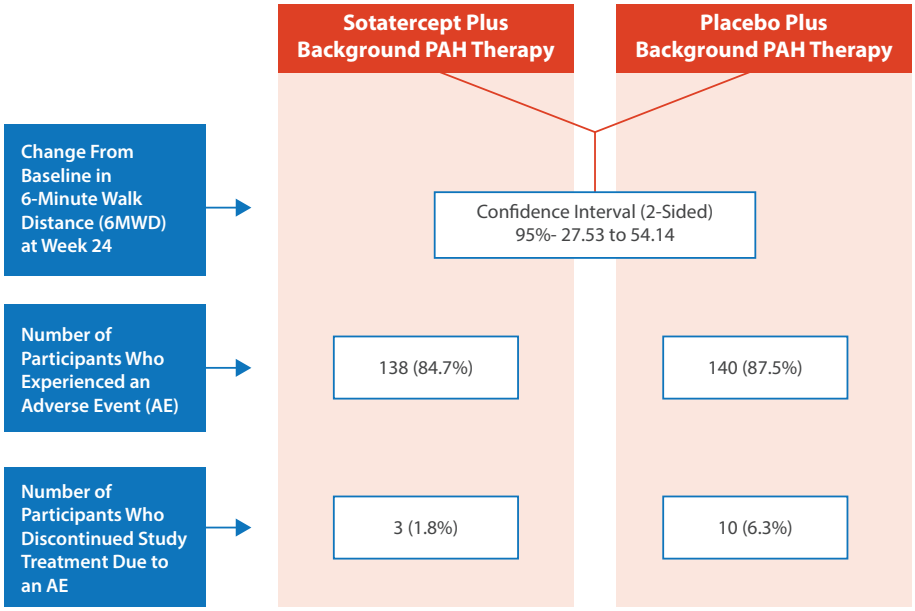


Regulatory Milestones

Marketed Registered Regulatory submission

April 2024	Expected Launch in US under Brand Name: WINREVAIR™, for injection, 45mg, 60mg)
March 2024	In US for the treatment of adults with pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) to increase exercise capacity, improve WHO functional class (FC), and reduce the risk of clinical worsening events
October 2023	In EU, MAA submission completed for sotatercept for the treatment of adults with PAH
September 2023	In US, BLA accepted for priority review and PDUFA date set for March 26, 2024

STELLAR study for PAH



Projected market trends for ambrisentan for PAH

Ambrisentan, a well-known drug for PAH introduced in 2007, experienced a decrease in market revenue in 2022 and 2023. It is anticipated that this downward trend will persist in the future due to reported adverse effects such as fluid retention, chest pain, cough, and headache. However, with the introduction of sotatercept, the company is expecting to achieve $1.13 billion in sales by 2029. Considered the first disease-modifying therapy for PAH, sotatercept is poised to revolutionize the landscape of PAH treatment.

Market trends and forecast for ambrisentan

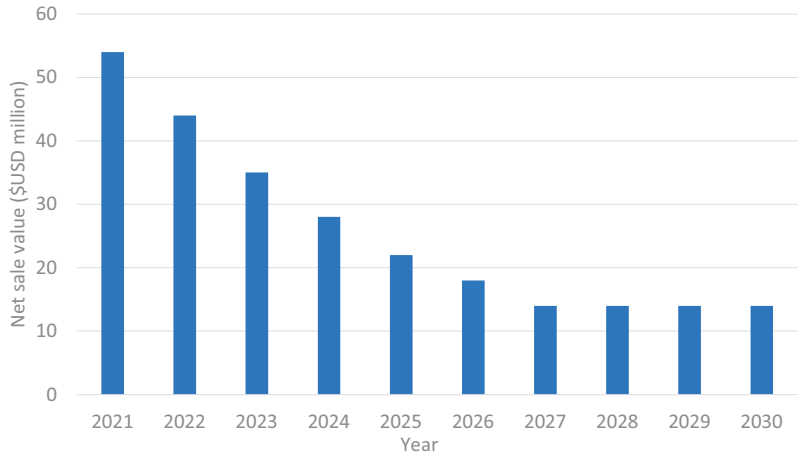


Fig 15: Market forecast for ambrisentan

Acquisitions/mergers

Acceleron Pharma	Sotatercept was originally developed by Acceleron Pharma and tested for oncology, to neutralize chemotherapy-induced anemia and bone loss in various tumor types. In 2017, Acceleron decided to evaluate sotatercept in pulmonary arterial hypertension.
February 20, 2008	Strategic collaboration has been announced between Acceleron Pharma, Inc. and Celgene Corporation for the joint development and commercialization of ACE-011 (Sotatercept), a first-in-class, novel bone-forming compound (formerly indicated for bone loss).
November 22, 2021	Merck has purchased Acceleron for US $11.5 billion in 2021.

Datopotamab deruxtecan (Dato-DXd)

Indication: Lung cancer, Breast cancer

Route: Intravenous

Owner: Daiichi Sankyo Company

Drug class: Antineoplastics; Immunoconjugates; Monoclonal antibodies

MoA: DNA topoisomerase I inhibitors

PDUFA date: December 20, 2024, January 29, 2025

Lung cancer is the top cause of cancer-related deaths globally, followed by breast cancer. NSCLC and HR+/HER2- breast cancer represent the majority of diagnoses

1 in 16 people will be diagnosed with lung cancer during their lifetime, while 2.3 million women were diagnosed with breast cancer in 2022

Datopotamab deruxtecan (Dato-DXd)

Lung cancer is the leading cause of cancer-related deaths worldwide, with approximately 85% of cases being non-small cell lung cancer (NSCLC), including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Breast cancer (BC) is the second most common cause of cancer-related deaths globally among women, and its incidence is on the rise. Furthermore, Hormone Receptor (HR)+/ human epidermal growth factor receptor 2 (HER2) negative breast cancer makes up 70% of all cases of breast cancer.

Prevalence

- In a lifetime, 1 out of every 16 people will receive a lung cancer diagnosis, with the rate being 1 in 16 for men and 1 in 17 for women. Each year, around 127,070 American lives are claimed by the disease. Currently, 654,620 individuals in the U.S. have previously been diagnosed with lung cancer.
- In 2022, 2.3 million women worldwide were diagnosed with breast cancer and 670,000 women died from the disease, according to the World Health Organization. Breast cancer can affect women in every country, beginning after puberty and becoming more common in later years.

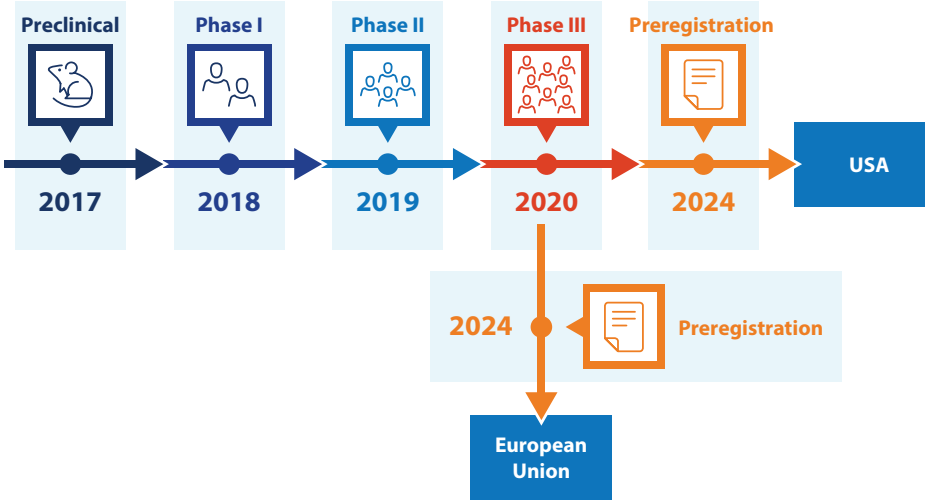
What is the need for Datopotamab deruxtecan

Traditional cancer treatment involves surgery, chemotherapy, and radiation therapy, while newer options like immunotherapy and targeted therapy show promise in treating NSCLC. However, treatment resistance and disease progression remain significant challenges for patients with NSCLC. Understanding the disease mechanism and developing targeted or combination therapies is crucial for improving treatment outcomes. In contrast, endocrine therapy is the standard approach for treating Breast cancer, with targeted therapy, endocrine therapy, and chemotherapy all being viable options. CDK4/6 inhibitors like palbociclib, abemaciclib, or ribociclib, along with other inhibitors, are commonly used for HR+/HER2–BC, but resistance and recurrence are common. Research into new treatment strategies is urgently needed to benefit patients with breast cancer.

Dato-DXd is a TROP2-targeting antibody-drug conjugate designed for NSCLC and HR+/HER2- breast cancer

Dato-DXd, a TROP2-targeting DXd antibody-drug conjugate (ADC) specially designed by Daiichi Sankyo and AstraZeneca, has shown promising results in advanced clinical trials conducted on patients with NSCLC and HR+/HER2- breast cancer. This engineered molecule binds to TROP2-expressing cells, leading to the drug's introduction into cancer cells. Subsequently, the release of its cytotoxic payload results in inhibition of DNA topoisomerase I, DNA damage, and induction of apoptosis, ultimately leading to cell death.

Development Timeline of Datopotamab deruxtecan

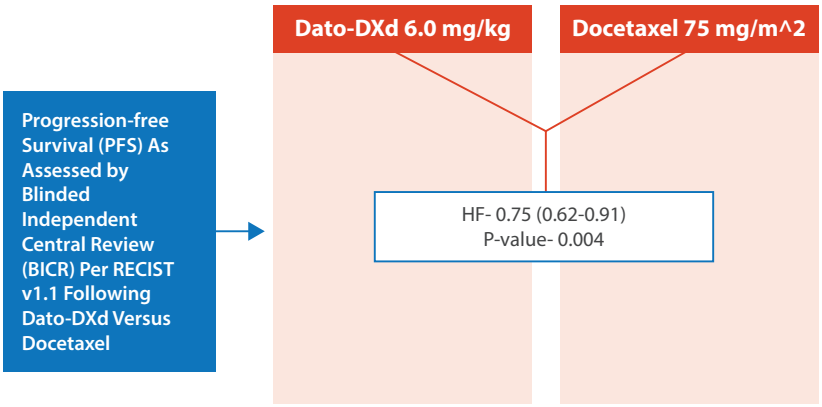


Regulatory Milestones

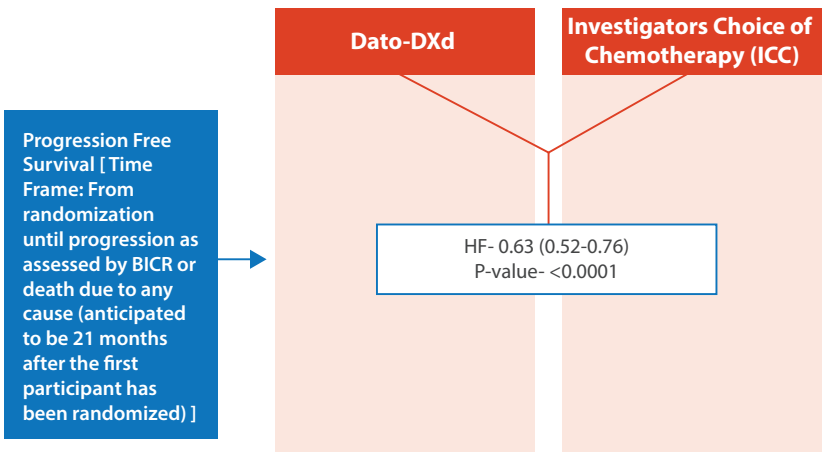
Marketed Registered Regulatory submission

January 2025	In US, PDUFA date set for Jan 2025 by US FDA for HR+/HER2 negative Breast Cancer
December 2024	In US, PDUFA date set for Dec 2024 by US FDA for Non-small cell lung cancer
April 2024	In US, BLA accepted for treatment of adult patients with unresectable or mHR-positive, HER2-negative breast cancer based on TROPION-Breast01 study
April 2024	In China and Japan, regulatory submissions for treatment of adult patients with unresectable or mHR-positive, HER2-negative breast cancer
March 2024	In EU, MAA validated by to EMA, for treatment of adult patients with unresectable or mHR-positive, HER2-negative breast cancer based on TROPION-Breast01 study
March 2024	In EU, MAA validated by to EMA, for treatment of adult mhorr patients with locally advanced or metastatic NSCLC based on TROPION-Lung01 study
February 2024	In US, BLA accepted for treatment of adult patients with locally advanced or metastatic non-squamous NSCLC based on TROPION study

TROPION-LUNG01 study for NSCLC



TROPION-BREAST01 study for BC



Projected market trends for pembrolizumab for lung cancer and breast cancer

The well-established drug pembrolizumab, used for the treatment of breast and lung cancer, has experienced a notable growth in revenue in recent years and is projected to continue this trend in the future. The introduction of Dato-DXd is expected to have a significant impact on the market, with anticipated annual revenue reaching $1.97 billion in the US by 2036.

Market trends and forecast for pembrolizumab

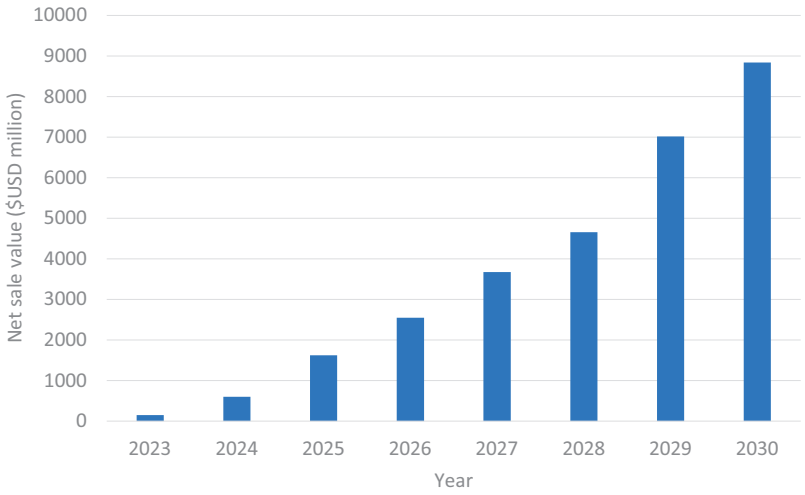


Fig 16: Market forecast for pembrolizumab

Agreements between Daiichi Sankyo and other institutes/companies

May 2020

Daiichi Sankyo — collaboration agreement — **Merck**

Combination of DS 1062 + pembrolizumab in patients with previously treated advanced or metastatic non-small cell lung cancer without actionable genomic alterations

July 2020

Daiichi Sankyo — commercialization agreement — **AstraZeneca**

Develop and commercialize DS 1062 worldwide, except in Japan where Daiichi Sankyo will maintain exclusive rights

Under the terms of the agreement:

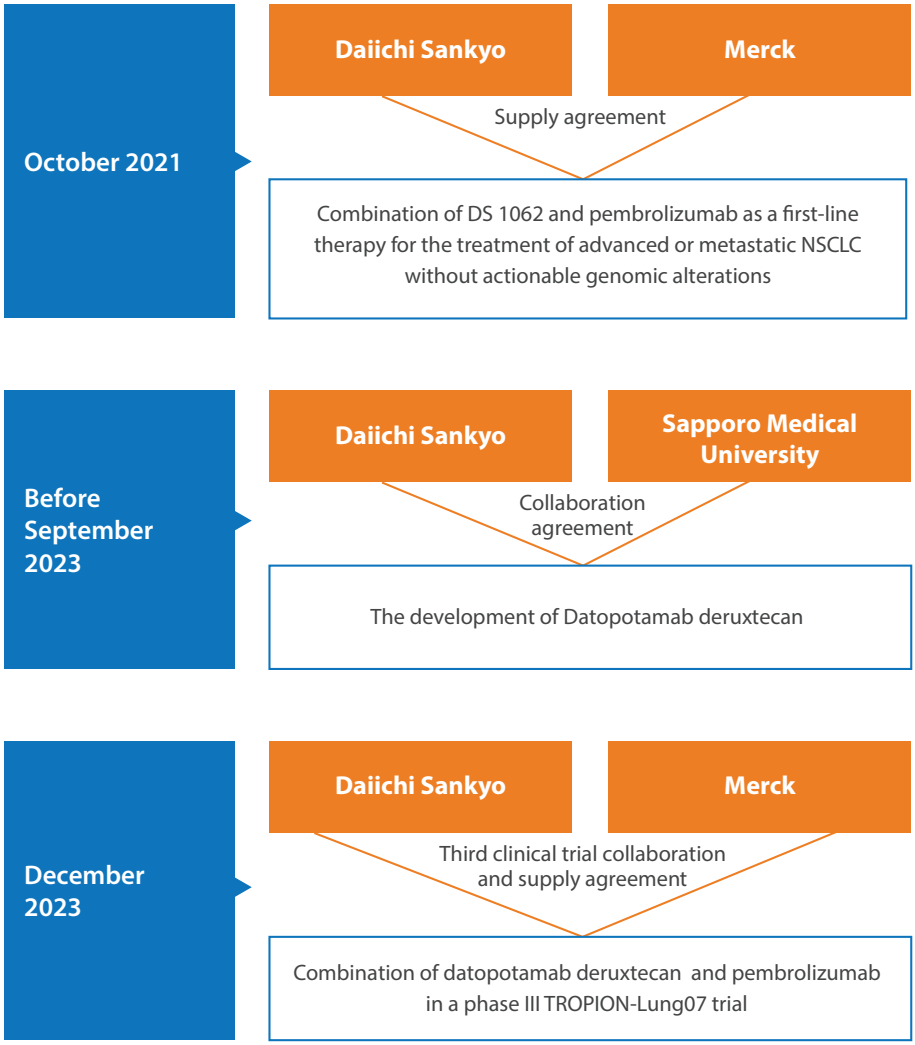
- AstraZeneca will pay $US350 million upon execution of the agreement
- $US325 million after 12 months
- $US325 million after 24 months
- $US1000 million upon regulatory milestones
- $US4000 million upon future sales milestones

Daiichi Sankyo — research collaboration — **Gustave Roussy**

Advanced research and clinical development of DS 1062 and U3 1402 in NSCLC and mBC

Under the terms of the agreement:

- Daiichi Sankyo will provide funding and support for clinical, translational and preclinical studies for DS 1062 and U3 1402



Under the terms of the agreement, Daiichi Sankyo will conduct the global phase III TROPION-Lung08 trial

Acoramidis (ALXN 2060)

Hereditary transthyretin (ATTRv) amyloidosis is a rare disease and the most common type of familial amyloidosis, with a widely variable prevalence worldwide. When hereditary transthyretin (TTR) forms amyloid fibrils, it is known as ATTR, and the disease caused by a mutation in TTR is called amyloid TTR variant (ATTRv) amyloidosis. The dysfunction of the TTR protein leads to the accumulation of misfolded proteins, resulting in the deposition of insoluble amyloid fibrils and damage to local tissues. There have been over 140 different mutations identified in the TTR gene, leading to a range of symptoms that vary from person to person. In contrast, wild-type TTR amyloidosis (ATTRwt) is a condition that primarily affects the heart and typically develops in men over 60 years of age. Given that ATTRv is a multisystem disorder, it is important to investigate its impact on the eyes, kidneys, and gastrointestinal system.

Acoramidis (ALXN 2060)

Indication: Transthyretin-related hereditary amyloidosis

Route: Oral

Owner: BridgeBio Pharma

Drug class: Small molecules

MoA: Prealbumin modulators

PDUFA date: November 29, 2024

ATTRv amyloidosis is the most common familial form of amyloidosis, whose prevalence varies greatly worldwide. Mutations in TTR lead to harmful amyloid fibril deposits causing tissue damage

Prevalence

According to a study published in Frontiers in Neurology in October 2023, the estimated global prevalence of ATTRv amyloidosis was projected to be 10,186 individuals (range: 5526–38468). C.

Estimated 10,186 individuals affected by ATTRv amyloidosis worldwide

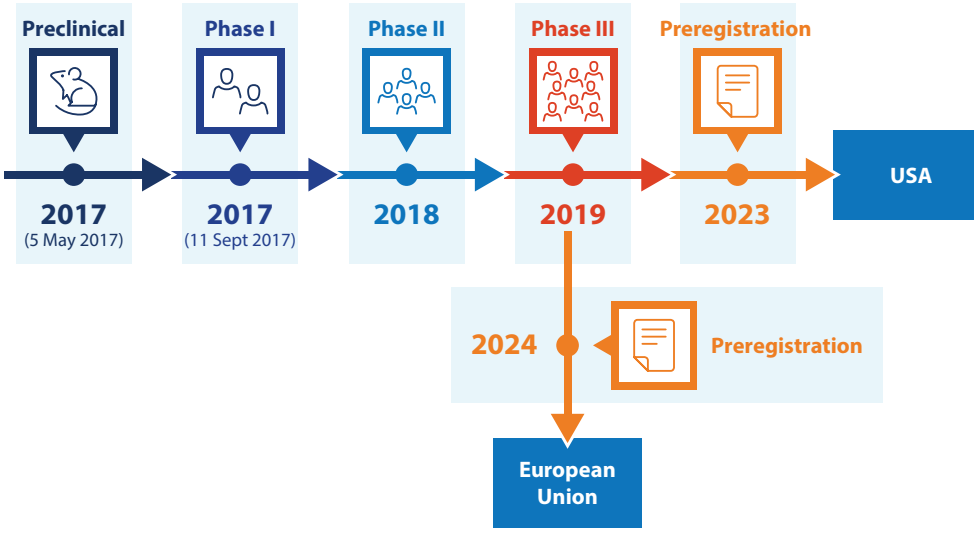
What is the need for Acoramidis

Several treatment options are available for the management of ATTRv, including TTR stabilizers such as diflunisal and tafamidis, as well as molecular therapies like inotersen and patisiran. Additionally, there are several therapeutics in the pipeline for ATTRv, such as TTR inhibitors like vutrisiran, a new ASO therapeutic agent, as well as eplontersen and the TTR stabilizer acoramidis (AG10) which are in late-stage clinical development.

Acoramidis is in late-stage clinical trials, showing greater TTR stabilization than similar existing treatments

Acoramidis (AG10) is a small stabilizer molecule that mimics the effects of the T119M variant, potentially through the formation of hydrogen bonds between residues of the TTR monomers. In vitro studies have shown that AG10 may have superior efficacy and selectivity compared to tafamidis and diflunisal. While tafamidis is currently the preferred treatment option for ATTRv, acoramidis belongs to the same class of drugs and has the potential to be a safe and effective alternative for the management of the disease. Moreover, acoramidis showed significantly greater TTR stabilization than tafamidis, even when the latter reached its peak clinical concentration.

Development Timeline of Acoramidis

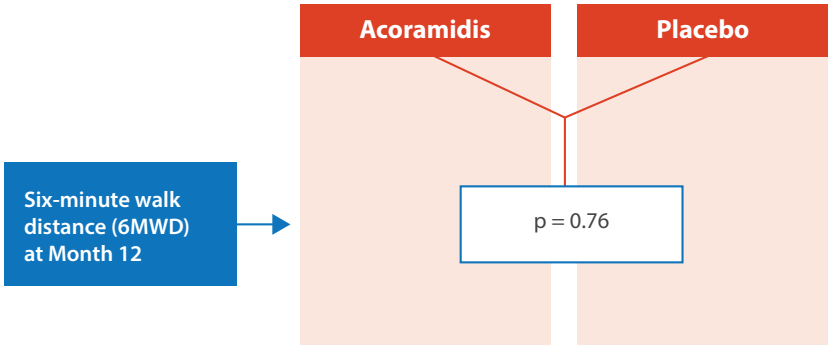


Regulatory Milestones

Marketed Registered Regulatory submission

2025	Expected approval in EU in 2025 for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM)
November 2024	In US, PDUFA date set for November 29, 2024 for the treatment of ATTR-CM
April 2024	Regulatory submission underway in Japan for acoramidis for the treatment of ATTR-CM
February 2024	In US, NDA accepted for US for acoramidis for the treatment of ATTR-CM
February 2024	In EU, MAA accepted by EMA, for acoramidis for the Treatment ATTR-CM

ATTRibute-CM study for ATTRv



Projected market trends for tafamidis meglumine for ATTRv

The well-established drug tafamidis meglumine has seen a significant increase in revenue up to the present day, with projected revenue expected to rise to $3945 million USD by 2025. However, market forecasts suggest a decline in revenue post-2025 due to the emergence of competing drugs for ATTRv. Acoramidis hydrochloride is anticipated to generate an annual revenue of $1.15 billion in the US by 2033.

Market trends and forecast for tafamidis meglumine

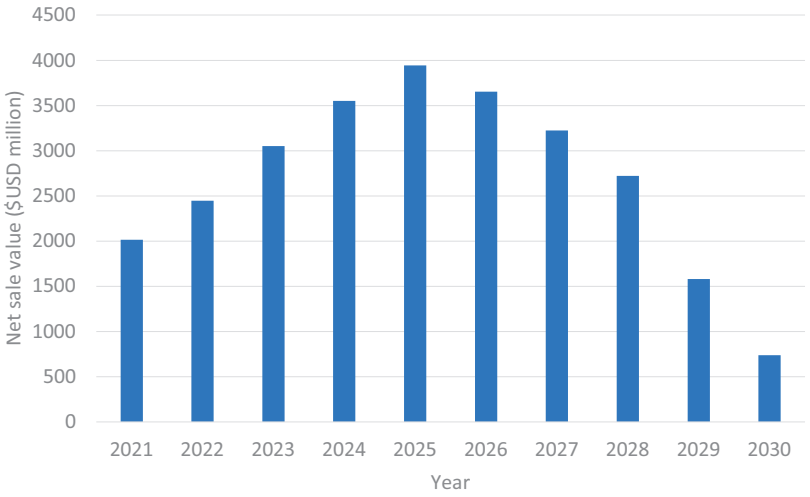


Fig 17: Market forecast for tafamidis meglumine

Licensing Agreement

April 2016

Stanford University — Licensing agreement — Eidos (Licensee)

license to make, use and sell products that are covered by the licensed patent rights

Stanford granted an exclusive worldwide license to make, use and sell products that are covered by the licensed patent rights. The license grant expires when the last licensed patent expires.

September 2019

Eidos — Licensing agreement — Alexion (Licensee)

Development and commercialization of acoramidis in Japan

Eidos will receive an upfront payment of $US25 million and an equity investment of $US25 million with the potential for additional Japanese millstones and royalty-dependent payments

July 2021

Alexion Pharmaceuticals was acquired by AstraZeneca and changed its name to Alexion AstraZeneca Rare Disease

January 2021

Eidos Therapeutics was acquired by BridgeBio Pharma

March 2024

BridgeBio Pharma — Licensing agreement — Bayer (Licensee)

Commercialize acoramidis for transthyretin-related hereditary amyloidosis in Europe

- BridgeBio will receive up to $US310 million comprising of upfront and near-term milestone payments, as well as additional undisclosed sales milestones.
- BridgeBio will also receive royalties in a tiered structure beginning in the low-thirties percent on sales of acoramidis in Europe

mRNA 1345

Indication: Respiratory syncytial virus infections

Route: Intramuscular

Owner: Moderna Therapeutics

Drug class: RNA vaccines

MoA: Immunostimulants

PDUFA date: May 12, 2024

RSV can lead to serious lower respiratory tract infections, especially in older adults and children

mRNA 1345

RSV, also known as respiratory syncytial virus, is a common respiratory pathogen that causes lower respiratory tract disease in infants, children, adults, and immunocompromised older adults. Nearly all children contract RSV by the age of 3, and it exhibits seasonal patterns in most regions worldwide. This virus can lead to severe illness in infants and older adults, resulting in symptoms in the upper and/or lower respiratory tract. RSV belongs to the Pneumoviridae family and has enclosed viral particles containing key surface glycoproteins like the G protein, which aids in attaching to host cells. The F protein, another important component, facilitates attachment and fusion to the host cell membrane. The F protein is a primary target for developing vaccines and prophylactic measures and can transition from a prefusion to a postfusion form. RSV is divided into two subclasses, A and B, and it leads to hospitalization and mortality in older adults, with approximately 60,000 to 120,000 hospitalizations and 6,000 to 10,000 deaths annually due to RSV infections in this population.

Prevalence

Hospitalized adults over 60 with RSV have a 7.13% mortality rate in high-income countries, while Kenya sees 2,461 annual deaths in children under 5 due to RSV

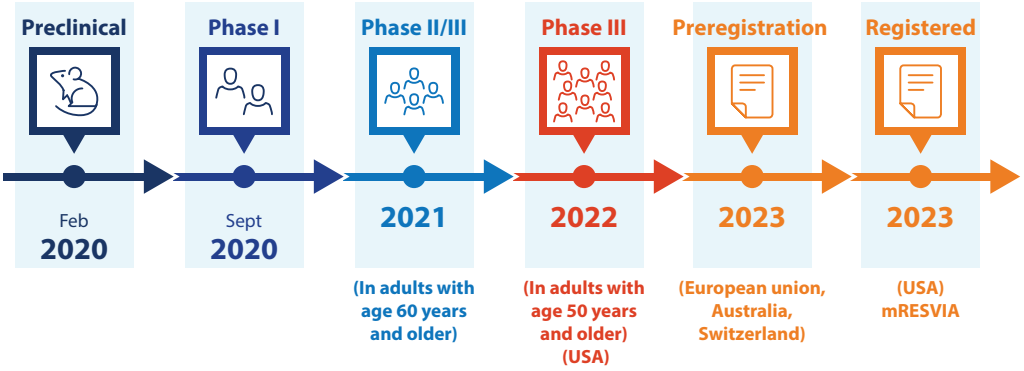
Based on the article published in the International Journal of Infectious Disease, a meta-analysis in high-income countries found that the estimated incidence of lower respiratory infections (LRIs) caused by RSV in adults aged over 60 was 1.62% (with a 95% CI of 0.84-3.08%), and the estimated mortality rate among hospitalized patients was 7.13% (with a 95% CI of 5.40-9.36%). In Kenya, an estimated 2,461 annual deaths in children under 5 were attributed to RSV infection (with a 95% CI of 1,914-3,553). Additionally, in Croatia, the annual hospitalization rate for LRIs caused by RSV in children under 5 was 7.56 (with a 95% CI of 6.83-8.34) per 1000 individuals.

What is the need for mRNA 1345

With no licensed vaccines, mRNA-1345 offers hope for RSV prevention

Currently, treatment options for RSV are limited to supportive care, as there are no licensed vaccines available for prevention or treatment. Various types of mRNA vaccines are currently being tested in clinical trials, with late-stage development of safe and effective RSV vaccines showing promise. One of these, mRNA-1345, has been found to induce a strong neutralizing antibody response against RSV. Additionally, Palivizumab, a monoclonal antibody, is used for the treatment and prevention of RSV infections in high-risk infants. However, due to the expensive nature of this medication, it is only prescribed to infants who face a heightened risk of adverse outcomes, such as being hospitalized for bronchiolitis.

Development Timeline of mRNA-1345

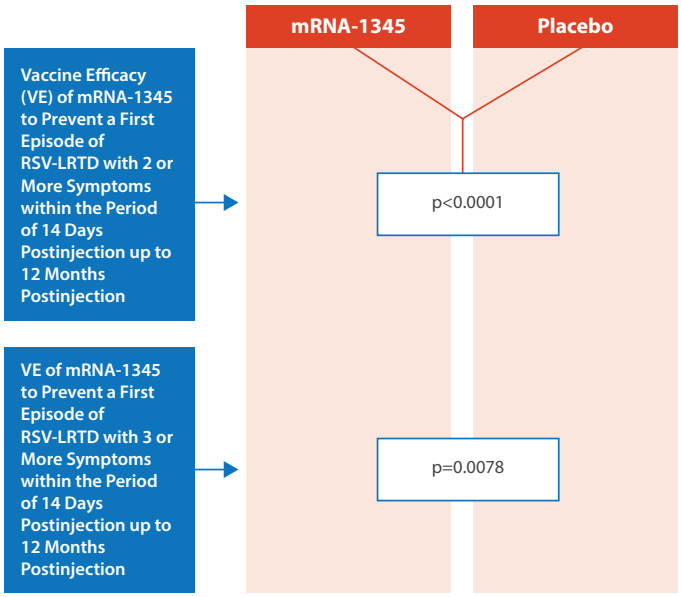


Regulatory Milestones

Marketed Registered Regulatory submission

2024	Expected Launch in Australia and Germany
May 2024	The US FDA approved the mRNA 1345 (mRESVIA) for the prevention of respiratory syncytial virus infections in patients above 60 years of age
July 2023	MAA submission to EMA in EU, to Swissmedic in Switzerland, and the TGA in Australia and rolling submission process for a BLA to the US FDA for the licensure of the mRNA-based RSV vaccine

ConquerRSV study for RSV



Projected market trends for palivizumab for RSV

AstraZeneca (formerly Medimmune) has created the prominent monoclonal antibody palivizumab for the treatment and prevention of respiratory syncytial virus (RSV) infections in high-risk infants. However, the projected market revenue for this drug is anticipated to decrease in the coming years due to the expensive nature of this medication. On the other hand, Moderna is optimistic about achieving $1.46 billion in peak U.S. sales for its mRNA-1345 product after its release, which is expected to greatly contribute to the company's growth in 2025 and break even in 2026.

Market trends and forecast for palivizumab

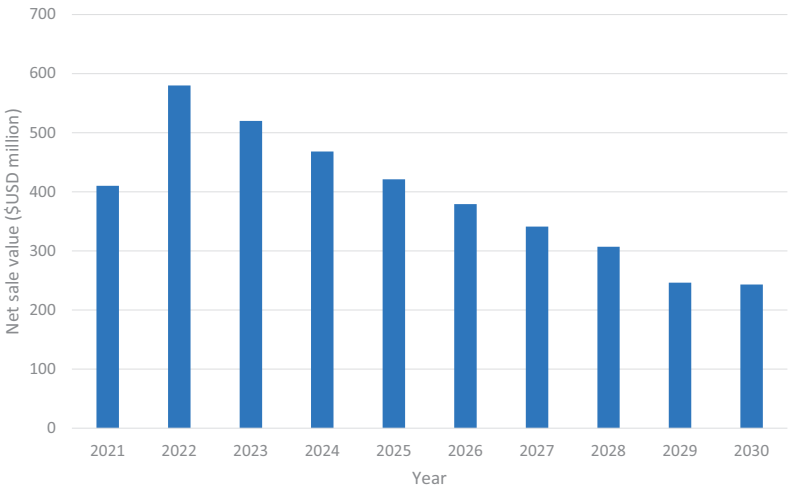


Fig 18: Market forecast for palivizumab

Nogapendekin alfa inbakicept (ANKTIVA)

Bladder cancer (Bca) ranks tenth in global cancer diagnoses, fourth among solid tumors in men, and twelfth among women in the United States . About 75% of bladder cancer patients have non-muscle-invasive bladder cancer (NMIBC). Factors such as a sedentary lifestyle, metabolic syndrome, diet, smoking, and prolonged exposure to diesel exhaust contribute to the development of bladder cancer.

Nogapendekin alfa inbakicept (ANKTIVA)

Indication: Bladder cancer

Route: Intravesicular

Owner: Altor BioScience Corporation

Drug Class: Immunoglobulin Fc fragments; Immunotherapies; Interleukins; Recombinant fusion proteins

MoA: Interleukin-15 receptor agonists

PDUFA date: April 23, 2024

Bladder cancer is the tenth most diagnosed cancer worldwide, with 573,000 new bladder cancer cases reported in 2020

Prevalence

According to research published in the Journal of Global Health (Sept 2023), the estimated number of individuals diagnosed with BCa worldwide in 2020 was 573,000, with an age-standardized incidence rate of 5.6 per 100,000. Additionally, it was reported that 213,000 individuals died from BCa globally in 2020, with an age-standardized mortality rate of 1.9 per 100,000.

What is the need for ANKTIVA

The main treatment for non-muscle-invasive bladder cancer is typically TURBT, which helps determine the patient's risk category and diagnosis. Additional therapies such as BCG therapy and radical cystectomy may be recommended if needed. However, some patients may not respond to BCG therapy, and alternative treatments like pembrolizumab and nadofaragene firadenovec are being investigated. Gemcitabine is another option, despite its side effects (nausea and vomiting, flu-like symptoms such as chills, fever, general feeling of illness, headache, muscle pain, and weakness) for treating bladder cancer.

ANKTIVA could provide alternative treatments for those unresponsive to standard therapies

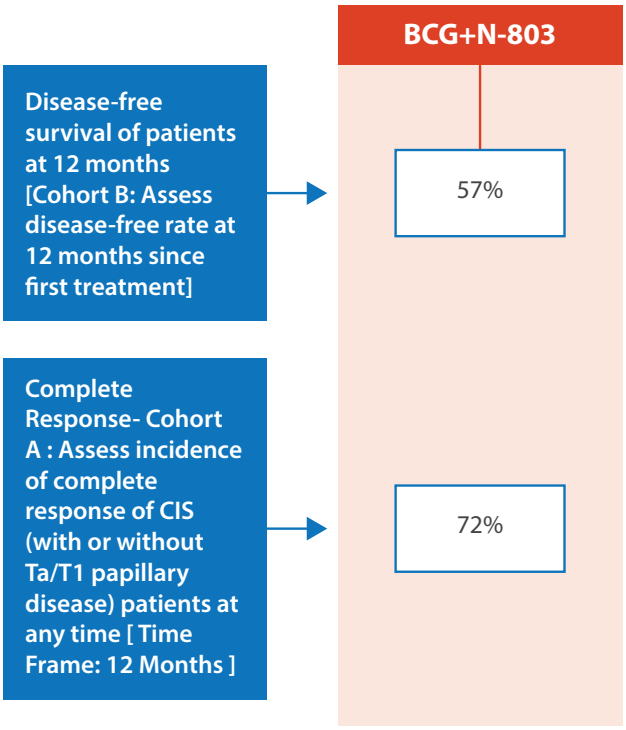
Development Timeline of Nogapendekin alfa inbakicept

Regulatory Milestones

Marketed Registered Regulatory submission

2024	Expected launch for Bladder cancer in combination with BCG
April 2024	In US, for adults with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours, based on phase II/III QUILT-3.032 trial
October 2023	The US FDA accepted the BLA resubmission for review nogapendekin alfa inbakicept (ANKTIVA) with PDUFA date of April 23, 2024
May 2023	In US, US FDA issued complete response letter for ANKTIVA
July 2022	US FDA accepted BLA for ANKTIVA with PDUFA date as May 23, 2023 which was previously submitted in May 2022
May 2022	Original BLA submitted in the US for ANKTIVA

QUILT-3.032 study for bladder cancer



Projected market trends for gemcitabine for bladder cancer

Gemcitabine, a successful drug developed by Eli Lilly for treating bladder cancer, initially generated strong revenue but is expected to decline in the future. In contrast, Market Opportunity Analysts predict that Anktiva could potentially generate annual peak revenues of nearly $900 million by 2028.

Market trends and forecast for gemcitabine

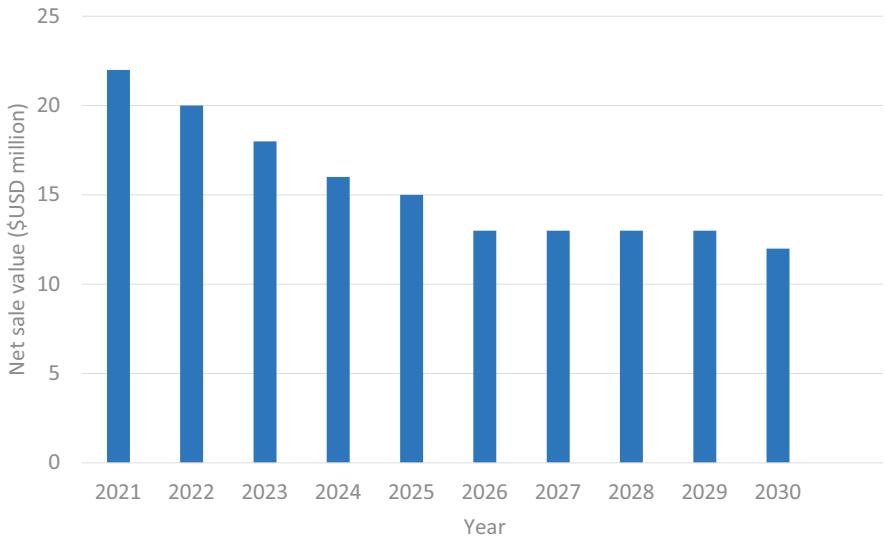


Fig 19: Market forecast for gemcitabine

Talquetamab (TALVEY)

Multiple myeloma (MM) is a type of blood cancer that arises in plasma cells located in the bone marrow, which is the soft, spongy inner part of bones. Healthy bone marrow contains normal plasma cells that produce antibodies to defend against infections. While researchers have gained more insight into the development of multiple myeloma in recent years, the precise cause remains unknown. Similar to other cancers, MM is diverse, with each case being distinctive in its presentation.

Talquetamab (TALVEY)

Indication: Multiple myeloma

Route: Subcutaneous

Owner: Genmab; Janssen Research & Development

Drug class: Antineoplastics; Bispecific antibodies; Immunotherapies

MoA: Antibody-dependent cell cytotoxicity; Cytotoxic T lymphocyte stimulants

Accelerated approval: August 2023

Multiple myeloma arises in plasma cells within the bone marrow, impacting blood cell and antibody production

The median overall survival for patients with multiple myeloma used to range from 2 to 3 years, leading to a significant impact on their quality of life due to various symptoms like pain, fatigue, infections, hospitalizations, fractures, renal failures, and other end-organ damage. However, advancements in treatment have now extended the lives of many individuals with this disease. Managing multiple myeloma can prove challenging as some patients experience relapse, while others may need to alter or discontinue treatment due to side effects. Additionally, changes in the myeloma cancer cells can result in resistance to treatment. Certain patient groups, such as those with extramedullary disease or those who are elderly, frail, or have underlying health conditions, may present additional difficulties in finding effective treatment options.

Prevalence

MM affects 1.78 per 100,000 people worldwide, with varying rates across regions

The Lancet (2020) report revealed that the age-standardized rate (ASR) of MM incidence globally was 1·78 (95% UI 1·69–1·87) per 100 000 people, with mortality at 1·14 (95% UI 1·07–1·21) per 100 000 individuals in 2020. Countries like Australia and New Zealand (ASR 4·86 [4·66–5·07]), northern America (4·74 [4·69–4·79]), and northern Europe (3·82 [3·71–3·93]) had the highest incidence rates, while western Africa (0·81 [0·39–1·66]), Melanesia (0·87 [0·55–1·37]), and southeastern Asia (0·96 [0·73–1·27]) reported the lowest incidences of multiple myeloma.

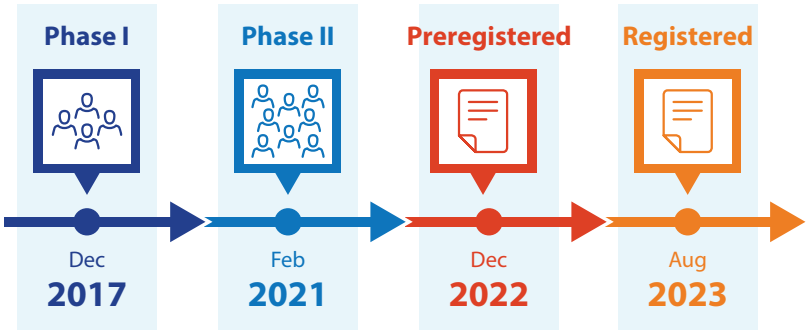
What is the need for TALVEY

Treatment for individuals with symptomatic myeloma includes disease management strategies as well as supportive care to enhance quality of life, such as symptom relief and proper nutrition. Disease-specific treatments typically involve medication therapies like targeted therapy, chemotherapy, and possibly steroids. Bone marrow or stem cell transplantation may be an option in certain cases. Additionally, radiation therapy and surgery may be utilized in specific circumstances. Traditional chemotherapy has been effective in treating myeloma, with drugs like cyclophosphamide, doxorubicin, melphalan, etoposide, cisplatin, carmustine, and bendamustine being commonly used. These chemotherapy drugs may be recommended in select situations. For newly diagnosed individuals, these treatments are less frequently used. For example, melphalan is often reserved for cases involving bone marrow transplantation, as it is used to suppress myeloma over an extended period and allow the patient's bone marrow to recover. Bortezomib, another commonly prescribed medication, may temporarily reduce white blood cell and platelet counts, potentially increasing the risk of infection and affecting blood clotting abilities.

Talquetamab is a promising bispecific antibody targeting MM, enhancing treatment options

Developed by Janssen Research & Development and Genmab, Talquetamab is a humanized, off-the-shelf bispecific antibody that targets both G-protein coupled receptor family C group 5 member D (GPRC5D) and CD3 antigens for the treatment of MM and smoldering MM. Utilizing Genmab's DuoBody® technology, Talquetamab binds to CD3 on T cells and GPRC5D on specific tumor cells, leading to the activation of a cytotoxic T-lymphocyte response against GPRC5D-expressing tumors through the cross-linking of T cells and tumor cells.

Development Timeline of Talquetamab



Regulatory Milestones

Marketed Registered Regulatory submission

August 2023	European Commission granted Conditional Marketing Authorisation as monotherapy for the treatment of adult patients with RRMM based on data from MonumenTAL-1 study
August 2023	US FDA granted accelerated approval as monotherapy for the treatment of adult patients with RRMM
July 2023	CHMP of the EMA recommended conditional marketing authorization
December 2022	BLA submitted in the US for the treatment of patients with relapsed and refractory multiple myeloma (RRMM)

MonumenTAL-1 (Phase 1) study for MM

	Part 1: Dose Escalation (Talquetamab) - Intravenous (IV)	Part 1: Dose Escalation (Talquetamab) - Subcutaneous (SC)	Part 2: Dose Expansion (Talquetamab)
Part 1 and Part 2: Number of Participants with Adverse Events (AEs) as a Measure of Safety and Tolerability [Time Frame: From signing of Informed Consent Form (ICF) up to follow up (until 100 days after the last dose of study drug or until the start of subsequent anticancer therapy, if earlier [approximately 2.10 years])]	showed a low discontinuation rate due to adverse events (AEs) (0.8 mg/kg Q2W dose, eight percent; 0.4 mg/kg QW dose, five percent)		

MonumenTAL-1 (Phase 2) study for MM

	Part 3: Cohort A (Talquetamab)	Part 3: Cohort B (Talquetamab)	Part 3: Cohort C (Talquetamab)	Part 3: Cohort D (Talquetamab)
Overall Response Rate (ORR) [Time Frame: Up to 2 years and 10 months] ORR is defined as the proportion of participants who have a partial response (PR) or better according to the international myeloma working group (IMWG) criteria.	In total, 79% (19/24) of patients achieved a partial response (PR) or better and switched from 0.8 mg/kg Q2W to either 0.4 mg/kg Q2W or 0.8 mg/kg monthly (Q4W) dosing			

Projected market trends for bortezomib for bladder cancer

Bortezomib, one of the top-marketed drugs for MM, experienced a decrease in market revenue starting in 2022 and is predicted to continue declining due to its high cost and various side effects. These side effects include fatigue, nausea, vomiting, constipation, fever, low platelet count, anxiety, and shortness of breath, which are expected to hinder the growth of bortezomib. It is forecasted that market revenue of cancer drugs will increase with the launch of Talvey's which is forecasted to reach $1.8bn by 2029.

Market trends and forecast for bortezomib

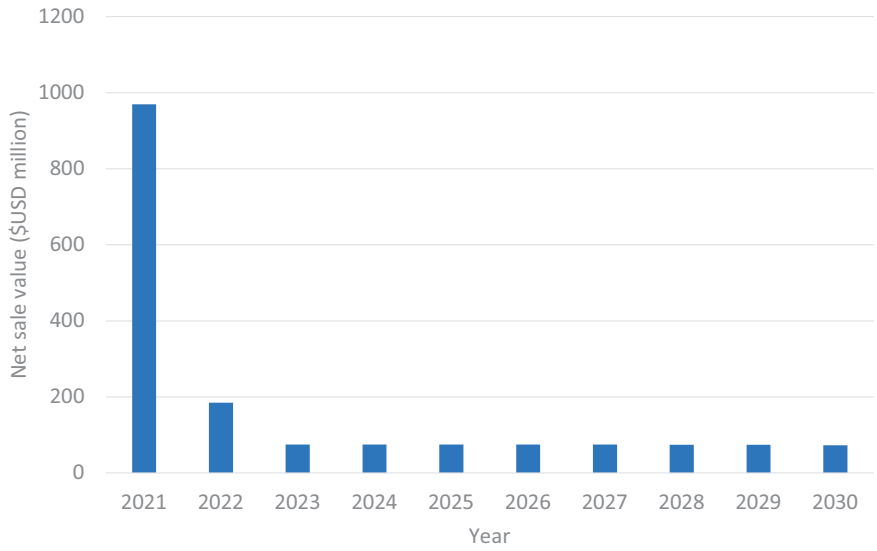
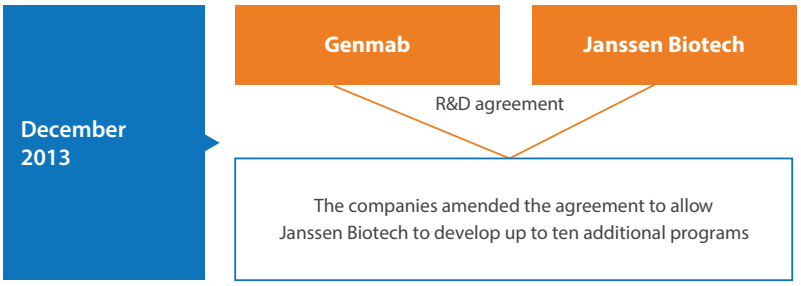


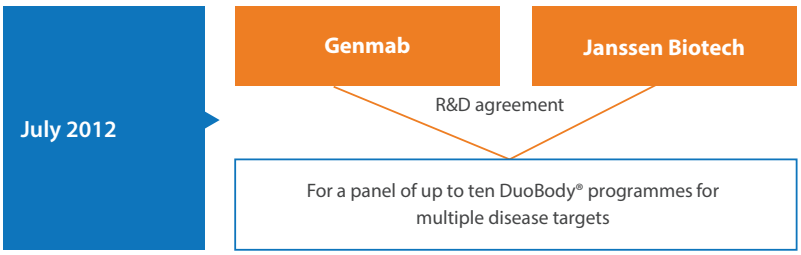
Fig 20: Market forecast for bortezomib

Research and development collaboration

Genmab received an upfront payment of $US2 million, as well as the potential to receive an average of $US191 million if every additional program



Genmab received an upfront payment of $US3.5 million and potential milestone payments of up to $US175 million from Janssen for each product, along with research funding and royalties on sales



Ensifentrine

Indication: Chronic obstructive pulmonary disease (COPD)

Route: Inhalation

Owner: Verona Pharma

Drug class: Small molecules

MoA: Cystic fibrosis transmembrane conductance regulator stimulants; Type 3 cyclic nucleotide phosphodiesterase inhibitors; Type 4 cyclic nucleotide phosphodiesterase inhibitors

PDUFA date: June 26, 2024

Ensifentrine

COPD is a diverse condition characterized by chronic respiratory symptoms including dyspnea, cough, and expectoration due to persistent abnormalities in the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema), leading to advanced airflow limitation. Various factors contribute to airway obstruction such as smoking, exposure to environmental pollutants, birth defects, frequent respiratory infections, and a deficiency of the alpha-1 antitrypsin gene. Symptoms commonly seen in COPD patients include difficulty breathing, fatigue, and a chronic cough.

Prevalence

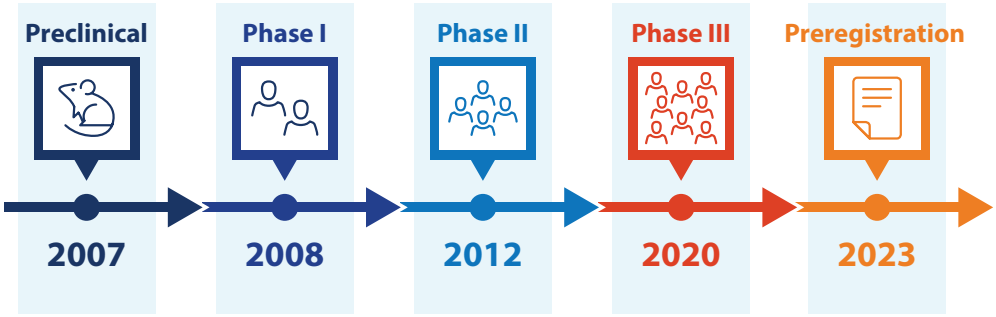
COPD ranks as the third highest cause of mortality globally, affecting 12% of the general population. The disease places a significant strain on individuals due to its high cost and detrimental effects on their quality of life. Despite its widespread prevalence, COPD is often overlooked and underdiagnosed on a global scale, primarily owing to a lack of awareness among both patients and healthcare providers, as well as a tendency to underestimate the signs and symptoms of the illness.

What is the need for Ensifentrine

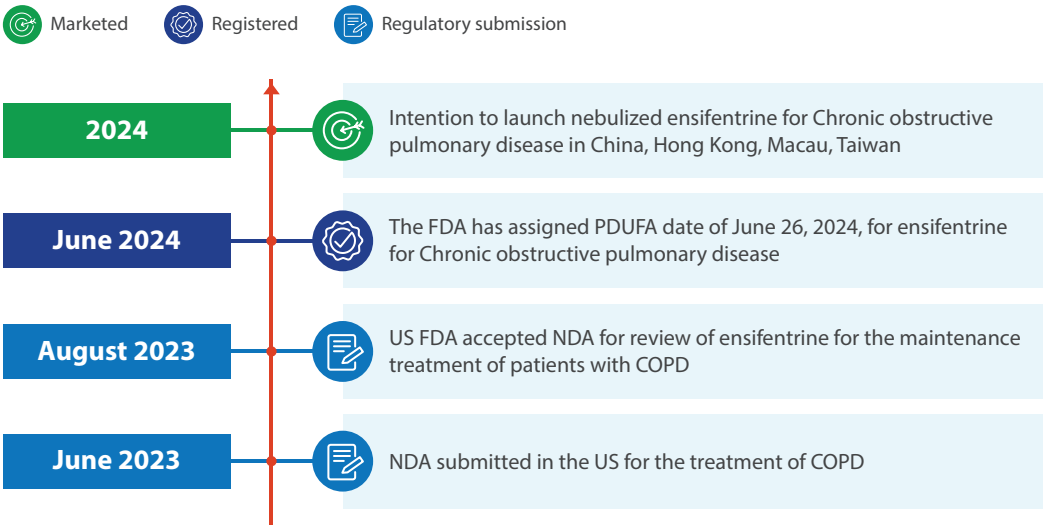
Bronchodilators and corticosteroids are frequently utilized in the treatment of COPD, while anti-inflammatory PDE4 inhibitors are typically used for sudden severe exacerbations of symptoms. Despite the variety of available therapies, a significant number of COPD patients still experience exacerbations, leading to a high number of emergency department visits and hospitalizations annually in the United States. Unfortunately, current treatments have not been able to halt the progressive decline in lung function or reduce the mortality rate associated with COPD. To address these issues, a new, potentially efficacious treatment needs to be developed to reduce the frequency and impact of symptoms and exacerbations. Some medications, like budesonide formoterol, have minimal side effects but may slightly elevate blood pressure and, in rare cases, trigger severe breathing difficulties immediately after use. A combination drug in this category is Riltrava Aerosphere, which includes formoterol, glycopyrronium bromide and budesonide. The most common side effects associated with Riltrava Aerosphere, affecting up to 1 in 10 individuals, include pneumonia, headaches, and urinary tract infections.

Ensifentrine (RPL554) is a new compound that inhibits both phosphodiesterase (PDE) 3 and 4 enzymes, impacting various respiratory functions on a cellular and tissue level. By targeting both PDE3 and PDE4, Ensifentrine works synergistically to decrease inflammation and improve bronchodilation since these enzymes are present in inflammatory cells and airway smooth muscles. In studies conducted before clinical trials, Ensifentrine demonstrated relaxation of bronchial smooth muscles and enhanced effects when combined with muscarinic antagonists. Additionally, this compound has shown promising results as a standalone treatment or when used alongside standard therapies in clinical trials, providing both bronchodilator and anti-inflammatory effects.

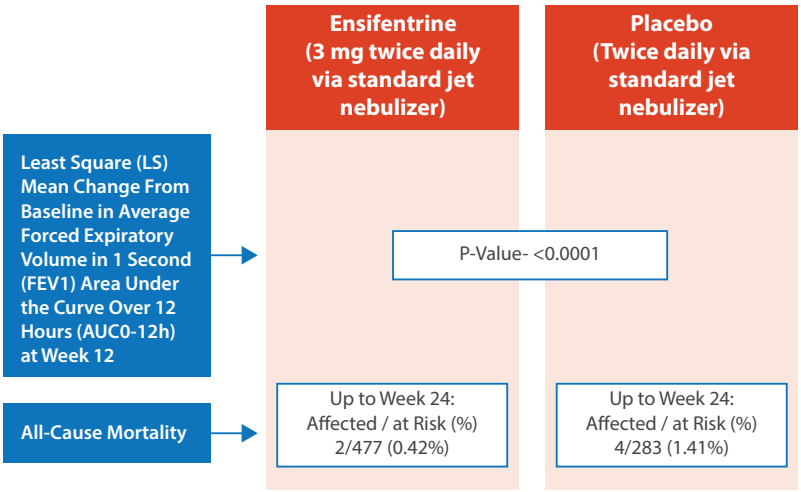
Development of Ensifentrine



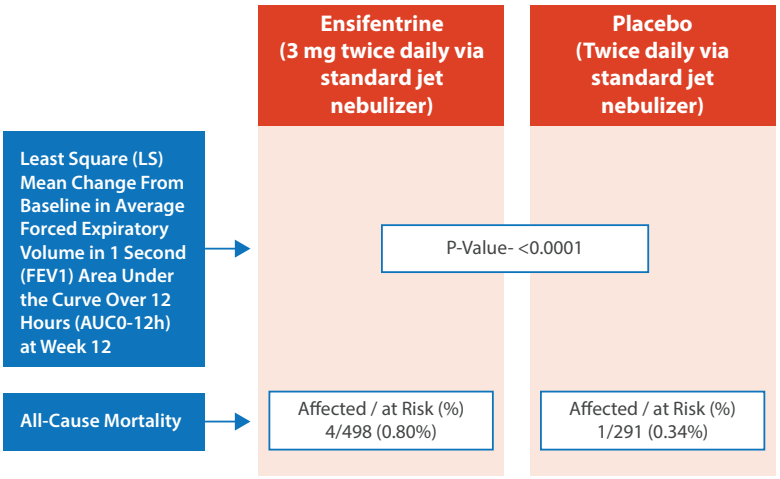
Regulatory Milestones



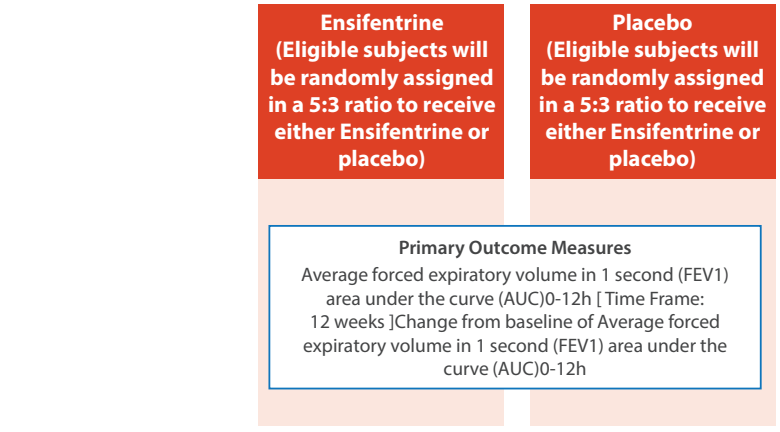
ENHANCE-1 study for COPD



ENHANCE-2 study for COPD



ENHANCE-CHINA study for COPD



Projected market trends for Riltrava Aerosphere for COPD

Riltrava Aerosphere, a well-established medication for COPD, has seen significant growth in market revenue in recent years and is projected to continue this trend in the future. However, a challenge in using this drug lies in its maintenance treatment for adults who do not respond well to a combination of inhaled medications, including a long-acting beta-2 agonist and either a corticosteroid or a long-acting muscarinic antagonist. In contrast, the introduction of Ensifentrine, a standalone treatment for COPD, is expected to achieve an annual revenue of $1.99 billion in the US by 2033.

Market trends and forecast for Riltrava Aerosphere

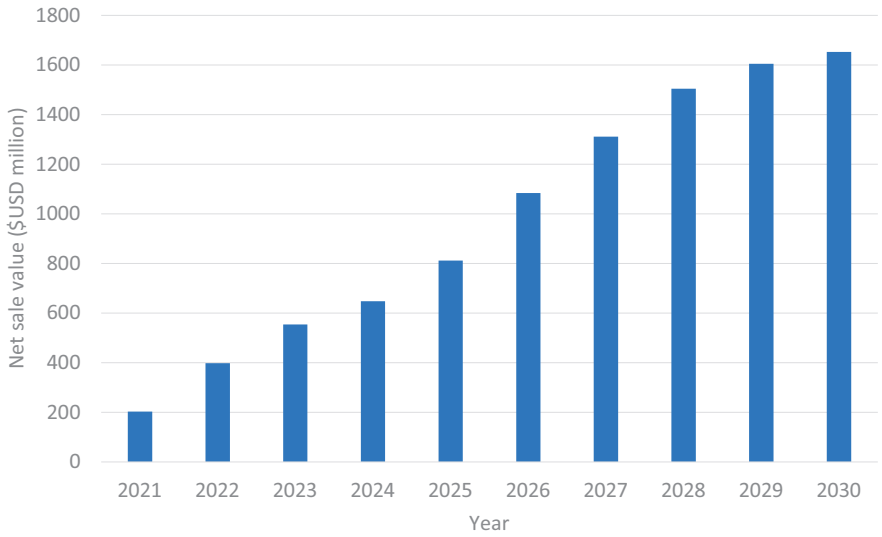


Fig 21: Market forecast for Riltrava Aerosphere

Licensing Agreement

June 2021

Verona Pharma entered into an agreement with Nuance Pharma for the development and commercialization of ensifentrine in Greater China (mainland China, Taiwan, Hong Kong and Macau).

Verona Pharma will receive an upfront payment of $US25 million in cash and an equity interest currently valued at $US15 million in Nuance Biotech with future milestone payments of up to $US179 million

April 2017

Verona Pharma entered into a collaboration with two European technology companies for the development of ensifentrine as dry powder inhaler (DPI) and metered dose inhaler (MDI) formulations for maintenance treatment of chronic obstructive pulmonary disease

June 2007

Verona Pharma entered into a contract with LAB Research Inc, to conduct formal preclinical safety evaluation studies of ensifentrine. The company also signed a contract with Onyx Scientific Ltd to synthesize ensifentrine for preclinical and clinical studies

November 2006

Verona Pharma entered into a contract with MedPharm Ltd to develop a formulation of ensifentrine for preclinical and clinical study.

Imetelstat (RYTELO™/GRN 163)

Myelodysplastic syndromes (MDS) are a diverse group of myeloid diseases characterized by the abnormal proliferation of myelodysplastic stem and progenitor cells in the bone marrow, resulting in peripheral-blood cytopenia and an increased risk of progression to acute myeloid leukemia (AML). Approximately 70% of MDS patients fall into the lower-risk category according to the International Prognostic Scoring System (IPSS) or the Revised IPSS, which includes those with low or intermediate-1 risk levels. These patients often experience symptoms such as anemia, which can lead to decreased cardiopulmonary function, a higher risk of falls, and cognitive decline, particularly in elderly individuals. Many lower-risk MDS patients eventually become dependent on red blood cell transfusions (RBC-TD), negatively impacting their quality of life and increasing mortality rates.

Imetelstat (RYTELO™/GRN 163)

Indication: Myelodysplastic syndromes

Route: Intravenous

Owner: Geron Corporation

Drug class: Lipids, Oligonucleotides

MoA: Telomerase inhibitors

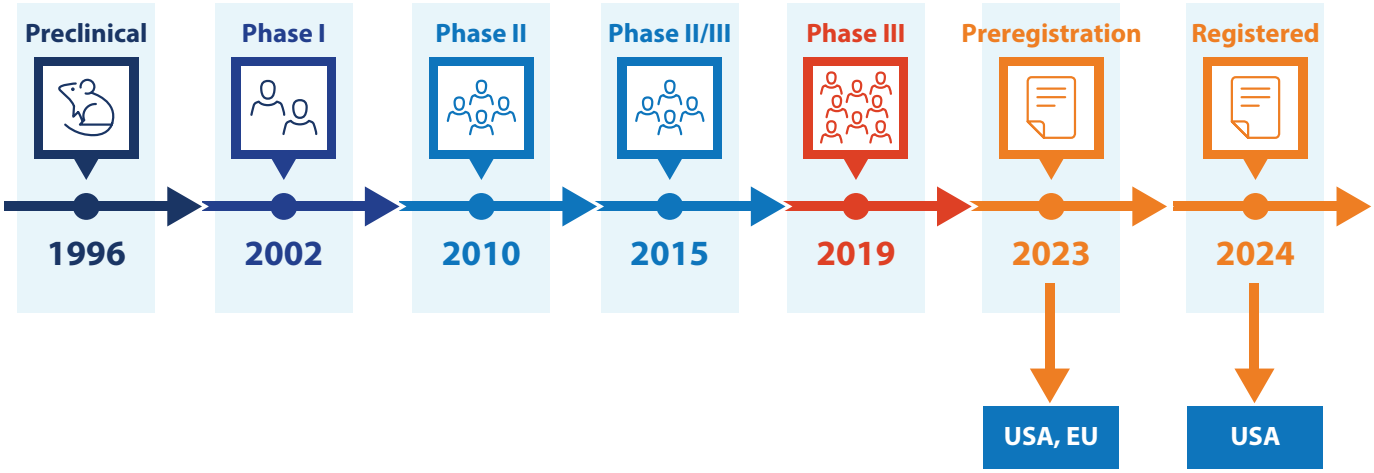
Prevalence

MDS typically affects older individuals, with a median age of around 70 years. Less than 10% of cases occur in individuals under the age of 50. The prevalence of MDS is around 4 cases per 100,000 people per year, rising to 40-50 cases per 100,000 in elderly patients aged 70 years and older. The cause of MDS is identified in only 15% of cases, with approximately one-third of pediatric MDS patients having a genetic predisposition to the disorder. Other contributing factors include gene mutations, prior exposure to chemotherapy, and tobacco smoking.

What is the need for Imetelstat

While the risk of AML progression is lower in LR-MDS, elderly patients typically succumb to other causes aside from MDS or AML. Therefore, prioritizing the treatment of cytopenias, such as anemia, and improving quality of life should be the focus. Management of LR-MDS involves increasing blood cell counts, reducing the need for transfusions, minimizing disease complications, and enhancing patient quality of life based on symptoms, pathology, and patient preferences. Treatment options for LR-MDS include erythropoiesis-stimulating agents (ESAs), Lenalidomide, hypomethylating agents like azacitidine or decitabine, and luspatercept, particularly effective for patients with the ring sideroblast phenotype. Imetelstat (GRN163L) is an oligonucleotide that inhibits human telomerase reverse transcriptase (hTERT) enzyme activity by binding to human telomerase RNA (hTR) template region, offering a novel approach to treatment.

Development Timeline of Imetelstat (RYTELO™)

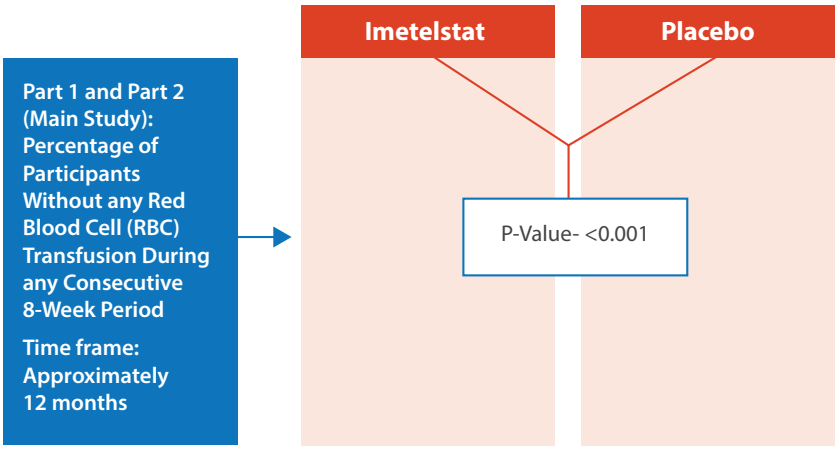


Regulatory Milestones

Marketed Registered Regulatory submission

June 2024	Approved by US FDA for the treatment of transfusion-dependent anemia in patients with lower risk myelodysplastic syndromes (MDS) (RYTELO™)
March 2024	FDA has scheduled an advisory committee meeting as part of the NDA review
August 2023	US FDA accepted the New Drug Application, in June 2023
September 2023	EMA validated MAA in Europe in lower-risk myelodysplastic syndromes based on results from IMerge Phase II/III trial

IMerge study for MDS



Projected market trends for luspatercept for MDS

Luspatercept, an established drug for MDS, has experienced a significant growth in market revenue in recent years and is expected to continue this trend in the future. The main challenge in treating lower-risk MDS (and often in PMF) is improving anemia to reduce the need for RBC transfusions and cardiovascular complications, as well as enhancing quality of life. Current anemia treatments for MDS have inconsistent and short-lived efficacy. In contrast, the introduction of imetelstat, a groundbreaking telomerase inhibitor, has the potential to capture 10-15% of the $2.4 billion global MDS treatment market.

Market trends and forecast for luspatercept

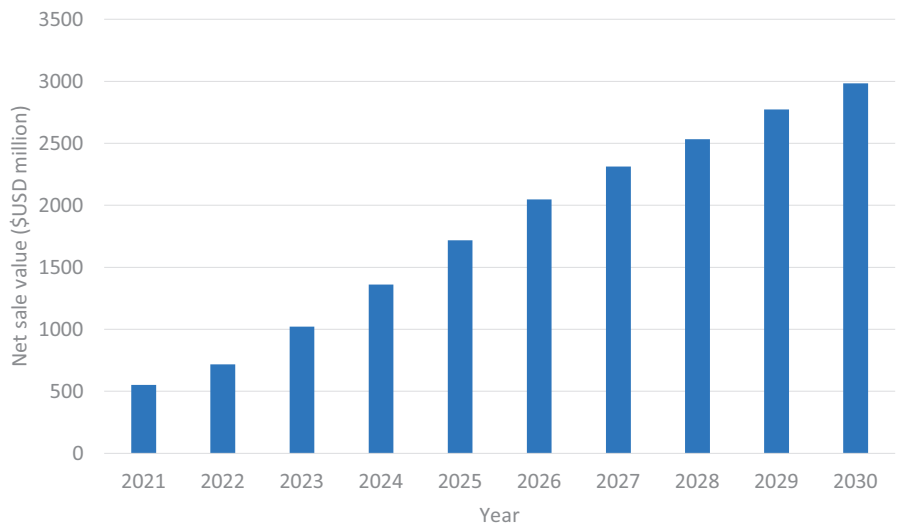


Fig 22: Market forecast for luspatercept

Licensing Agreement

Geron Corporation + Sirna Therapeutics

Geron and Sirna Therapeutics (formerly Ribozyme Pharmaceuticals) have an agreement that allows Sirna Therapeutics to manufacture imetelstat (GRN 163). The initial agreement was signed in December 2001.

Geron Corporation + Janssen Biotech

In November 2014, Geron Corporation entered into an exclusive worldwide license and collaboration agreement with Janssen Biotech, Inc to develop and commercialize, imetelstat, for the treatment of hematologic malignancies for an initial payment of $US35 million and additional payments up to a potential total of $US900 million for the achievement of development, regulatory and commercial milestones, as well as royalties on worldwide net sales.

Collaboration terminated in September 2018 as a result of the strategic portfolio evaluation and prioritization of assets within their portfolio. with immediate effect, Geron corporation has regained the global licensed rights to develop and commercialize imetelstat, intellectual property rights generated under the collaboration without any continuing economic obligations to Janssen.

Zolbetuximab (VYLOY)

Indication: Gastric cancer

Route: Intravenous

Owner: Ganymed Pharmaceuticals

Drug class: Antineoplastics; Immunotherapies; Monoclonal antibodies

MoA: Antibody-dependent cell cytotoxicity

Approval: MHLW approved zolbetuximab in combination with chemotherapy for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-negative, CLDN18.2 positive, unresectable, advanced or recurrent gastric cancer (March 2024)

Zolbetuximab (VYLOY)

Gastric cancer (GC) remains a prominent contributor to cancer-related mortality and morbidity on a global scale. The management of advanced gastric cancer typically involves a combination of treatments. A comprehensive approach that includes a thorough surgical resection and lymph node removal is essential for improving long-term outcomes in patients with operable disease.

Surgery may be required to remove part or all of the stomach in certain cases of stage 1 cancer. However, for stage 2 and stage 3 stomach cancers, surgery may not be the initial treatment choice. Chemotherapy and radiation therapy may be used as the first line of treatment to reduce the size of the cancer, potentially making it easier to fully remove.

Prevalence

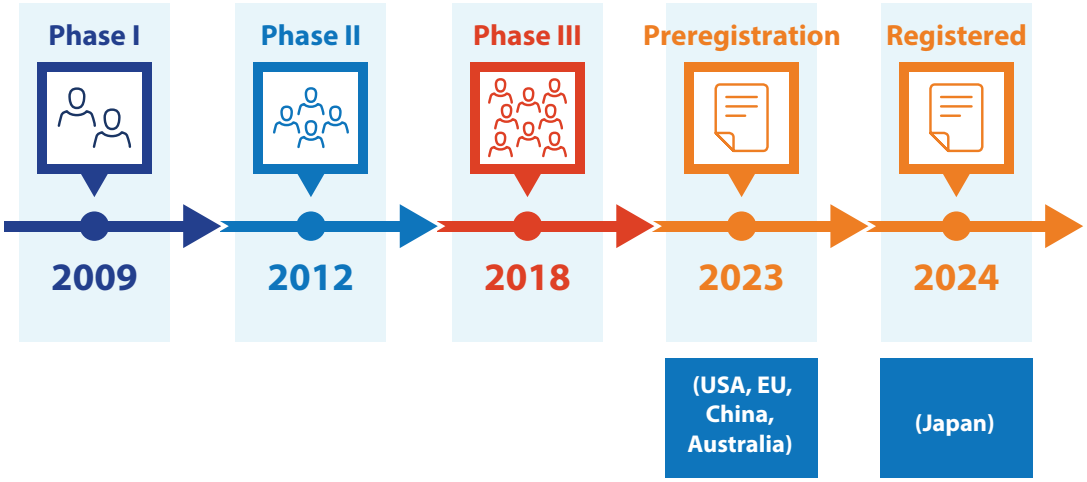
According to the American Cancer Society, stomach cancer predominantly impacts older individuals, with the average age of diagnosis being 68 years old. Approximately 6 out of 10 cases of stomach cancer each year affect people aged 65 or older. Men have a higher lifetime risk of developing stomach cancer compared to women, with about 1 in 101 men and 1 in 155 women being affected. However, individual risk factors can play a significant role in determining one's likelihood of developing the disease.

What is the need for VYLOY

Chemotherapy involves the administration of medication to eliminate cancer cells, typically by inhibiting their growth, division, and proliferation. Treatment typically consists of a specific number of cycles administered over a predetermined period. Patients may receive a single drug or a combination of medications simultaneously. The aim of chemotherapy may be to eradicate any remaining cancer post-surgery, slow tumor growth, or alleviate cancer-related symptoms. It is often utilized in conjunction with radiation therapy. While there is no universally accepted standard chemotherapy regimen, treatments for stomach cancer typically involve combinations of drugs such as Cisplatin, Oxaliplatin, Fluorouracil, and Nivolumab. Other medications commonly used include Capecitabine, Docetaxel, Irinotecan, Paclitaxel, Ramucirumab, Trastuzumab deruxtecan, and Trifluridine/tipiracil. The side effects of chemotherapy can vary among individuals and may include fatigue, susceptibility to infections, nausea, vomiting, hair loss, decreased appetite, and diarrhea. These side effects typically diminish following the completion of treatment.

Zolbetuximab, a chimeric IgG1 monoclonal antibody developed by Astellas Pharma, is designed to target claudin 18.2 (CLDN18.2) in the treatment of gastric cancer, gastroesophageal junction (GEJ) adenocarcinoma, and pancreatic adenocarcinoma. Claudin 18.2 is a transmembrane protein similar to CD20, primarily found in the tight junctions of the gastric mucosa, where it plays a role in cell adhesion. However, in cancerous cells, claudin 18.2 is often overexpressed on the cell surface, promoting cancer cell survival and metastasis. Zolbetuximab specifically binds to the claudin-18 splice variant 2 (CLDN18.2) and induces cell death through mechanisms such as antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Clinical studies have shown that treatment with zolbetuximab, in conjunction with chemotherapy, leads to improved overall survival rates in patients with CLDN18-positive tumors.

Development Timeline of Zolbetuximab



Regulatory Milestones

Marketed Registered Regulatory submission

March 2024
MHLW approved in combination with chemotherapy in Jan for treatment HER2-negative, CLDN18.2 positive, unresectable, advanced or recurrent gastric cancer.

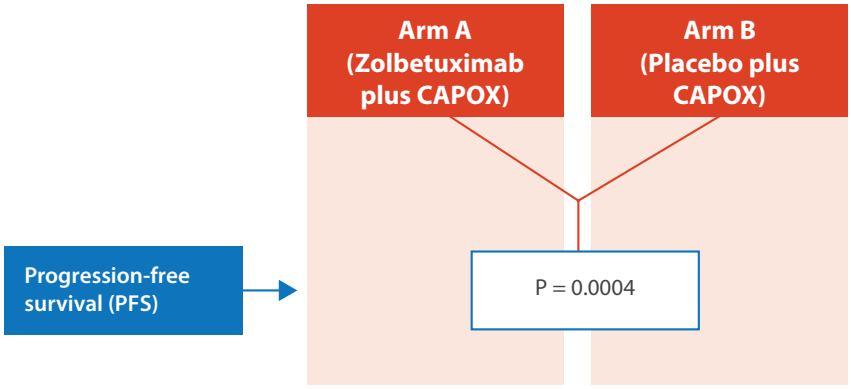
January 2024
The US FDA issued a CRL stating that it cannot approve the BLA by the PDUFA action date (12 Jan 2024) due to unresolved deficiencies following its pre-license inspection of a third-party manufacturing

December 2023
The Therapeutic Goods Administration accepted BLA

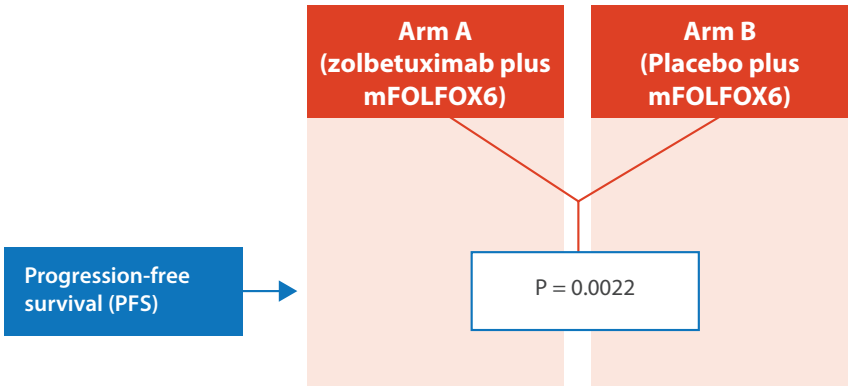
July 2023
EMA accepted for regulatory review of MAA

July 2023
The Center for Drug Evaluation of NMPA has accepted BLA for first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are CLDN18.2-positive, based on results from the phase III GLOW and SPOTLIGHT clinical trials

GLOW study for GC



Spotlight study for GC



Projected market trends for nivolumab for GC

Nivolumab, a well-established drug for gastric cancer, has seen a consistent increase in revenue over the years and is expected to continue this trend in the future. However, despite this financial success, the objective response rate for nivolumab in treating gastric cancer is only 11.2%. In contrast, zolbetuximab has shown a higher survival rate. When combined with capecitabine/oxaliplatin, zolbetuximab is projected to incur an additional cost of $91,551 but provide an extra 0.24 quality-adjusted life-years (QALY) compared to a placebo plus CAPOX. This results in an incremental cost-effectiveness ratio of $388,186/QALY, well above the willingness-to-pay threshold of $38,223/QALY.

Market trends and forecast for nivolumab

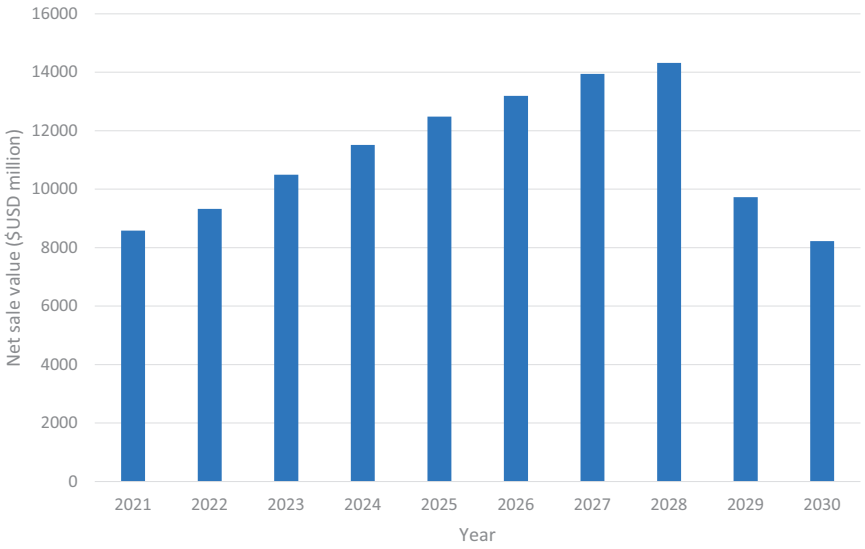
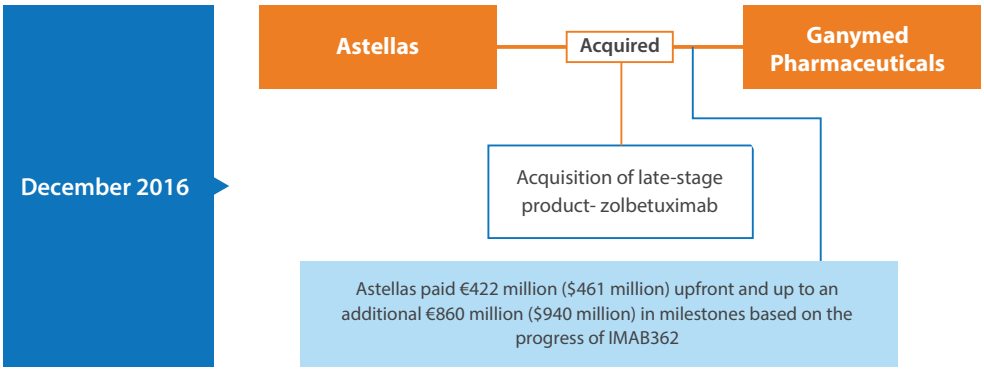


Fig 23: Market forecast for nivolumab

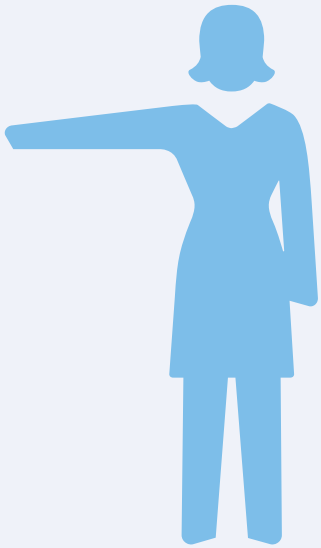
Acquisitions/mergers



Conclusion:

This report highlights the significant strides made in the pharmaceutical industry in the past few years. Throughout 2023, the introduction of nine breakthrough therapies has showcased the sector's innovative capabilities. These include new vaccines, gene therapies, and novel formulations aimed at combating a variety of diseases.

Additionally, the anticipation surrounding the 12 potential blockbuster drugs set for launch in 2024 is palpable. These drugs target a range of conditions, including Alzheimer's disease, cancer, schizophrenia, RSV infection immunization, Crohn's disease, and various blood disorders. Their development and impending release underscore a critical shift towards more effective, personalized, and precise treatments.



The advancements discussed in this report not only offer hope for improved patient outcomes but also set the stage for a transformative period in medical treatment. As these therapies and drugs become available, they will play a pivotal role in enhancing the quality of life for millions, addressing previously unmet medical needs, and shaping the future of healthcare. The pharmaceutical industry stands at the cusp of a new era, driven by relentless innovation and a commitment to tackling the most challenging health issues of our time.

What did you think of this report? Tell us here.

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You need data insights to deliver your organization's objectives and overcome your biggest challenges. That data needs to be trustworthy, up to date, and accurate. How to access and

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