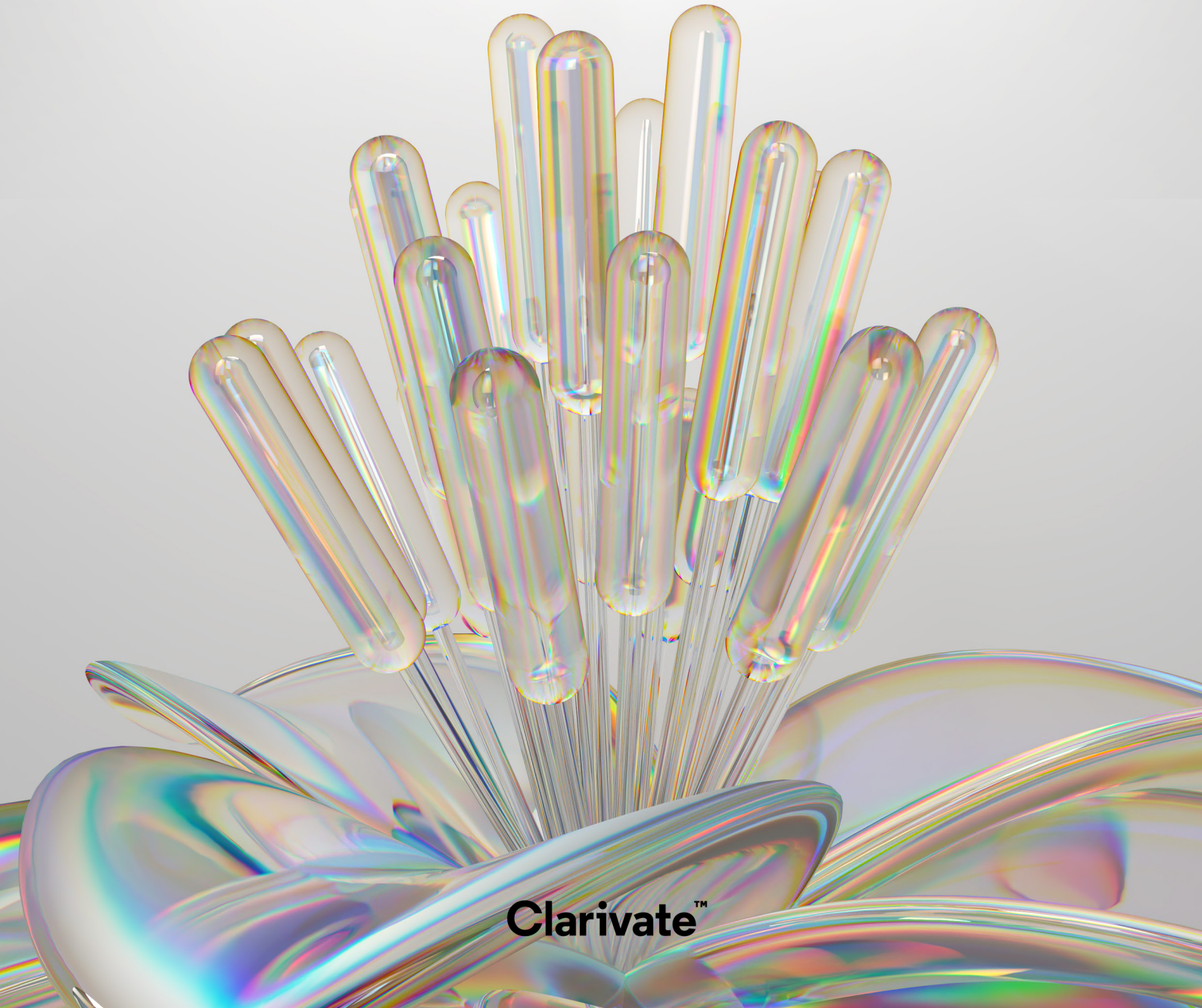
Drugs to Watch 2025

A new generation of treatments coming to fruition



Clarivate™

Carefully nurtured by innovators and regulators, medical advancements bear fruit for public health

The life sciences landscape is currently undergoing an exciting transformation spurred by evolving regulatory standards and an increasing emphasis on patient-centered care. Regulatory agencies are championing equitable access to healthcare and valuing patient preferences, which open up a wealth of opportunities for pharmaceutical and biotechnology companies.

As these organizations work through the intricacies of drug development, they have the chance to embrace new paradigms that prioritize the patient voice, enhance health outcomes and tackle health disparities head-on. To showcase the benefits of new medical innovations in this dynamic environment, it's critical to leverage real-world data (RWD), patient-reported outcomes (PROs) and cutting-edge technologies like artificial intelligence (AI) and machine learning (ML). This approach not only fosters innovation but also builds a brighter future for healthcare.

The drug development landscape is evolving and presents a wealth of opportunities despite some challenges. While regulatory hurdles exist, the industry's commitment to innovation is paving the way for more efficient approval processes. By focusing on the importance of generating robust data, companies are empowered to utilize PROs and RWD to showcase the long-term benefits and safety of their therapies, enhancing their submissions to regulatory bodies. This proactive approach is also beneficial for health technology assessment (HTA) agencies and payers, ensuring thoughtful evaluations. Additionally, prioritizing data security and privacy reflects our dedication to safeguarding sensitive information. Together, these elements can truly transform healthcare for the better!

The landscape for new therapies is evolving, presenting exciting opportunities for innovation despite some challenges related to market access. While delays in pricing and reimbursement decisions can sometimes slow the introduction of these groundbreaking treatments, it is heartening to note that proactive planning can lead to successful outcomes. As the healthcare landscape adapts, the demand for comprehensive data to illustrate real-world effectiveness in new pricing models is becoming increasingly recognized, encouraging a collaborative spirit among stakeholders.

Integrating innovative therapies into existing healthcare systems is an opportunity to enhance provider education and improve treatment protocols. Embracing the complexities of personalized medicine, we have the chance to identify suitable patient populations and customize treatments based on individual genetic profiles. By developing relevant clinical outcome assessments, we can truly optimize the impact of new therapies.

Ethical and social considerations are paramount and can significantly influence public perception of these innovative therapies. Companies are encouraged to take a proactive stance in ensuring that access to advanced treatments, particularly those that are high cost, is equitable. Early strategic planning within life science companies can turn potential challenges into opportunities, such as enhancing diversity in clinical trials. This not only enriches our understanding of disease performance across varied populations but also aligns with best practices in scientific research.

Gene therapy is beginning to realize its promise

Last year, we flagged 13 molecules as Drugs to Watch. Of these, 12 have been approved and launched, while one is on the launchpad. While some launches have met or exceeded expectations, some have been slower off the mark.

12 of 13

Drugs from last year's report have now been approved and launched.

The most groundbreaking of the new medicines highlighted in the 2024 edition were CASGEVY®, a gene-edited medicine to treat both sickle cell disease (SCD) and beta thalassemia from Vertex Pharmaceuticals Inc and CRISPR Therapeutics, and LYFGENIA™, a one-time gene therapy from bluebird bio Inc to treat SCD. Both products have won approvals across the globe, and CASGEVY has already begun to generate revenue.

During Vertex Pharmaceuticals Inc's third quarter earnings call, the company announced that 40 patients have already had at least one cell collection (double the number in Q2), and the company has set up 45 authorized treatment centers globally. It can take three or four attempts to get enough healthy cells to be turned into the therapy – the cells are then sent back to a manufacturer to be edited to encourage the body to express fetal hemoglobin, before being transfused back into the patient.

Bluebird bio Inc has also reported "significant progress" with access to LYFGENIA in the U.S. So far, bluebird bio Inc says it has collected cells from four patients to start its SCD therapy LYFGENIA.[1]

The only one of the 2024 picks yet to be approved is datopotomab deruxtecan, a TROP2-directed antibody drug conjugate (ADC) being jointly developed by AstraZeneca and Daiichi Sankyo to treat adults with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who have previously received systemic therapy and to treat adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer.

For the NSCLC indication, the FDA has set a Prescription Drug User Fee Act (PDUFA) date of December 20, 2024, while the PDUFA date for the regulatory decision for its use to treat breast cancer is January 29, 2025.

Meeting the moment and delivering for patients

Innovation remains at the heart of drug development, with remarkable progress already evident in 2024 through significant approvals for therapies targeting rare diseases and cancers. The introduction of novel radiopharmaceuticals represents a remarkable advancement, offering a "see it and treat it" approach that enhances precision in cancer management. Additionally, the surge of new obesity medications highlights a growing commitment to addressing weight management as a vital public health concern, promising impressive outcomes for individuals seeking effective solutions.

Looking ahead, the life sciences sector is poised to adopt a multifaceted approach encompassing robust research and development, strategic regulatory preparation, strong stakeholder engagement and continuous innovation. The synergy between regulatory agencies and the life sciences industry will be crucial as we work together to address treatment gaps.

By leveraging advanced technologies and maintaining a patient-centered focus, we are equipped to not only navigate the complexities of today's healthcare environment but also drive substantial advancements in treatment options for patients across the globe.

Henry Levy
President, Life Sciences & Healthcare, Clarivate

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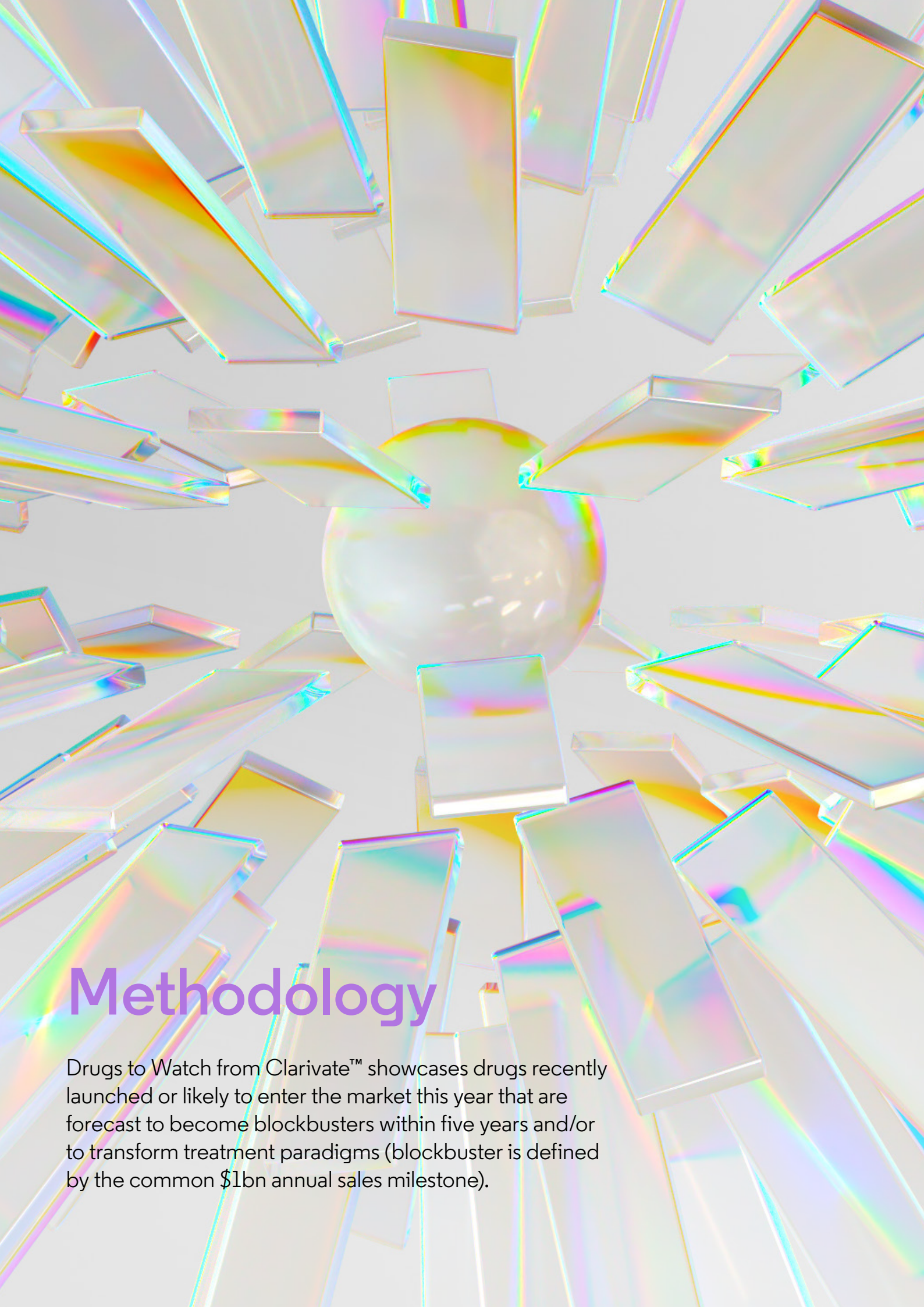

Methodology

Drugs to Watch from Clarivate™ showcases drugs recently launched or likely to enter the market this year that are forecast to become blockbusters within five years and/or to transform treatment paradigms (blockbuster is defined by the common $1bn annual sales milestone).

To identify this year's Drugs to Watch 2025 list, we drew on expertise from over 160 Clarivate analysts covering hundreds of diseases, drugs and markets and 11 integrated data sets that span the R&D and commercialization lifecycle.

Clarivate experts then manually evaluated each drug in its individual context, based on factors such as expected approval or launch dates, competitive landscape, regulatory status, trial results, market dynamics and other factors and added novel drugs that, while likely to fall short of blockbuster status, are poised to be therapeutic game-changers.

Drug selection criteria:

- Candidate drugs in phase 2 or phase 3 trials, at pre-registration or registration stage or already launched early in 2024 were selected for analysis, including drugs launched for a new indication that could be particularly impactful on the industry; drugs launched prior to 2024 were excluded.

- The dataset was then filtered for drugs that had total forecast sales of $1bn or more in 2030.

- Expert analysts then added recently launched and soon-to-launch therapeutics set to significantly transform treatment paradigms, even if they are not forecast to be blockbusters within five years.

From there, we determined 11 Drugs to Watch in 2025:

- AWIQLI® (insulin icodec)
- CagriSema (cagrilintide + semaglutide)
- COBENFY™ (KarXT; xanomeline-trospium)
- EBGLYSS™ (lebrikizumab)
- Fitusiran
- GSK-3536819
- IMDELLTRA™ (tarlatamab-dlle)
- mRESVIA (mRNA-1345)
- SEL-212
- Vepdegestrant (ARV-471)
- Zanzalintinib (XL092)

The drug snapshots within the report draw from interviews with therapy experts for the respective drug markets; Clarivate drug, disease landscape and forecast reports; Cortellis™ sales data (sourced from Refinitiv I/B/E/S); and other industry sources including biopharma company press releases and peer-reviewed publications. This year's Drugs to Watch report includes sections looking at Drugs to Watch for the Mainland China market, the regulatory landscape, the role of radiopharmaceutical theranostics in oncology treatment, the growing obesity market and the impact of gene editing on drug discovery and development. Please note that Clarivate analysts generated the data shown in this report on October 31, 2024.

Data sources

Since 2013, Clarivate has applied proprietary technologies, tools and techniques trusted by its global life sciences customers to produce the annual Drugs to Watch report.

Cortellis Competitive Intelligence™ provides access to data such as drug pipeline, deals, patents, global conferences and company content, along with the latest industry news and press releases. The Cortellis Competitive Intelligence Drug Timelines & Success Rates methodology is a patented analytic tool that applies statistical modeling and machine learning to more reliably and accurately forecast drug development milestones, timelines and probability of success. The AI-enhanced search in Cortellis Competitive Intelligence provides an intuitive way to search using natural language questions.

Disease Landscape & Forecast provides comprehensive market intelligence on current and emerging therapies, addressable population size and the market outlook across 85+ indications to help identify opportunities and optimize long-term disease strategy.

Epidemiology Intelligence provides insight to size the market and understand patient populations with a combination of incidence and prevalence literature review across 1200+ diseases and procedures. In-depth disease-specific forecasts and U.S. claim-based insights are available for 220+ indications.

BioWorld™ is an industry-leading suite of news services delivering actionable intelligence on the most innovative therapeutics and medical technologies in development.

Cortellis Regulatory Intelligence™ is a timely and comprehensive database spanning all regulatory functions across the R&D lifecycle, providing a single point of access and including detailed summaries of local regulatory practices for drugs and biologics and medical devices and IVDs.

Cortellis Clinical Trials Intelligence™ is a comprehensive source of detailed insights on clinical sites and trial protocols including biomarkers, targets and indications to optimize clinical trial planning.

Cortellis Deals Intelligence™ combines a robust and comprehensive source of deals intelligence with enhanced visualizations of the highest quality data, to quickly find the optimal deal without compromising due diligence. The Cortellis Deals Intelligence Deals Predictive Analytics methodology applies statistical modeling and machine learning to produce first-in-class, deal value prediction technology.

Access and reimbursement payer studies provide brand-level insight regarding the impact of payer policy on physician prescribing behavior so clients can optimize their market access strategy and determine how to best position their brand to specific stakeholders.

Real World Data and Analytics provides a comprehensive view of the market and a deep, impartial view of all stakeholders and sites of service through medical claims, Electronic Health Record (EHR) data, Rx data and more.

Web of Science™ is the world's largest publisher-neutral citation index and research intelligence platform. It organizes the world's research information to enable academia, corporations, publishers and governments to accelerate the pace of research.

Derwent Innovation™ is a market-leading patent research and analytics platform delivering access to globally trusted patents and scientific literature. Enhanced content, proprietary search and data intelligence technology helps a global community of more than 40,000 innovators and legal professionals find answers to complex questions.

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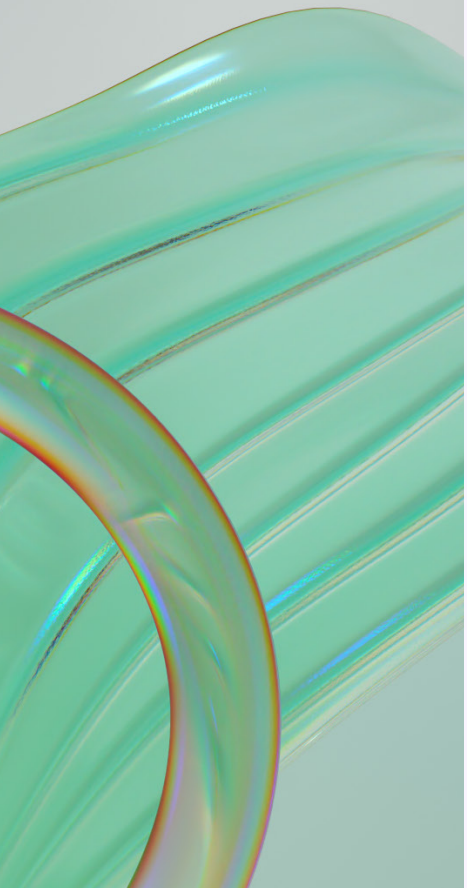
AWIQLI

(LAI 287; insulin icodec)

Type 1 and type 2 diabetes mellitus (T1DM and T2DM)



AWIQLI at a glance

Producers

Novo Nordisk

Type

Long-acting basal insulin analog

Usage

Once-weekly SC administration to treat T1DM and T2DM

Impact

~1.8m

diagnosed prevalent cases of T1DM in the G7 markets in 2023

~10.6m

diagnosed cases of T2DM on insulin therapy in 2023

Review and approval status

April 2023

- BLA submitted: U.S. FDA
- MAA submitted: E.U. EMA

August 2023

- NDA submitted: Japan PMDA

May 2024

- Approved: E.U. EMA

June 2024

- Approved: Japan PMDA, Mainland China NMPA

July 2024

- CRL: U.S. FDA

Actual and expected launch:

- **2024:** European Union, Japan, Mainland China (type 2 diabetes only), United Kingdom
- **2025:** United States

Patents estimated to expire:

- Beginning in **2023**

Launched in Australia, Canada, the European Union, Mainland China and Japan, AWIQLI is the first once-weekly, SC-administered insulin. This dosing regimen represents a notable advantage over the currently available daily administered basal insulin, which could reduce the dosing burden associated with insulin treatment for T1DM and T2DM.

Why is it a drug to watch?

AWIQLI is a once-weekly SC-administered basal insulin analog with a ~8-day half-life for both T1DM and T2DM. In addition, Novo Nordisk developed a mobile app, DoseGuide, to be used with AWIQLI to help find individually optimized insulin doses based on an individual's earlier doses and blood glucose levels. However, the launch in the United States has been delayed by a CRL from the FDA based on a recommendation from the Endocrinologic and Metabolic Drugs Advisory Committee. The CRL issues requests related to the manufacturing process and the data for T1DM. The company is working closely with the FDA to address the concerns but does not expect to complete the requests during 2024.

Approvals in other countries and regions were supported by data from the phase 3 ONWARDS program, which reported positive efficacy and safety data and hypoglycemia rates that were not statistically significant for AWIQLI compared with other insulin analogs.

The trials involving individuals with T2DM encompassed all major groups that are likely to be prescribed AWIQLI:

ONWARDS 1: insulin-naive adults with T2DM

- AWIQLI (weekly SC) versus insulin glargine (daily SC), both plus background antidiabetic therapy
- Reduction in HbA1c at week 52 from baseline: -1.55% with AWIQLI vs -1.35% with insulin glargine (statistically significant)
- Higher percentage of AWIQLI-treated participants achieved <7% HbA1c target without reporting level 2 or 3 hypoglycemia compared with insulin glargine
- 0.30 clinically significant or severe hypoglycemia events per patient-year with AWIQLI vs 0.16 events with insulin glargine (not statistically significant)

ONWARDS 2: adults with T2DM previously treated with insulin

- AWIQLI (weekly SC) versus insulin degludec (daily SC), both plus background antidiabetic therapy
- Reduction in HbA1c at week 26 from baseline: -0.93% with AWIQLI vs -0.71% with insulin degludec (statistically significant)
- 0.73 clinically significant or severe hypoglycemia events per patient-year with AWIQLI vs 0.27 events with insulin degludec (not statistically significant)

ONWARDS 3: insulin-naive adults with T2DM

- AWIQLI (weekly SC) versus insulin degludec (daily SC), both plus background antidiabetic therapy
- Reduction in HbA1c at week 26 from baseline: -1.57% with AWIQLI vs -1.36% with insulin degludec (statistically significant)
- 0.31 clinically significant or severe hypoglycemia events per patient-year with AWIQLI vs 0.15 events with insulin degludec (not statistically significant)

ONWARDS 4: adults with T2DM on basal-bolus regimen

- AWIQLI (weekly SC) plus insulin aspart (SC 2-4 times daily) versus insulin glargine (daily SC) plus insulin aspart (SC 2-4 times daily)
- Reduction in HbA1c at week 26 from baseline: -1.16% with AWIQLI vs -1.18% with insulin glargine (statistically significant)
- 5.64 clinically significant or severe hypoglycemia events per patient-year with AWIQLI vs 5.62 events with insulin glargine (not statistically significant)

ONWARDS 5: insulin-naive adults with T2DM

- AWIQLI (weekly SC; used with the DoseGuide app) versus insulin glargine (daily SC)
- Reduction in HbA1c at week 52 from baseline: -1.68% with AWIQLI vs -1.31 with insulin glargine (statistically significant)
- 0.19 clinically significant or severe hypoglycemia events per patient-year with AWIQLI vs 0.14 events with insulin glargine (not statistically significant)

ONWARDS 6: adults with T1DM

- AWIQLI (weekly SC) plus insulin aspart (SC 3 times daily at mealtimes) versus insulin degludec (daily SC) plus insulin aspart (SC 3 times daily at mealtimes)
- Reduction in HbA1c at week 26 from baseline: -0.47% with AWIQLI versus -0.51% with insulin degludec
- 19.93 clinically significant or severe hypoglycemia events per patient-year with AWIQLI vs 10.37 events with insulin degludec (statistically significant)

In phase 2 trials, AWIQLI had a higher rate of hypoglycemic events compared with insulin glargine; however, the results from these phase 3 trials indicate that, for individuals with T2DM, the number of events were similar to those experienced by the comparator groups.

How will AWIQLI impact the market for T1DM and T2DM?

The T2DM market is expected to grow due to population demographics such as increasing obesity and cardiovascular risks and an aging population.

The therapeutic pipeline for T2DM is extremely crowded, with more than 150 drugs in active clinical development. Furthermore, GLP-1 RAs are dominating the phase 3 pipeline and include more convenient oral options (e.g., Eli Lilly and Co.'s orforglipron), GLP-1 combination therapies (e.g., Novo Nordisk's IcoSema [insulin icodec + semaglutide] and Novo Nordisk's CagriSema [cagrilintide + semaglutide]) and other insulin analogs (Eli Lilly and Co.'s insulin efsitora alfa).

Insulin replacement remains the first-line therapy for T1DM, and AWIQLI is expected to be welcomed for its weekly administration.

Although the insulin market for both T1DM and T2DM is well established, improved insulin formulations are being investigated.

AWIQLI is forecasted to have first-to-market advantage over Eli Lilly and Co's once-weekly insulin efsitora alfa.

Coupled with an increasing drug-treated population, AWIQLI is forecast to partially offset the declining sales of long-acting insulins in the major markets, raising it from $17.0bn in 2022 to $23.0bn in 2032. Overall, AWIQLI's launch will lead to a limited overall expansion to the insulin market, as most patients who need insulin therapy will already be prescribed daily long-acting insulin.

However, the availability of nonbranded, biosimilar or interchangeable versions of insulin analogues, such as insulin glargine and insulin degludec; increasing use of insulin pumps; and significant use of GLP-1 RA products further delaying the initiation of insulin therapy in T2DM patients will pose a challenge for AWIQLI.

What gaps in treatment does AWIQLI fill?

The launch of AWIQLI is expected to enhance the quality of life for many patients by notably reducing the dosing burden associated with insulin injections, though more significantly for patients with T1DM than for patients with T2DM. This could indirectly result in better treatment adherence.

What hurdles might it need to overcome to reach blockbuster status?

Barriers to commercial success include the uncertainty about the safety of weekly insulins. This is particularly true for the risk of hypoglycemia, especially for patients with T2DM. In addition, there are concerns about off-schedule administration and a lack of understanding about dose adjustments or dose titration with less frequent weekly dosing. A need also exists for long-term real-world data to increase confidence in the efficacy and safety of weekly insulins. Competition from other therapies could also constrain the market for AWIQLI.

Market overview

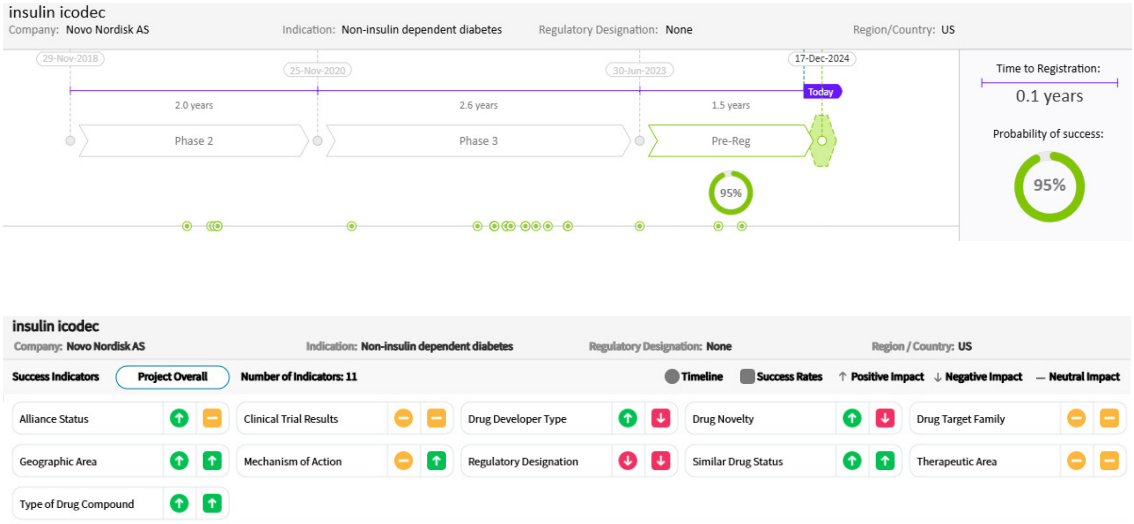
$4.70B

expected sales in the G7 markets in 2030

"The weekly insulin analogues are promising for some elderly patients who really need to use insulin therapy but cannot use it themselves. Insulin icodec and basal insulin-Fc can be beneficial for those patients in terms of home care."

Endocrinologist, Japan

Cortellis data indicate there is a 95% probability of success for AWIQLI in the United States.



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

CagriSema

(cagrilintide + semaglutide)
Obesity and type 2 diabetes mellitus

CagriSema at a glance

Producers

Novo Nordisk

Type

Fixed dose combination (FDC) of a GLP-1 RA (semaglutide) + long-acting amylin analog (cagrilintide)

Usage

Once-weekly SC administration to treat obesity and T2DM

Impact

~3.32m

drug-treated prevalent cases of overweight and obesity in the G7 markets in 2024

~45.4m

drug-treated prevalent cases of T2DM in the G7 markets in 2024

Review and approval status

Actual and expected launch:

- **2026:** United States (obesity)
- **2027:** European Union (obesity), Japan (obesity), Mainland China (obesity and T2DM)
- **2028:** European Union (T2DM), Japan (T2DM), United Kingdom (T2DM), United States (T2DM)

Patents estimated to expire:

- Beginning in **2026**

With its addition of cagrilintide, a long-acting amylin analog, to semaglutide, CagriSema promises to offer better efficacy than semaglutide (OZEMPIC/WEGOVY®) and tirzepatide (MOUNJARO/ZEPBOUND®) for both obesity and T2DM.

This next-generation GLP-1 agent combines the known advantages of GLP-1s, such as enhanced post-prandial insulin secretion by pancreatic beta cells and slowed gastric emptying for reduced appetite, with the activity of amylin, including slowed intestinal glucose absorption and release of post-prandial hepatic glucose. If approved, CagriSema will be the first FDC amylin and GLP-1 RA to launch in the obesity and T2DM markets.

Why is it a drug to watch?

Obesity and T2DM are widespread diseases that are responsible for considerable levels of morbidity and mortality globally, primarily in the form of cardiovascular disease (CVD). Therapies based on incretin hormones, spearheaded by GLP-1 RAs, are becoming the preferred choice of treatment for obesity and T2DM. Moreover, there is now clinical evidence suggesting that these agents also have the potential to provide cardiovascular and renal benefits.

CagriSema, a once-weekly SC FDC injection, resulted in a significant weight reduction in a phase 2 clinical trial with individuals with T2DM and BMI ≥27.0 kg/m^2:

- CagriSema vs cagrilintide vs semaglutide for 32 weeks
- Weight reduction: 15.6% vs 8.1% vs 5.1%
- CagriSema was well-tolerated.

Phase 3 trials are ongoing for obesity, in which the dose for CagriSema (2.4 mg) is the same as the dose of WEGOVY for obesity and higher than the approved doses of OZEMPIC for T2DM (0.5 mg, 1 mg and 2 mg):

REDEFINE 1: adults ≥18 years old with BMI ≥27.0 kg/m^2 and at least one weight-related comorbidity (e.g., hypertension, dyslipidemia, obstructive sleep apnea or CVD)

- Once-weekly SC CagriSema vs SC semaglutide vs SC cagrilintide vs placebo for 68 weeks
- Primary endpoints:
  - Mean placebo-adjusted change in body weight from baseline
  - Percentage of participants achieving ≥5% body weight reduction
- Expected completion: October 2024

REDEFINE 2: adults ≥18 years old with BMI ≥27.0 kg/m^2 and T2DM

- Once-weekly SC CagriSema vs SC semaglutide in combination with placebo for 68 weeks
- Primary endpoints:
  - Mean placebo-adjusted change in body weight from baseline
  - Percentage of participants achieving ≥5% body weight reduction
  - Weight reduction: 22.7% vs 16.1% vs 11.8% vs 2.3%
  - Proportion with weight loss >25%: 40.4% vs 16.2% vs 6.0% vs 0.9%
  - Proportion at the highest dose: 57.3% vs 70.2% vs 82.5%

REDEFINE 3: adults ≥18 years old with BMI ≥27.0 kg/m^2 and established CVD, with or without T2DM

- Once-weekly SC CagriSema vs placebo for 163 weeks
- Primary endpoints:
  - Time to first occurrence of MACE-3 (CVD death, nonfatal myocardial infarction, nonfatal stroke)
- Expected completion: May 2027

NDA submission is expected to be supported by the results from REDEFINE 1 and REDEFINE 2

The following trials are also ongoing for T2DM, with varying doses of CagriSema within and between trials:

REIMAGINE 1: adults ≥18 years old with T2DM

- Once-weekly SC CagriSema for a 16-week dose escalation period and 24-week maintenance period vs placebo
- Primary endpoints:
  - Change in HbA1c
- Expected completion: December 2025

REIMAGINE 2: adults ≥18 years old with T2DM inadequately controlled with metformin with or without an SGLT2 inhibitor

- Once-weekly SC CagriSema vs SC semaglutide vs SC cagrilintide vs placebo for 68 weeks
- Primary endpoints:
  - Change in HbA1c
  - Relative change in body weight
- Expected completion: May 2026

REIMAGINE 3: adults ≥18 years old with T2DM on once-daily insulin with or without metformin

- Once-weekly SC CagriSema for an 8-week dose escalation period and up to a 32-week maintenance period vs placebo for 40 weeks
- Primary endpoints:
  - Change in HbA1c
- Expected completion: November 2025

REIMAGINE 5: adults ≥18 years old with T2DM inadequately controlled with metformin, an SGLT2 inhibitor or both

- Once-weekly SC CagriSema for an 8-week dose escalation period and 52-week maintenance period vs once-weekly SC tirzepatide for a 4-week dose escalation period and 56-week maintenance period
- Primary endpoints:
  - Change in HbA1c
  - Relative change in body weight
- Expected completion: August 2026

How will CagriSema impact the market for obesity and T2DM?

The obesity therapy market is poised for significant expansion, with major-market sales of branded, generic and off-label obesity drug treatments expected to grow from $2.8bn in 2022 to more than $22bn in 2032, a CAGR of 23%.

GLP-1 RAs accounted for approximately 96% and 91% of total obesity market sales in the United States and EU5, respectively, in 2023, placing them as sales leaders.

The T2DM market is forecast to expand, with major-market sales growing from $102bn in 2022 to more than $127bn in 2032. This robust growth will be driven by the launch and uptake of emerging therapies, the growing use of branded therapies (such as GLP-1 RA products) and an increasing drug-treated population. However, the entry of non-branded versions of many key T2DM brands is expected to exert downward pressure on market sales.

Sales of the GLP-1 RA products are expected to continue to increase significantly through 2032. These drug classes are forecast to continue being the most lucrative throughout the forecast period, with anticipated combined sales of more than $74bn in 2032 in the major markets.

Although WEGOVY has led GLP-1 RAs in sales, ZEPBOUND and CagriSema, with potentially better efficacy at competitive pricing, are expected to erode WEGOVY's patient share. The two will also compete with each other, constraining each other's sales.

Premium prices of highly efficacious drugs will continue to drive market growth, along with increasing prevalences and treatment rates of obesity and T2DM, drugs that are easier to use and easing of access and reimbursement constraints based on improved disease outcomes beyond obesity and T2DM.

The therapeutic pipeline for obesity and T2DM is becoming extremely competitive, and new GLP-1 RAs as monotherapy and in combination with other agents (e.g., insulin icodec [IcoSema]) being developed by market leaders are in the early-stage and late-stage pipeline. This promises to make this area even more crowded and competitive in the future.

Dual and triple RAs promise superior efficacy, similar safety and tolerability profiles and prices equal to or less than GLP-1 RAs and GLP-1/GIP RAs already on the market.

The ability to provide benefits for glucose management, CVD, renal and weight loss has helped drive GLP-1 RA uptake and will help differentiate several of the novel drugs such as CagriSema launching in the next few years, in addition to assisting with reimbursement.

CagriSema is expected to benefit from its semaglutide backbone, which is well-established for obesity and T2DM.

For T2DM, emerging therapies from existing drug classes might have difficulty distinguishing themselves because of the available well-established GLP-1 RAs, according to KOLs interviewed by Clarivate. GLP-1 RA and GLP-1/GIP RA use has been displacing the use of other antidiabetic drug classes such as meglitinides and thiazolidinediones across the major markets.

What gaps in treatment does CagriSema fill?

Changes to lifestyle and behavior have insufficient long-term efficacy in most individuals with obesity and/or T2DM; metabolic surgery, although effective, is not practically deliverable on the scale that is required to address the public health concern represented by these diseases. The limited efficacy of current therapies and gastrointestinal side effects associated with GLP-1 RA products often lead to treatment discontinuation, weight regain and poor glycemic control. Further concerns for T2DM include the occurrence of microvascular complications, including retinopathy, neuropathy and nephropathy, which are not addressed by the long-standing mainstays of treatment. Despite their promise to address obesity and T2DM, GLP-1 and GLP-1/GIP RAs remain expensive in markets such as the United States and have limited coverage by payers except in the presence of CVD risks. With the launch of CagriSema and other dual and triple GLP-1 RAs that could be more effective for obesity and T2DM, barriers to improved coverage could be improved, making these drugs available to a larger population.

What hurdles might it need to overcome to reach blockbuster status?

The only amylin analog approved to date is SYMLIN® (pramlintide acetate; AstraZeneca), which is only available in the United States for T2DM. Safety concerns, such as the risk of severe hypoglycemia has prevented approval in the E.U. and Japan. The phase 3 program for CagriSema will need to alleviate any safety concerns associated with cagrilintide, both for approval and to foster positive physician perceptions. Even with robust safety data, physicians and patients alike might choose well-established and better known GLP-1 RAs and GLP-1/GIP RAs over CagriSema. In addition, comparable efficacy regarding weight loss and HbA1c management needs to be established in the phase 3 programs for obesity and T2DM. Furthermore, despite its promising efficacy profile, sales of CagriSema might be limited due to the ongoing challenging reimbursement environment, high out-of-pocket costs and limited physician familiarity with amylin analogs.

Market overview

$4.7B

expected sales in in the G7 markets in 2030 for obesity

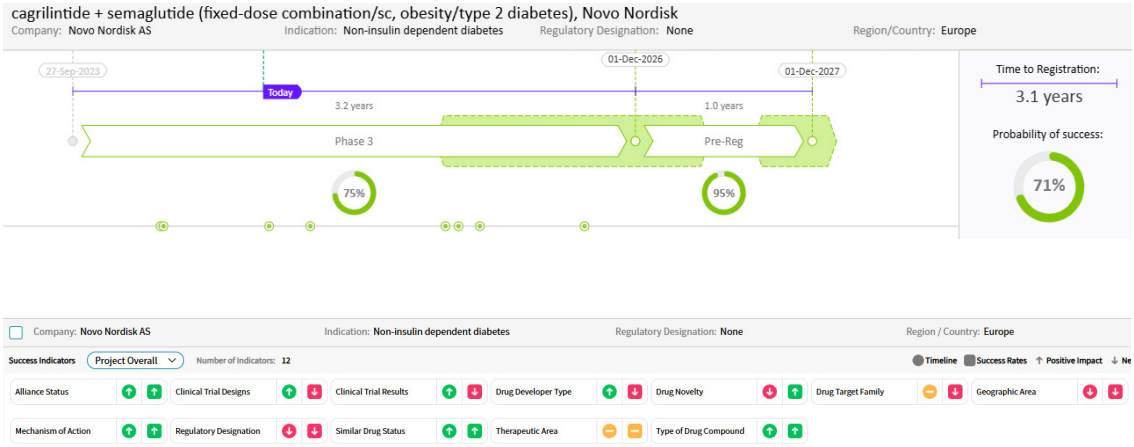
$3.6B

expected sales in the G7 markets in 2030 for type 2 diabetes

"In phase 2, CagriSema seems to work a bit better than semaglutide. If it works as good as tirzepatide and reports a similar clinical profile in terms of weight loss and glucose lowering efficacy, then instead of giving a competition to the GLP-1 receptor agonists, we will see competition between CagriSema and tirzepatide."

Endocrinologist, Italy

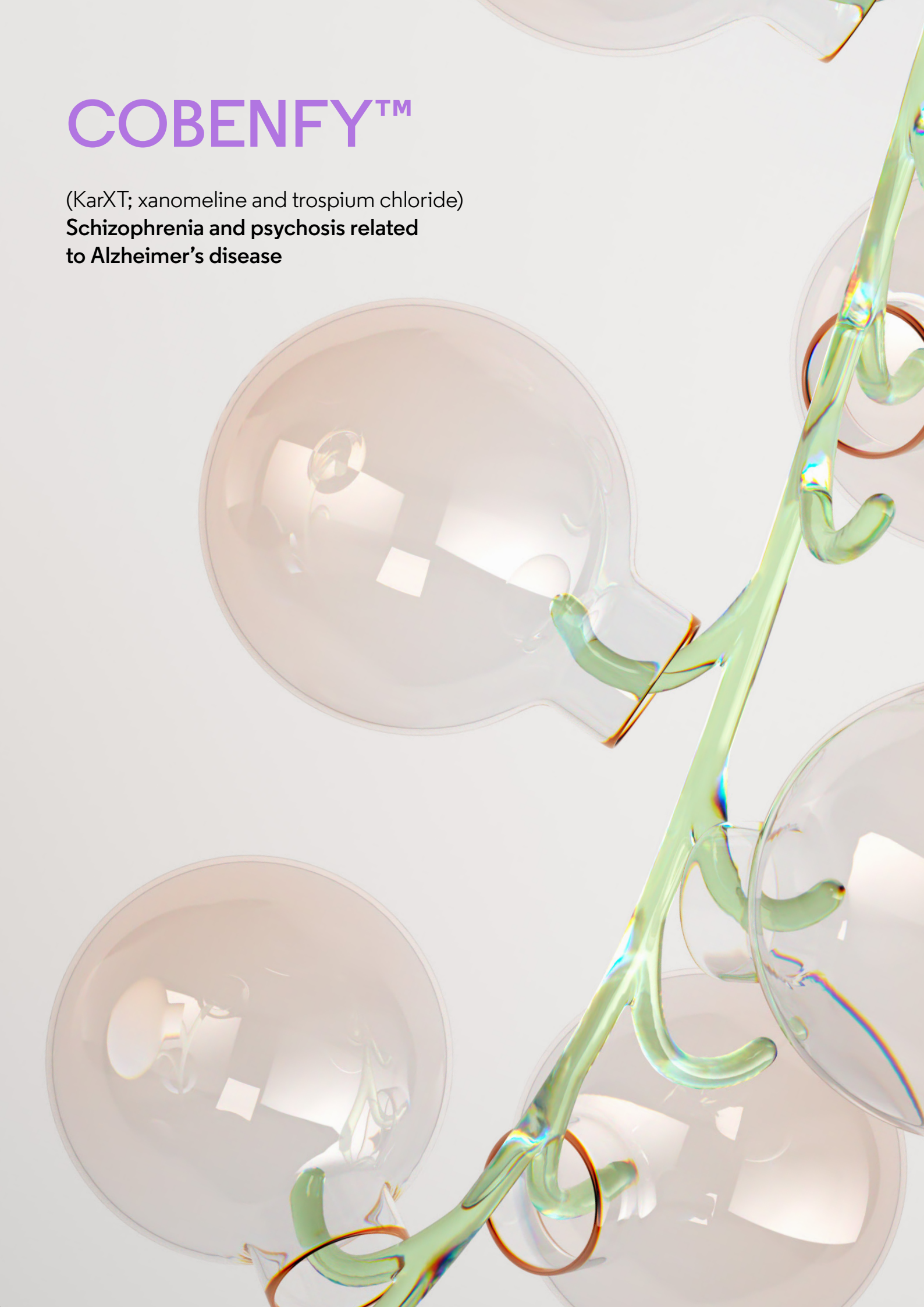
Cortellis data indicate there is a 71% probability of success for CagriSema for T2DM in the European Union.



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

COBENFY™

(KarXT; xanomeline and trospium chloride)
Schizophrenia and psychosis related to Alzheimer's disease



COBENFY™ at a glance

Producers

Karuna Therapeutics (acquired by Bristol Myers Squibb)

Type

Dual M1/M4 muscarinic acetylcholine receptor agonist

Usage

Twice daily oral administration to treat schizophrenia in adults

Also in development for inadequately responding schizophrenia patients and psychosis related to Alzheimer's disease (AD)

Impact

~5.4m

diagnosed prevalent cases of schizophrenia in the G7 markets in 2024

~3.2m

diagnosed prevalent cases of psychosis related to AD in the G7 markets in 2024

Review and approval status

September 2023

- NDA submitted: U.S. FDA (schizophrenia)

September 2024

- NDA approved: U.S. FDA (schizophrenia)

Actual and expected launch:

- **2024:** United States (schizophrenia)
- **2026:** Mainland China (schizophrenia)
- **2027:** United States (AD psychosis), European Union (schizophrenia [inadequate responders])
- **2028:** European Union (AD psychosis)
- **2029:** Mainland China (AD psychosis)

Patents estimated to expire:

- Beginning in **2030**

In the midst of a number of setbacks for emerging schizophrenia treatments (e.g., Acadia Pharmaceuticals Inc's pimavanserin and Minerva Neurosciences Inc's roluperidone), the approval of COBENFY represents a transformative moment for schizophrenia treatment.

It is the first drug approved with a novel mechanism of action for schizophrenia in more than 30 years. Using an FDC of xanomeline and trospium, COBENFY selectively targets M1 and M4 receptors, rather than the traditional dopamine pathways, using the xanomeline component, while the trospium chloride component is a muscarinic receptor antagonist that does not appreciably cross the blood-brain barrier (BBB) and minimizes cholinergic side effects of xanomeline outside the brain. At present, there is not enough data to make definitive conclusions about COBENFY's use in psychosis related to Alzheimer's disease (AD). However, if the results show effectiveness in treating hallucinations and delusions associated with AD psychosis, the drug is anticipated to have strong commercial potential.

Why is it a drug to watch?

It can be challenging to find an effective treatment for all individuals with schizophrenia. The fact that all existing drugs target dopamine D2 receptor signaling in the brain limits the treatment choices and makes effective treatment for many even more difficult. The approval of COBENFY adds another option to the schizophrenia armamentarium and represents a significant achievement for Bristol Myers Squibb's recent re-entry into the field of neuropsychiatry. The company is also launching COBENFY Cares™, a program designed to support patients who have been prescribed COBENFY.

Bristol Myers Squibb acquired COBENFY developer Karuna Therapeutics Inc, which was founded by PureTech Health plc to develop COBENFY, in a deal that closed in March 2024. Muscarinic receptors were linked to schizophrenia in research carried out in the 1980s and 1990s, and xanomeline had previously been taken into phase 2 development in AD and schizophrenia by Eli Lilly and Co but was dropped because of the dose-limiting side effects (e.g., gastrointestinal side effects). This was likely due to xanomeline activating M1 and M4 receptors in the periphery as well as in the brain. By adding trospium chloride, which does not cross the BBB, M1/M4 receptors in the periphery are likely blocked, overcoming the tolerability issues.

The FDA approval of COBENFY was supported by data from the EMERGENT clinical program, which included three placebo-controlled trials and two open-label studies evaluating long-term safety and tolerability and showed statistically significant reductions in positive schizophrenia symptoms and, to some extent, negative symptoms, with an impressive effect size when compared with placebo.

EMERGENT-2 and EMERGENT-3: adult inpatients with schizophrenia

- COBENFY vs placebo for five weeks
- Change in total Positive and Negative Syndrome Scale (PANSS) score:
  - EMERGENT-2: -21.2 with COBENFY vs -11.6 with placebo (effect size=0.61)
  - EMERGENT-3: -20.6 with COBENFY vs -12.2 with placebo (effect size=0.60)
- Change in Clinical Global Impression-Severity (CGI-S) score:
  - EMERGENT-2: -1.2 with COBENFY vs -0.7 with placebo
  - EMERGENT-3: -1.1 with COBENFY vs -0.6 with placebo
- Treatment discontinuation due to adverse events:
  - EMERGENT-2: 7% vs 6% (COBENFY vs placebo)
  - EMERGENT-3: 6.4% vs. 5.5% (COBENFY vs placebo)
- Treatment effects were demonstrated as early as two weeks, which could promote its use in the acute hospital setting and continued use in the outpatient setting.
- The most common AEs in both studies were nausea (19% vs 4%), dyspepsia (18% vs 5%), constipation (17% vs 7%), vomiting (15% vs 1%), hypertension (11% vs 2%), abdominal pain (8% vs 4%), diarrhea (6% vs 2%), tachycardia (5% vs 2%), dizziness (5% vs 2%) and gastroesophageal reflux disease (5% vs <1%).
- Notably, the rates of somnolence, weight gain and extrapyramidal symptoms (EPS) were similar to those with placebo; these are typical side effects with existing treatments and can be reasons for discontinuing treatments.

EMERGENT-4: open-label extension with participants who completed EMERGENT-2 or EMERGENT-3; interim analysis:

- COBENFY for 52 weeks
- >75% of participants achieved ≥30% improvement in symptoms
- Change in total PANSS score: -33.3 points
- Change in CGI-S score: -1.7 points

EMERGENT-5: open-label study with adult outpatients with schizophrenia administered COBENFY for up to 52 weeks

- Not associated with weight gain, metabolic dysfunction and extrapyramidal symptoms

In addition, the company is evaluating COBENFY as adjunctive therapy to treat patients with inadequate response to their current atypical antipsychotic treatment in a phase 3 and extension trials, which is anticipated to be used to file an sNDA for COBENFY as adjunctive treatment:

ARISE: adults with schizophrenia who have not achieved an adequate response to their current atypical antipsychotic treatment (U.S., Europe, Japan, others)

- COBENFY vs placebo for six weeks
- Primary endpoint: change in total PANSS score
- Expected completion: February 2025

Additional phase 3 trials for psychosis related to AD (e.g., hallucinations, compulsiveness, wandering) are underway:

ADEPT-1: adults (55 to 90 years old) with AD across the severity spectrum (MMSE: 8-22 inclusive) with psychosis (moderate-to-severe delusions or hallucinations)

- COBENFY (titrated to a maximum dose) for 12 weeks
- Responders (≥ 40% decline from baseline in Neuropsychiatric Inventory-Clinician: Hallucinations and Delusions [NPI-C: H+D] score at week 10 or 12 and CGI-C score of "improved" or "very much improved") randomized to continue COBENFY or placebo for 26 weeks
- Primary endpoint: time from randomization to relapse
- Expected completion: October 2026

ADEPT-2: adults (55 to 90 years old) with AD across the severity spectrum (MMSE: 8-22 inclusive) with psychosis (moderate-to-severe delusions or hallucinations)

- COBENFY for 14 weeks
- Primary endpoint: change in NPI-C: H+D score
- Expected completion: July 2025

ADEPT-3: open-label extension study with participants who completed ADEPT-1 or ADEPT-2

- COBENFY for 52 weeks
- Primary endpoint: incidence of treatment-emergent adverse events (TEAEs)
- Expected completion: April 2026

ADEPT-4: randomized, double-blind, placebo-controlled, parallel-group study

- COBENFY for up to 14 weeks
- Primary endpoint: change in NPI-C: H+D score
- Expected primary completion: October 2026

How will COBENFY impact the market for schizophrenia and psychosis related to AD?

The schizophrenia therapy market is expected to increase from $8.6bn in 2022 to nearly $15.2bn in 2032 (6% CAGR) in the G7 markets, with growth partially driven by the increase in the drug-treated population. Sales of new and emerging therapies are expected to outweigh the impact of generics entering the markets.

Oral atypical antipsychotics will remain firmly entrenched as the key first-line therapeutic choices for schizophrenia, given physician comfort and familiarity with the efficacy, safety and tolerability of these drug classes and the availability of generics, particularly of therapies heavily used in early lines of treatment (e.g., aripiprazole, risperidone, olanzapine).

Of the two drugs in novel drug classes launching in the next few years, COBENFY and iclepertin (Boehringer Ingelheim; glycine transporter-1 inhibitor), the latter is forecast to have the greater impact on sales because it will manage cognitive impairment associated with schizophrenia (CIAS), an area of high unmet need and with a high prevalence.

However, COBENFY will help address the need for drugs with novel MOAs to treat schizophrenia. It is expected to be used as monotherapy as well as adjunctive therapy to antipsychotics in schizophrenic patients with insufficient response to other agents or who experience side effects and could command up to 9.5% patient share in the U.S. in 2032.

COBENFY is expected to be used as second- or later-line monotherapy initially because payers are expected to encourage prescriptions of generics first before switching to COBENFY when patients display positive or negative symptoms that respond inadequately to other treatments or cannot tolerate side effects.

Given its demonstrated two-week onset of action, COBENFY could also be prescribed for hospitalized acutely psychotic individuals with schizophrenia, and treatment could be continued for treatment-responsive patients as outpatients.

For psychosis related to AD, the unique MOA, specific labeling for psychosis related to AD and potential lack of a boxed warning for mortality risk in older adults could drive COBENFY uptake, but it will compete with entrenched, lower cost atypical antipsychotics.

The prevalence, diagnosis and treatment rates of AD are increasing, along with population aging.

The success of COBENFY could encourage continued growth in the muscarinic pipeline, which has recently received heavy investment from large pharma companies with an interest in neuropsychiatric drugs.

What gaps in treatment does COBENFY fill?

Existing schizophrenia treatments, which all target dopamine D2 receptor signaling in the brain, provide some relief from the "positive" symptoms, such as hallucinations and delusions, but have varying efficacy by patient. They do not address negative symptoms, such as anhedonia and emotional withdrawal, or disease-related cognitive impairment. In addition, side effects—such as sedation, weight gain and motor effects—are burdensome and can be dose-limiting. The heterogeneous nature of schizophrenia also creates challenges for effective treatment, and 20-30% of individuals with schizophrenia have symptoms that are refractory or resistant to treatment. These patients are often prescribed higher doses or polypharmacy, which increases the risk of side effects and poor compliance. Therefore, a significant need exists for antipsychotics with improved efficacy and a better safety profile. With its novel MOA, COBENFY has the potential to impact the treatment paradigm for schizophrenia.

Psychosis and agitation related to AD are distressing to the patient, increase caregiver burden and are a primary reason for institutionalization. There is a high unmet need for safe, effective therapies for these symptoms, given REXULTI® (Otsuka America Pharmaceutical Inc and Lundbeck) is the only approved drug for this indication. However, physicians often prescribe antipsychotics off-label, as well as other drugs such as hypnotics, despite their modest efficacy and the safety concerns associated with antipsychotic use in older adults with dementia due to an increased incidence of cerebrovascular events.

What hurdles might it need to overcome to reach blockbuster status?

Antipsychotic sales are often limited by poor compliance and adherence. Although COBENFY has demonstrated better tolerability than other available antipsychotics, it could still be affected by the schizophrenia-related cognitive dysfunction that can impair adherence with burdensome, frequently administered treatment regimens. Clinicians might also be reluctant to prescribe COBENFY in first-line treatment because of the potentially long adjustment period, competition from the generically available antipsychotics, high treatment discontinuation rates in clinical trials and lack of documented results in individuals with primarily negative symptoms. In addition, the $1,850/month price tag for COBENFY, which is more than the annual cost of most currently available generic antipsychotics, might limit access, particularly as the disabling nature of schizophrenia places many patients in poor economic circumstances, with limited or no insurance coverage and less-than-optimal healthcare. Launch in Europe and Japan could be delayed by the EMA's requirement for long-term clinical study results for schizophrenia drug approval and some markets' lengthy HTA processes and the lack of Japanese sites in the completed phase 3 trials.

Market overview

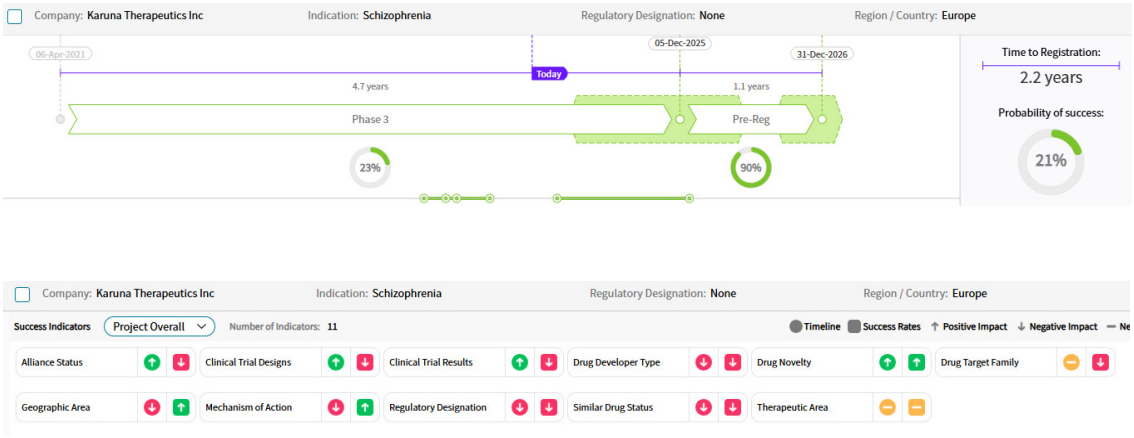
$1.60B

expected sales in 2030

"We would probably co-administer it in people who are on long-acting injectable antipsychotics and are partially responsive. That would benefit their cognition, and the M4 agonism could very well downregulate dopamine in the striatum and augment the efficacy of antipsychotics."

Psychiatrist, United States

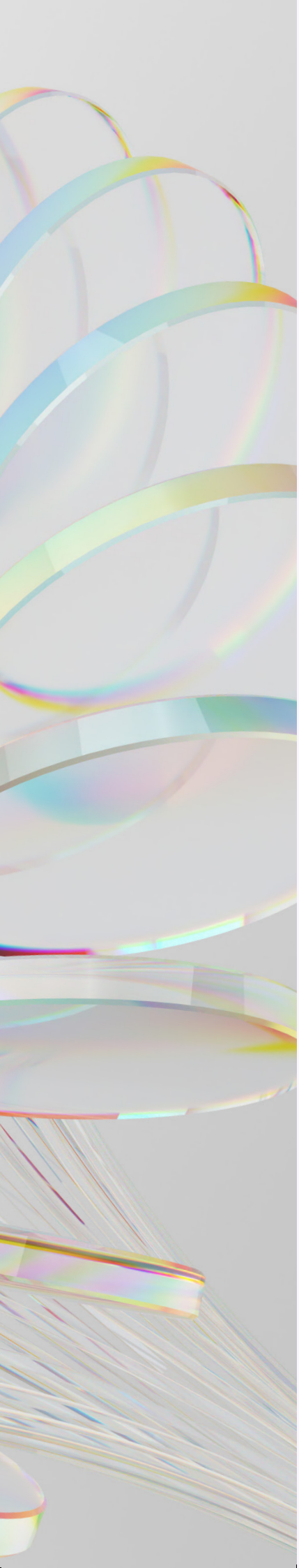
Cortellis data indicate there is a 21% probability of success for COBENFY for schizophrenia in the European Union.



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

EBGLYSS

(lebrikizumab)
Atopic dermatitis



EBGLYSS at a glance

Producers

Eli Lilly and Co

Almirall

Type

IL-13-targeting mAb

Usage

Subcutaneous injection to treat moderate-to-severe atopic dermatitis in adults and children 12 years of age and older weighing ≥88 pounds (40 kg)

Every two weeks until adequate clinical response (starting at week 16), followed by monthly administration for maintenance

Impact

~70.5m

prevalent cases of atopic dermatitis in the G7 markets in 2023

~40%

of atopic dermatitis cases are moderate to severe

Review and approval status

December 2012

- Fast track designation: U.S. FDA

October 2023

- CRL: U.S. FDA

November 2023

- Approved: E.U. EMA

December 2023

- Approved: U.K. MHRA

January 2024

- Approved: Japan MHLW

September 2024

- Approved: U.S. FDA

Actual and expected launch:

- **2023:** European Union, United Kingdom
- **2024:** Japan, United States
- **2028:** Mainland China

Patents estimated to expire:

- Beginning in **2024**

EBGLYSS™ was the third biologic targeting IL-13 to market for atopic dermatitis, behind DUPIXENT® (dupilumab; Sanofi and Regeneron Pharmaceuticals Inc) and ADBRY®/ADTRALZA® (tralokinumab; LEO Pharma).

Nevertheless, its less frequent dosing, more selective inhibition of IL-13 and extensive efficacy and safety data will likely contribute to its uptake as first-line treatment of moderate-to-severe atopic dermatitis when topical corticosteroid (TCS) prescriptions are insufficient.

Why is it a drug to watch?

EBGLYSS joined Eli Lilly and Co's immunology-focused pipeline when the company acquired Dermira Inc in 2020 for $1.1bn. Licensed to Almirall for the European market, EBGLYSS is also under investigation for the pediatric population as young as 6 months old, which will further establish its competitiveness against existing atopic dermatitis treatments.

EBGLYSS can be used with or without TCS and is dosed as a single monthly maintenance injection following the initial phase of treatment (two 250 mg injections each at week 0 and week 2, followed by 250 mg every two weeks until week 16 or later when adequate clinical response is achieved). It is differentiated from existing IL-13-targeting treatments by its ability to prevent the formation of the IL-13Rα1/IL-4Rα heterodimer complex.

Approvals for EBGLYSS are based on positive data from three pivotal global phase 3 clinical trials:

ADvocate 1 and ADvocate 2: adults and children (aged 12 to <18 years; weighing at least 40 kg) with moderate-to-severe eczema

- 52-week randomized, double-blind, placebo-controlled, parallel-group studies
- EBGLYSS as monotherapy (16-week treatment induction period: 500 mg initially and at two weeks; maintenance period: 250 mg or placebo every two weeks)
- 38% achieved Investigator's Global Assessment (IGA) 0 or 1 at 16 weeks (vs 12% with placebo); 10% at four weeks
- 77% of responders maintained their results at one year with once-monthly dosing
- 48% of responders who were switched to placebo at 16 weeks maintained their results at one year
- 43% experienced itch relief at 16 weeks (vs 12% with placebo) measured using the Pruritus Numeric Rating Scale (PNRS)
- 85% of itch responders maintained their results at one year with once-monthly dosing
- 66% of itch responders who were switched to placebo at 16 weeks maintained their results at one year

ADhere: adults and children (aged 12 to <18 years; weighing at least 40 kg) with moderate-to-severe eczema and symptoms inadequately controlled by topical medications at baseline

- 16-week randomized, double-blind, placebo-controlled, parallel-group studies
- EBGLYSS in combination with TCS (500 mg initially and at two weeks; maintenance period: 250 mg or placebo every two weeks) vs placebo in combination with TCS
- 41.2% achieved IGA 0 or 1 with EBGLYSS + TCS vs 22.1% with placebo + TCS
- 69.5% achieved 75% improvement in the Eczema Area and Severity Index (EASI-75) with EBGLYSS + TCS vs 42.2% with placebo + TCS

Other phase 3 trials include the following and are expected to contribute to label extensions in the future:

ADore: global open-label study with adolescents (≥12 years to <18 years) with moderate-to-severe AD and weighing ≥40 kg

- EBGLYSS as monotherapy (two doses two weeks apart, followed by every two weeks from week 4 to week 52) for 52 weeks
- Primary endpoint: proportion of patients who discontinued study treatment due to AEs through the last treatment visit
- 2.4% discontinued treatment due to AEs, and another 2.4% discontinued treatment due to SAEs
- 65% reported at least one TEAE, most mild or moderate in severity
- 62.6% achieved IGA 0 or 1 with ≥2-point improvement from baseline
- 81.9% achieved EASI-75
- 86.0% mean improvement in the EASI

ADmirable: open-label study in the United States with adults and children (≥12 years old) with moderate-to-severe atopic dermatitis who self-report race other than White

- EBGLYSS as monotherapy (two doses two weeks apart, followed by every four weeks from week 16 to week 24) for 24 weeks
- Expected completion: December 2024

ADapt: open-label study in the United States with adults and children (≥12 years old) with moderate-to-severe atopic dermatitis previously treated with DUPIXENT and not adequately controlled with topical medications

- EBGLYSS as monotherapy (two doses two weeks apart, followed by every four weeks from week 16 to week 24) for 24 weeks
- Expected completion: December 2024

ADhope: open-label study in Germany, the Netherlands, Spain and the United Kingdom with adults and children (≥12 years old) with moderate-to-severe atopic dermatitis who failed topical therapies

- EBGLYSS as monotherapy (two doses two weeks apart, followed by every four weeks from week 16 to week 24)
- Expected completion: May 2025

ADjoin: long-term global extension study with adults and children (≥12 years old) who received EBGLYSS in a prior study and adequately completed the study treatments and last patient visit of the parent trial

- EBGLYSS as monotherapy (every two or four weeks for 100 weeks)
- Expected completion: April 2025

ADlong: long-term extension study in Germany and Poland with adults and children (≥12 years old) who completed treatment with EBGLYSS in ADjoin and their last participant assessment visit (week 100) in that study

- EBGLYSS as monotherapy (every four weeks for 104 weeks)
- Expected completion: April 2026

ADorable-1: global RCT with children (6 months to <18 years old) with moderate-to-severe atopic dermatitis

- EBGLYSS in combination with TCS
- Expected completion: September 2025

ADorable-2: long-term global extension study with children (6 months to <18 years old) with moderate-to-severe atopic dermatitis who adequately completed all visits of the ADorable 1 study

- EBGLYSS in combination with TCS
- Expected completion: June 2026

How will EBGLYSS impact the market for atopic dermatitis?

TCSs are the cornerstone of atopic dermatitis treatment based on their proven efficacy, low cost, manageable side effect profile and clinicians' familiarity with the class. However, there is a need for effective systemic therapies that are more effective than TCSs.

Eight treatment options have entered the market since 2020, and several emerging therapies will be launched over the next five years, which should meaningfully grow the drug-treated population. New and emerging therapies will benefit those with moderate-to-severe atopic dermatitis, and this segment will likely drive market growth.

The biologic market is currently dominated by DUPIXENT, which first gained approval in 2017 and was expanded to children as young as six months in 2022.[2] This dominance is not expected to change in the near future, especially given the real-world data that support clinical trial findings and physician familiarity with its use.

However, the introduction of additional biologics such as EBGLYSS will likely help shift the treatment paradigm to greater biologic use and contribute to overall market share by biologics. Within this group, therapies targeting IL-13 are expected to dominate sales.

The incremental improvements in tolerability and more convenient dosing with EBGLYSS could help it carve out some market share.

Oral JAK inhibitors, such as CIBINQO® (Pfizer Inc), OLUMIANT® (Eli Lilly and Co) and RINVOQ® (AbbVie), that are also approved for atopic dermatitis in some countries and regions also provide highly efficacious orally administered treatment options. They will likely generate sizable revenues in this space; however, they are estimated to be used as post-biological options, at least until more real-world safety data are collected.

These more expensive targeted therapies that are effective and safe have the potential to partially displace less expensive, mostly general topical and systemic mainstays of atopic dermatitis treatment.

What gaps in treatment does EBGLYSS fill?

Even with currently available therapies, many individuals with moderate-to-severe atopic dermatitis still struggle to control their disease, especially in the long term, or develop resistance, and severe itch can significantly impact their daily lives. Other negative impacts include impaired mental health, social stigma, poor sleep and disruptions to work and school. In addition, atopic dermatitis-related weakening of the skin barrier function, compounded by scratching, increases the risk of viral, bacterial and fungal skin infections, as well as strep throat, ear infections and urinary tract infections (UTIs). However, adherence to other treatment regimens, such as moisturizers, can mitigate this risk though they can be burdensome and require consistency in use and skin coverage. Administration of DUPIXENT and ADBRY/ ADTRALZA can be challenging because of the injection frequency, which can be disruptive, and therefore a burden, for some patients and caregivers. More convenient, effective and safer nonsteroidal topical or systemic treatments are needed for moderate-to-severe atopic dermatitis that is not adequately managed by available topical treatments or for those who have an incomplete response to DUPIXENT and other newer treatments. The once-monthly administration of EBGLYSS and the lower risk of conjunctivitis than with DUPIXENT might give EBGLYSS an advantage.

What hurdles might it need to overcome to reach blockbuster status?

Uptake of EBGLYSS might be constrained by its status as the third IL-13-targeted therapy to market and competition from the currently available oral JAK inhibitors. In addition, many individuals with atopic dermatitis are well-served by over-the-counter (OTC) or generic agents. Also, many treatment providers prefer to prescribe generic moderate- to high-potency TCSs (applied once or twice weekly) as a prophylactic approach for moderate-to-severe atopic dermatitis with recurrent flares. This could limit the number of patients who would receive a higher priced targeted therapy. In addition, more expensive biologic therapies such as EBGLYSS might face reimbursement challenges.

Market overview

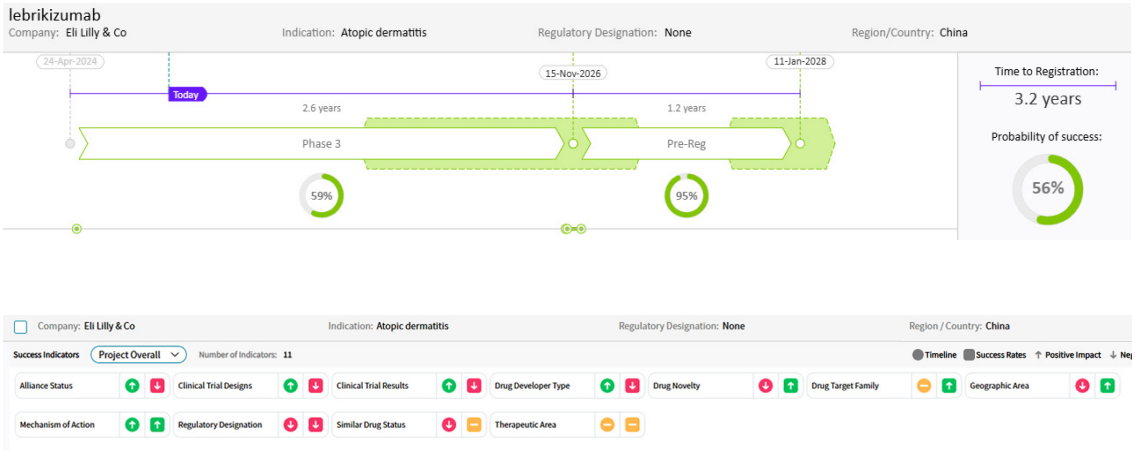
$6.00B

expected sales in the G7 markets in 2030

"We still have severe patients who are not managed by Dupixent and patients who are intolerant to JAK inhibitors, so we need more options."

Dermatologist, France

Cortellis data indicate there is a 56% probability of success for EBGLYSS in Mainland China.



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

Fitusiran

Hemophilia A and B

Fitusiran at a glance

Producers

Alnylam® Pharmaceuticals Inc

Sanofi

Type

Antithrombin-targeting small interfering RNA (siRNA)

Usage

Subcutaneous administration once monthly or bimonthly for prophylactic treatment of hemophilia A or B with or without inhibitors

Impact

~45K

diagnosed prevalent cases of hemophilia A in the G7 markets in 2023

~11K

diagnosed prevalent cases of hemophilia B in the G7 markets in 2023

Review and approval status

July 2014

- Orphan designation: E.U. EMA (hemophilia A)

February 2021

- Fast track status granted: U.S. FDA

December 2023

- Breakthrough Therapy Designation (hemophilia B with inhibitors): U.S. FDA

May 2024

- MAH submitted: Mainland China NMPA

June 2024

- NDA accepted: U.S. FDA

March 28, 2025

- PDUFA date

Actual and expected launch:

- **2025:** European Union, Japan, Mainland China, United Kingdom, United States

Patents estimated to expire:

- Beginning in **2022**

With demonstrated efficacy in phase 3 trials for both hemophilia A and B regardless of inhibitor status, fitusiran has the potential to be a transformative therapy for all people with hemophilia.

A siRNA therapy, fitusiran works by inhibiting and degrading SerpinPC1 mRNA, which reduces antithrombin levels. This promotes thrombin generation, rebalances hemostasis and prevents bleeds. Fitusiran uses Alnylam® Pharmaceutical Inc's ESC-GalNAc conjugate technology and, depending on the approval timeline, could be a first-in-class antithrombin-lowering therapy based on a double-stranded RNA molecule.

Why is it a drug to watch?

Data from completed phase 3 trials indicate that prophylaxis treatment with fitusiran results in significant reductions in the annualized bleeding rate (ABR), compared with on-demand factor concentrate, and no bleeding events in approximately one-half of participants. Also, it enables the safe execution of major surgeries in individuals with hemophilia A or B with or without inhibitors. Additional safety data have emerged from studies using an antithrombin-based dosing regimen (AT-DR), which was adopted in 2021 when trials resumed after a pause in late 2020 due to safety concerns. With AT-DR, fitusiran effectively mitigates the risk of thrombotic events and reduces the incidence of elevated liver enzymes, gallbladder inflammation and gallstones.

The efficacy and safety of fitusiran are being investigated in the ATLAS clinical development program, with results reported from the following completed phase 3 studies:

ATLAS-A/B study with 120 participants (≥12 years old) with hemophilia A or B without inhibitors

- Once-monthly prophylactic SC fitusiran administration for 9 months vs on-demand factor concentrate
- 89.9% reduction in treated ABR in the fitusiran group
- Median ABR: 0.0 (fitusiran) vs 21.8 (on-demand factor concentrate)
- 0 treat bleeds: 50.6% (fitusiran) vs 5.0% (on-demand factor concentrate)
- TEAEs of interest with fitusiran: any alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (>3x upper limit of normal), reported for 19% of the fitusiran group

ATLAS-INH study with 60 participants (≥12 years old) with hemophilia A or B with inhibitors

- Once-monthly prophylactic SC fitusiran administration for 9 months vs on-demand bypass agent
- 90.8% reduction in treated ABR in the fitusiran group
- Median ABR: 0.0 (fitusiran) vs 16.8 (on-demand bypass agent)
- 25 patients (65.8%) treated with fitusiran: no bleeding events
- TEAEs of special interest of any ALT or AST elevation (>3x upper limit of normal) and suspected, or confirmed thromboembolism were reported in the fitusiran arm in 10 patients (24.4%)

ATLAS-PPX study with 80 patients (≥12 years old) with severe hemophilia A or B with or without inhibitors previously treated prophylactically with a factor or bypass agent

- Once-monthly prophylactic SC fitusiran administration for 7 months (prior treatment as comparator)
- ABR for all bleeds: 2.9 (fitusiran) vs 7.5 (prior factor concentrate or bypass agent prophylaxis)
- Spontaneous bleeds: 2.2 (fitusiran) vs 5.0 (prior factor concentrate or bypass agent prophylaxis)
- No bleeding events: 44 (67.7%; fitusiran) vs 22 (33.8%; prior factor concentrate or bypass agent prophylaxis)
- SAEs: 9 (13.4%; fitusiran) vs 5 (7.7%; prior factor or bypass agent prophylaxis)

The following trials are ongoing:

ATLAS-OLE: open-label extension study for ATLAS-A/B, ATLAS-INH and ATLAS-PPX with 281 participants (≥12 years old) with severe hemophilia A or B with or without inhibitors

- Once-monthly or bimonthly prophylactic SC fitusiran administration using the AT-DR, which was designed to maintain an antithrombin target range of 15-35% (lower doses, less frequent dosing) for up to 48 months
- Primary endpoint: number of participants with TEAEs
- Secondary endpoint: ABR plus three
- Expected completion: November 2026

Phase 3 ATLAS-PEDS: dose-finding study with 32 children (1 year to <12 years old) with hemophilia A or B with or without inhibitors

- SC fitusiran administration for 256 weeks
- Primary endpoint: plasma antithrombin activity levels
- Expected completion: August 2028

Phase 3 ATLAS-NEO study with 75 male participants (≥12 years old) with severe hemophilia A or B with or without inhibitors previously treated with SOC

- SOC (clotting factor concentrate or bypass agent; antithrombin concentrate [ATIIIC]) for six months, SC fitusiran using the AT-DR for 36 months, anthithrombin follow-up for six months
- Primary endpoint: ABR
- Expected completion: March 2028

How will fitusiran impact the market for hemophilia A and B?

With the introduction of multiple non-factor and gene therapies over the next four to five years, the treatment paradigm for hemophilia B is expected to significantly evolve, and clinicians will have multiple effective, convenient options for all patients with hemophilia.

Hemostatic-rebalancing, non-factor therapies, including fitusiran, Alhemo™ (concizumab; Novo Nordisk) and HYMPAVZI™ (marstacimab; Pfizer Inc), could be a more convenient option than factor concentrates for hemophilia B without inhibitors. However, extended half-life FIX therapies have similar efficacy and safety and a low dosing burden and could be the treatment of choice for patients who are already well managed on them. With HEMLIBRA® (emicizumab; Genentech, a member of the Roche Group, and Chugai Pharmaceutical Co Ltd) and now ALTUVOCT®/ALTUVIIIO® (Sobi® and Sanofi), patients with hemophilia A have the option of once-weekly non-factor or factor dosing. Therefore, emerging therapies without a distinct efficacy or safety advantage and a similar dosing burden are not expected to overtake established therapies.

The SC route of administration and less frequent dosing of fitusiran and HYMPAVZI will likely encourage treatment switching among the treated population. This will be important for market share since drug treatment rates are high and there is limited scope to increase them. In fact, the overall market is expected to grow very slowly over the next decade.

The use of on-demand bypass agents like NovoSeven® (Novo Nordisk), FEIBA (Takeda) and SEVENFACT® (HEMA Biologics), which have a high injection burden and lower efficacy against bleeds, is expected to decline as patients shift to non-factor and gene therapies such as HEMGENIX® (etranacogene dezaparvovec; CSL Behring) and BEQVEZ™ (fidanacogene elaparvovec; Pfizer Inc) that offer better clinical profiles, similar safety, greater convenience and lower cost (in the case of non-factor therapies).

Fitusiran is expected to have a significant impact on all four markets (hemophilia A and B with or without inhibitors):

- The largest impact will likely be for individuals with hemophilia B with inhibitors.
- For hemophilia A, fitusiran's similar risk-benefit profile and monthly/bimonthly administration might provide an advantage over HEMLIBRA, which is shifting toward once-weekly injections, according to KOLs. This indicates that once-monthly administration might be less clinically efficacious.

What gaps in treatment does fitusiran fill?

A primary goal in the treatment of hemophilia A and B is to prevent bleeding, particularly bleeding into the joints, which is associated with permanent joint damage. Another important outcome is improved quality of life. However, the route of administration (i.e., intravenous) for current FVIII and FIX replacement therapies and dosing frequency (once or twice a week) of current FVIII replacement therapies are burdensome, increase the risk of infections and thrombosis and contribute to suboptimal compliance rates. As a subcutaneously infused therapy once a month or once every two months, fitusiran could improve patient convenience, reduce the treatment burden and enhance treatment compliance. In addition, 20-30% of patients treated with replacement therapies will develop inhibitors at some point, but treatments are limited for this population, increasing disease-related morbidity and mortality. Fitusiran could help fill that gap.

What hurdles might it need to overcome to reach blockbuster status?

Fitusiran is entering a highly competitive market, with a fairly narrow patient population and well-established prophylactic and on-demand treatment options with which both patients and clinicians are familiar. Some treatments, like ALTUVOCT/ALTUVIIIO, Elocta®/Eloctate® (Sobi and Sanofi), ADYNOVATE® (Takeda) and HEMLIBRA for hemophilia A and IDELVION® (CSL Behring) for hemophilia B, also have more convenient dosing schedules than standard half-life and extended half-life therapies. Therefore, switching to another treatment might not be as attractive for patients already being managed on those drugs. In the non-inhibitor population, many patients are well managed on factor concentrates, which could make it challenging for new non-factor therapies to have an impact. Clinician concerns about safety, such as occurrence of thrombotic events, could also limit the initial uptake of fitusiran, at least until sufficient real-world data are collected.

Market overview

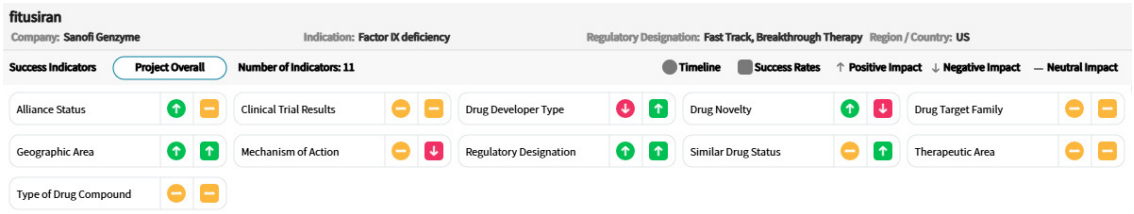
$1.00B

expected sales in the G7 markets in 2030

Fitusiran's dosing is very convenient. It's once a month, and in fact, they're even now moving toward once every two months. It's also a drug that can be kept at room temperature, and the volume is very low. This is the one drug that, from a convenience aspect alone, is actually better than HEMLIBRA.

Hematologist, United States

Cortellis data indicate there is a 95% probability of success for fitusiran for hemophilia B in the United States.



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

GSK-3536819

Meningococcal disease

GSK-3536819 at a glance

Producers

GSK plc

Type

Recombinant protein, outer membrane vesicle (OMV), conjugated, pentavalent vaccine targeting the five groups of the bacteria *Neisseria meningitidis* (A, B, C, W and Y)

Usage

Two-dose intramuscular injection administered six months apart for active immunization of individuals aged 10-25 years

Impact

64m

MenABCWY vaccine-eligible individuals in the U.S. and E.U.4 markets in 2024

~600

incident new cases of invasive meningococcal disease (IMD) in the G7 markets in 2024

Review and approval status

April 2024

- BLA accepted: U.S. FDA

February 14, 2025

- PDUFA date

Actual and expected launch:

- **2025:** United States, European Union, United Kingdom

GSK plc's 5-in-1, first-generation GSK-3536819 vaccine candidate targets the five groups of the bacteria N. meningitidis (A, B, C, W and Y; MenABCWY) that cause most IMD cases globally.

It combines the antigenic components of the company's already licensed meningococcal vaccines, BEXSERO (meningococcal group B [MenB]) and MENVEO (MenACWY), both of which are well established with demonstrated efficacy and safety profiles.

Why is it a drug to watch?

The combination of the separate MenB and MenACWY vaccines into one reduces the number of injections required to receive the same level of protection, potentially improving coverage and compliance with the vaccination schedule.

Although second to market after Pfizer Inc's pentavalent PENBRAYA™ vaccine, GSK-3536819 has the advantage of approval of BEXSERO in the E.U. for individuals from the age of 2 months old, while PENBRAYA is limited by approval of Trumenba® starting at the age of 10 years. This could result in a greater population eligible for vaccination with GSK-3536819 in the E.U. These multivalent vaccines could help support the WHO's strategy to eradicate meningitis by 2030.

GSK-3536819 was non-inferior (for all five serogroups) and had a similar safety profile to BEXSERO and MENVEO (control group) in terms of eliciting an immune response in the:

- Pivotal global phase 3 trial, in which the vaccine was administered in two doses (day 1 and day 181) to 3,650 healthy individuals aged 10-25 years. This also served as the confirmatory trial for BEXSERO. In this trial, the vaccine was effective against 110 diverse meningitis B invasive strains.

- Phase 3B clinical trial with 1,247 healthy individuals aged 15-25 years who were previously vaccinated with MENVEO (day 1 and day 181), where GSK-3536819 was administered on day 211. One dose of MENVEO on Day 1 and two doses of BEXSERO on Day 181 and Day 211 acted as the active comparator.

How will GSK-3536819 impact the market for meningococcus disease prevention?

GSK-3536819 will compete with PENBRAYA, the first and only approved pentavalent vaccine against the same five serogroups (A, B, C, W and Y), as well as currently licensed MenACWY vaccines: MENVEO, MenQuadfi® (Sanofi) and NIMENRIX® (Pfizer Inc).

The simplified dosing schedule offered by PENBRAYA and GSK-3536819 is viewed favorably by physicians, and there is expected to be room in the market for both products.

The use of the separate ACWY and B vaccines from both companies is anticipated to decline as the pentavalent versions become more widespread.

Sales of both BEXSERO (available in >50 countries) and MENVEO (available in >60 countries) increased in 2023, by 14% to £849m and 12% to £380m, respectively.[3] It is possible that some of these sales, and the growth, could transfer to GSK-3536819 once it is launched.

What gaps in treatment does GSK-3536819 fill?

Although rare, IMD is a serious illness that can result in long-term consequences such as brain damage or amputations, life-threatening complications or death, primarily in children and adolescents. GSK-3536819 provides another option, in addition to Pfizer Inc's PENBRAYA, to protect against the five major serogroups that account for nearly all IMD cases globally. The drug eliminates the need to be vaccinated twice and reduces the total number of injections to only two. This could increase compliance with vaccination and encourage greater coverage across the at-risk population.

What hurdles might it need to overcome to reach blockbuster status?

Low disease awareness can lead to poor vaccination rates; for example, only approximately 31% of adolescents in the U.S. have received a meningococcus B vaccine, and <12% have received both required doses.[4] PENBRAYA has the advantage of being the first pentavalent (A, B, C, W, and Y) meningococcal vaccine approved and available for individuals aged 10-25 years in the U.S. market for more than a year (September 2023). Even if approved worldwide, GSK-3536819 might experience slow uptake in some areas because it is more expensive than the monovalent vaccines that are available against the most prevalent strains in limited-resource countries and regions.

Market overview

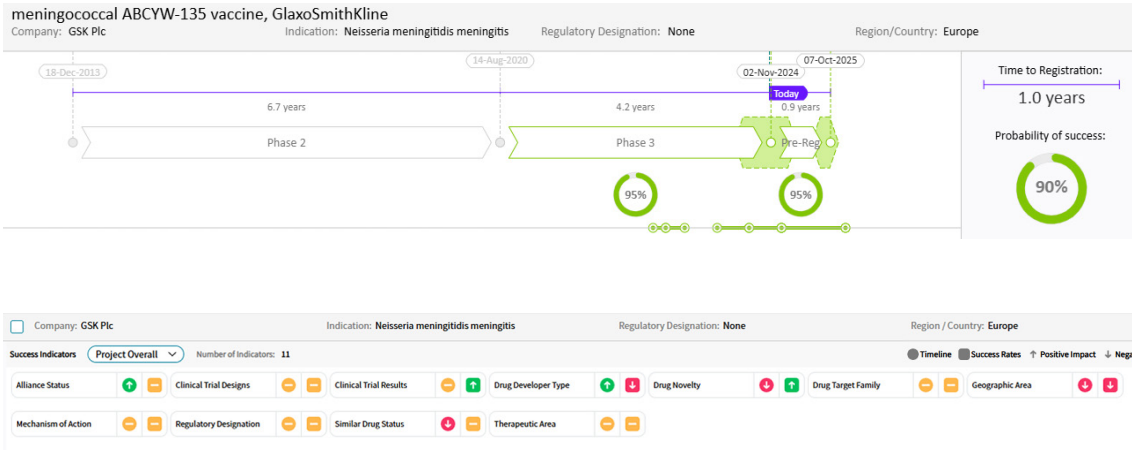
$905M

in the U.S. and E.U.4 markets in 2030

Trumenba has never made it to lower age groups in Europe or in the U.S. Therefore, the pentavalent based on the Trumenba part cannot be used in a childhood program, only in adolescents. Once the pentavalent from GSK is available, it will certainly replace Bexsero and ACWY vaccines."

Infectious disease specialist, Germany

Cortellis data indicate there is a 90% probability of success for GSK-3536819 in the European Union.

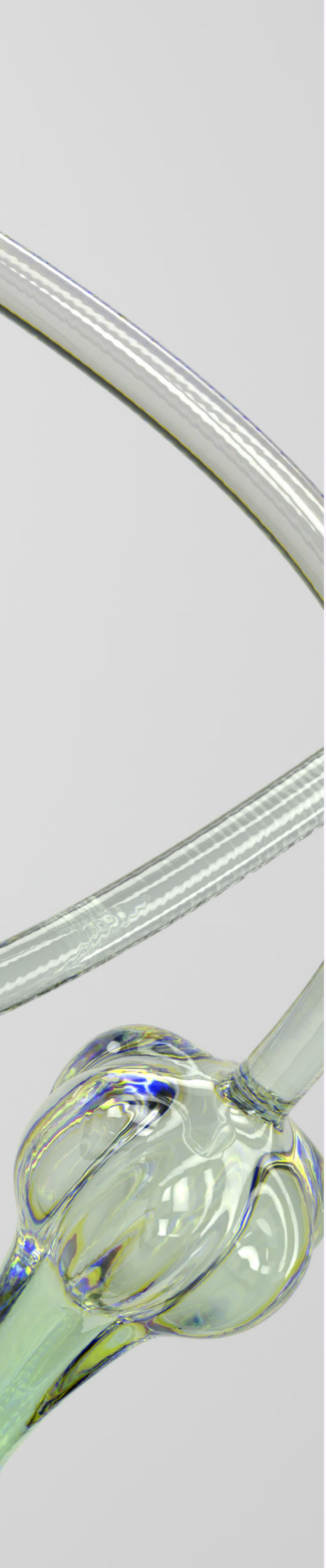


Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

IMDELLTRA™

(tarlatamab)

Small-cell lung cancer (SCLC)



IMDELLTRA™ at a glance

Producers

Amgen

Type

DLL3 × CD3-targeting BiTE® molecule

Usage

Biweekly IV infusion to treat adults with extensive-stage SCLC (ES-SCLC) with disease progression on or after platinum-based chemotherapy

Also being evaluated for other cancer indications, including neuroendocrine prostate cancer

Impact

~81K

new cases of relapsed or refractory (second- and later-line) ES-SCLC in the G7 markets in 2024

Review and approval status

October 2023

- Breakthrough therapy designation: U.S. FDA

December 2023

- Priority review: U.S. FDA

May 2024

- Accelerated approval: U.S. FDA

Actual and expected launch:

- **2024:** United States
- **2025:** European Union, Japan
- **2027:** Mainland China

Patents estimated to expire:

- Beginning in **2036**

IMDELLTRA™ is a first-in-class immunotherapy for (ES-SCLC), which is difficult to treat and has a poor prognosis.

Using Amgen's bispecific T cell engager (BiTE®) molecules, which are a type of fusion protein, IMDELLTRA engages two targets: CD3 on T cells and DLL3 on the tumor cell. This enables the T cell to recognize and attack the tumor cell leading to its lysis. DLL3 is expressed on the surface of SCLC cells in more than 85% of patients, regardless of chemotherapy treatment, but is minimally expressed on healthy cells, making it an attractive target. Its MOA explains the optimism surrounding IMDELLTRA, and it is expected to be established as the standard of care for previously treated ES-SCLC.

Why is it a drug to watch?

SCLC is an aggressive malignancy characterized by rapid, uncontrolled cell growth and early onset of metastases. The treatment landscape for relapsed or refractory SCLC is currently dominated by chemotherapy, which has a median OS of only about 5 months, indicating a significant unmet need.

The exceptional efficacy outcomes of the phase 2 DeLLphi-301 trial of IMDELLTRA led to the U.S. FDA granting it accelerated approval:

- ORR: 40%
- Median DOR: 9.7 months.
- Median PFS: 4.9 months (median follow-up of 10.6 months)
- Median OS: 14.3 months (median follow-up of 10.6 months)

The updated data from the DeLLphi-301 study after a follow-up of 16.6 months presented during World Conference on Lung Cancer (WCLC) 2024 provided further evidence to support the approval of IMDELLTRA for patients with relapsed or refractory SCLC with disease progression on or after platinum-based chemotherapy:

- Median OS: 15.2 months (median follow-up of 20.7 months)
- 6-month OS rate: 73.4%
- Median PFS: 4.3 months
- ORR: 40%
- CR: 3%
- PR: 37%
- Median DOR: 9.7 months
- Median DCR: 70%
- AEs leading to dose-reduction: 16%
- AEs leading to treatment discontinuation: 4%
- At least grade 3 CRS: 4%

Additional phase 3 trials are ongoing for confirmatory purposes and label expansion:

DeLLphi-304: adults with second-line SCLC who have relapsed after platinum-based first-line chemotherapy (confirmatory trial for regular approval of IMDELLTRA for relapsed or refractory SCLC)

- IMDELLTRA vs standard of care (lurbinectedin, topotecan, amrubicin)
- Primary endpoint: OS
- Estimated primary and study completion: July 2027

DeLLphi-305: adults with first-line ES-SCLC who were treated with first-line induction therapy with IMFINZI® (durvalumab; AstraZeneca) plus chemotherapy

- First-line extensive-stage SCLC after first-line induction therapy with IMFINZI and chemotherapy
- IMDELLTRA in combination with IMFINZI vs IMFINZI monotherapy
- Primary endpoint: OS
- Estimated primary completion: September 2027
- Estimated study completion: September 2028

DeLLphi-306: adults with limited-stage SCLC (LS-SCLC) who have not progressed following concurrent chemoradiotherapy

- IMDELLTRA vs placebo
- Primary endpoint: PFS
- Estimated primary and study completion: October 2029

How will IMDELLTRA impact the market for SCLC?

The SCLC drug therapy market is expected to grow from $1.7bn in sales in the major markets in 2022 to $5.8bn in 2032 (13% CAGR).

Growth will partially be driven by a rise in diagnosed incident cases leading to a larger drug-treatable population from 2022 to 2032 and increased drug treatment rates for previously treated SCLC, with disease relapse and recurrence remaining common features of SCLC. Therefore, second- and third-line drug treatment rates will gradually rise, from approximately 70% to 76% and from 48% to 56%, respectively.

In addition, the relapsed or refractory patient population is and will remain the most commercially lucrative patient setting in SCLC. It accounts for more than half of all drug-treatable opportunities and will remain the same through 2032. IMDELLTRA is expected to garner huge sales given its approval for the second- or later-line setting.

For the third-line patient segment, sales are anticipated to grow from $53.0m in 2022 to $817m in 2032, with IMDELLTRA and ifinatamab deruxtecan (Merck and Daiichi Sankyo) significantly contributing to sales in the later lines.

IMDELLTRA and ifinatamab deruxtecan will help address the substantial unmet need for more efficacious therapies in the later-line setting and provide some diversification to later-line treatment options but will struggle to compete with chemotherapy given their higher cost and hard-to-manage toxicity profile.

SCLC is highly sensitive to platinum-based chemotherapy, and a systemic chemotherapy regimen is almost always recommended for LS-SCLC and ES-SCLC. However, novel, effective therapies such as IMDELLTRA are expected to experience rapid uptake, especially when positioned as an add-on to current standards of care.

What gaps in treatment does IMDELLTRA fill?

SCLC is an aggressive cancer, with few therapeutic options. Second-line options typically offer a duration of response of just 3.6 to 5.3 months and OS of less than 8 months. LS-SCLC is generally treated with curative intent, while the aims of ES-SCLC treatment are prolonged survival, delayed disease progression and palliation of symptoms. Although ES-SCLC is highly sensitive to chemotherapy, development of resistance is inevitable, and few patients derive benefit from later-line therapy, with many experiencing significant side effects and poor quality of life. The increasing use of immunotherapies in the first-line ES-SCLC has limited their use in second and later lines. Therefore, treatments that extend OS for LS-SCLC and ES-SCLC and effectively fill gaps in the second- and third-line settings are critical needs, which IMDELLTRA has the potential to address.

What hurdles might it need to overcome to reach blockbuster status?

The high number of comorbidities and the disabling effects of the disease itself make many treatments with toxic or severe side effects unsuitable for some patients. The novel agent IMDELLTRA, due to its premium pricing and average per patient cost of $150,500, will find it difficult to compete with chemotherapy, which will remain the standard of care, as well as generic cytotoxic agents. Additionally, the challenging safety profile of IMDELLTRA, particularly the boxed warning for CRS and ICANS, may discourage physicians from prescribing it due to the added complexity of managing these toxicities. Potential future competitors for IMDELLTRA include the emerging DLL3 × CD3 bispecific BI-764532 (Boehringer Ingelheim) and trispecific antibodies MK-6070 (Merck) and RG6524 (Roche), both targeting DLL3, CD3 and CD137. Its use in later-line therapy will also limit IMDELLTRA's sales, especially due to the short treatment durations that result from rapid disease progression and short survival rates.

Market overview

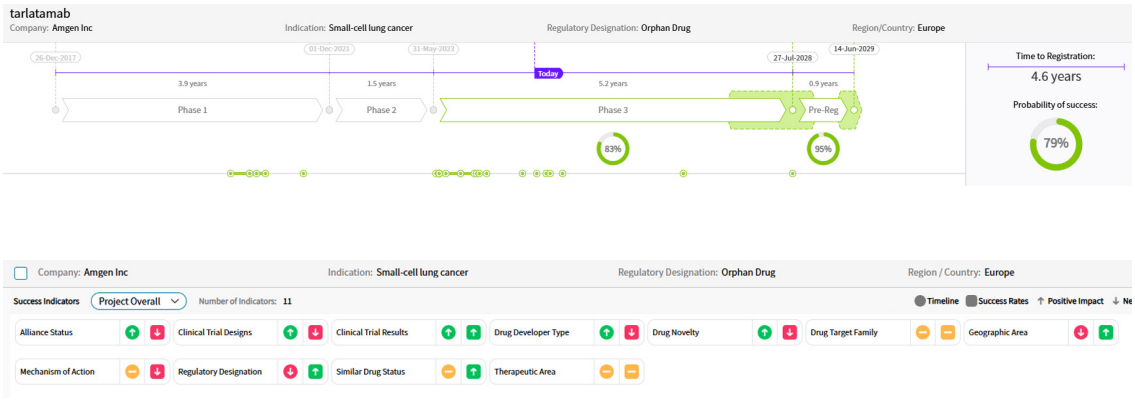
$2.10B

expected sales in the G7 markets in 2030

"I would like to see new drugs such as tarlatamab being developed because there are few effective treatment options for SCLC. The data for the BiTE antibody are not bad, so I think they are promising based on the data published in the NEJM."

Medical oncologist, Japan

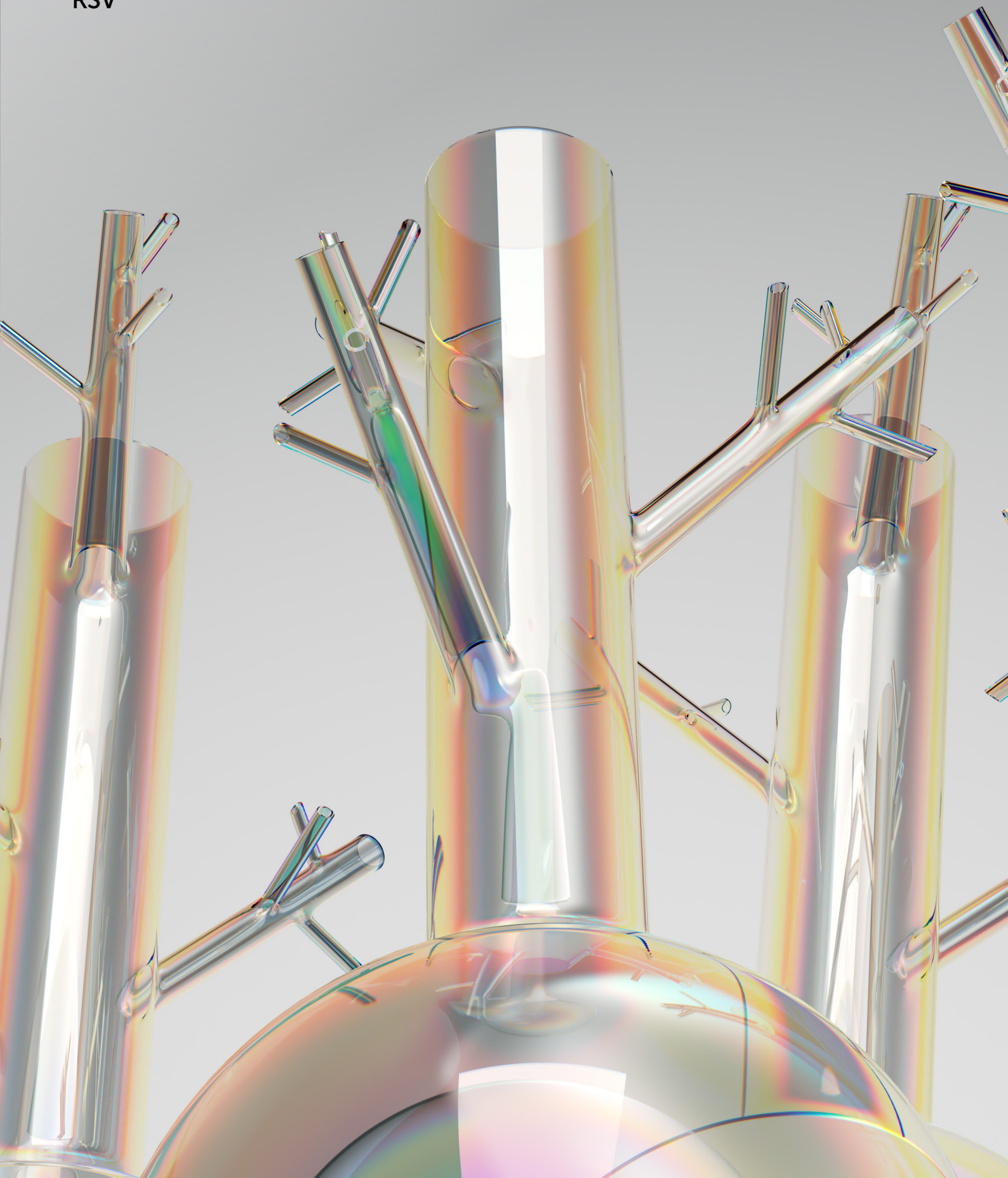
Cortellis data indicate there is a 79% probability of success for IMDELLTRA in the European Union.



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

mRESVIA®

(mRNA-1345)
RSV



mRESVIA® at a glance

Producers

Moderna Inc

Type

mRNA sequence
encoding a stabilized
prefusion F glycoprotein

Usage

Single-dose, 0.5-mL,
intramuscular injection
for active immunization
to prevent lower respiratory
tract disease (LRTD)
caused by respiratory syncytial virus
(RSV) in individuals ≥60 years old

Impact

~5m

diagnosed RSV inpatient
hospitalizations and outpatient
events in the G7 markets in 2024

Review and approval status

August 2021

- Fast track designation: U.S. FDA

January 2023

- Breakthrough therapy
  designation: U.S. FDA

May 2024

- Approved: U.S. FDA

August 2024

- Approved: E.U. EMA

Actual and expected launch:

- **2024:** European Union, United States
- **2025:** Japan, United Kingdom

Patents estimated to expire:

- Beginning in **2038**

With its U.S. FDA approval in May 2024, mRESVIA® joined AREXVY and ABRYSVO, both featured in Drugs to Watch 2024, as respiratory syncytial virus (RSV) vaccines currently available for adults ages 60 years and older, helping further support the public health initiative to reduce the RSV-related disease burden.

Even with available vaccines, RSV infections continue to be a public health concern, particularly for infants and older adults (65 years and older).

Why is it a drug to watch?

Using the same lipid nanoparticles (LNPs) as Moderna Inc's COVID-19 vaccines, mRESVIA builds on the company's foundational development of its mRNA platform. mRESVIA represents the first mRNA-based RSV vaccine, the first approval of an mRNA vaccine for a disease other than COVID-19 and the only RSV vaccine available in single-dose pre-filled syringes.

This vaccine further validates the clinical efficacy of vaccines based on the RSV F protein, which was a ground-breaking discovery that accelerated the recent development of vaccines against RSV, including AREXVY and ABRYSVO.

Approvals for mRESVIA are based on positive data from the global phase 3 clinical trial ConquerRSV:

- Participants included ~37,000 adults ages 60 years or older in 22 countries
- Vaccine efficacy against RSV-related LRTD was 83.7% (95% CI 66.0%, 92.2%) over a median 3.7-month follow-up

In supplementary analysis of data from a median 8.6-month follow-up, sustained vaccine efficacy against RSV-related LRTD was:

- 63.3% (95% CI 48.7%, 73.7%) for two symptoms
- 74.6% (95% CI 50.7, 86.9) for two or more symptoms, including shortness of breath
- 63.0% (95% CI 37.3%, 78.2%) for three or more symptoms

The most commonly reported adverse events were injection site pain, fatigue, headache, myalgia and arthralgia.

The approval in the United States was followed by the CDC ACIP official recommendation for the use of the vaccine in adults 60 years of age and older.

Trials are ongoing to expand the population eligible for mRESVIA:

Phase 3 study with high-risk individuals aged 18 years to <60 years (Part A) and individuals aged ≥18 years who received solid organ transplant (Part B)

- Single intramuscular injection (Part A)
- Two intramuscular injections on days 1 and 57 (Part B)
- Expected completion: July 2026

Phase 2 study with children aged 2 years to <5 years (cohorts 1 and 3) and 5 years to 18 years at high risk of RSV (cohort 2)

- Single intramuscular injection (cohort 2) vs placebo (cohorts 1 and 3)
- Expected completion: April 2025

Phase 2 study with individuals aged ≥18 years to <40 years who are pregnant and infants born to vaccinated mothers

- Single intramuscular injection in the period from 28 weeks to 36 weeks of gestation
- Expected completion: February 2026

Phase 1 study with infants aged 5 months to <24 months

- Single intramuscular injection on days 1, 57 and 113
- Expected completion: July 2026

How will mRESVIA impact the market for RSV prevention?

The landscape looks likely to become increasingly crowded, with the RSV vaccine and prophylaxis market for the general vaccination population (adults 75 years and older and pregnant women to protect their babies through maternal immunization) potentially reaching $7bn by 2030 in the G7 countries.

The two existing vaccines, ABRYSVO and AREXVY, identified as drugs to watch in the 2024 report, have fared very differently from each other.

- AREXVY was the first to enter the U.S., Canada, the E.U. and Japan and has since been approved in the E.U., the U.S. and Japan for at-risk individuals 50 years to 59 years old. 60% of adults in the U.S. aged ≥60 years who were vaccinated against RSV were vaccinated with AREXVY, contributing to the £1.238bn ($1.65bn) total global sales in 2023. In fact, almost all of AREXVY's 2023 sales were in the U.S.,[3] and it currently leads in RSV vaccine market share, mostly due to its contracts with retail pharmacies. However, sales slowed in 2024, reaching only £432m ($555.7m) in the first three quarters of 2024, but this could change with the 2024-2025 RSV season.[5]
- ABRYSVO had the advantage of being launched with a broader population that includes both older adults (May 2023) and pregnant individuals (August 2023), and it was approved for high-risk adults aged 18 years to 59 years in October 2024 (the first to be approved for adults younger than 50 years). However, its sales only reached $890m after its launch in 2023, approximately the same amount AREXVY earned in Q3 2023 alone. Revenue was primarily from the older population in the U.S., although the company held hope for its impact on maternal immunization in 2024.[6] Despite the population expansion, sales decreased to $356m in the first three quarters of 2024.[7]

Other candidates in clinical development include the following:

- ADV-110 (Advaccine Biopharmaceuticals): Recombinant protein vaccine for RSV
- BLB-201 (Blue Lake Biotechnology and CyanVac LLC): Recombinant viral vector vaccine for RSV
- CodaVax-RSV (Codagenix): cLive-attenuated viral vaccine for RSV
- D46/NS2/N/deltaM2-2-HindIII (NIAID): Recombinant viral vector vaccine for RSV
- DS-Cav1 (NIAID): Protein subunit vaccine for RSV
- IVX-A12 (Icosavax Inc/AstraZeneca): Virus-like particle and protein subunit vaccine for human metapneumovirus and RSV
- mRNA-1045 (Moderna Inc): mRNA vaccine for influenza and RSV
- mRNA-1230 (Moderna Inc): mRNA vaccine for SARS-CoV2, influenza and RSV
- mRNA-2365 (Moderna Inc): mRNA vaccine for RSV and human metapneumovirus (hMPV)
- MV-012-968 (Meissa Vaccines): Live-attenuated vaccine for RSV
- RSV 6120/deltaNS2/1030s (NIAID): cLive-attenuated viral vaccine for RSV
- RSV-276 (NIAID): Live-attenuated viral vaccine for RSV
- SP0125 (Sanofi): Live-attenuated viral vaccine for RSV
- V-306 (Virometix AG): Synthetic virus-like particle vaccine for RSV
- VN-0200 (Daiichi Sankyo): VAGA-9001a antigen; MABH-9002b adjuvant for RSV
- VXB-241 (Vicebio Ltd): Protein subunit vaccine using the company's molecular clamp technology for human parainfluenza virus type 3 (PIV3), hMPV and RSV
- VXB-251 (Vicebio Ltd): Protein subunit vaccine using the company's molecular clamp technology for hMPV and RSV

What gaps in treatment does mRESVIA fill?

Seasonal hospitalizations due to serious respiratory illness caused by RSV continue to be a public health issue, particularly for infants, young children, older adults and individuals with underlying health conditions such as COPD and asthma. The approvals of RSV vaccines address a significant need for infectious disease control, reduced morbidity and mortality, and decreased hospital burden, especially during the "tripledemic" of RSV, flu and COVID-19.

What hurdles might it need to overcome to reach blockbuster status?

As the third to market, mRESVIA will compete with ABRYSVO and AREXVY as well as other RSV vaccines that are in late-stage development. Although mRESVIA has the advantage over the other RSV vaccines of not requiring preparation by health professionals, it has a shorter shelf-life and requires very cold storage temperatures to remain intact, which could limit where it is used. In addition, the CDC ACIP's delay on a decision around recommending RSV vaccines for those aged 50-59 years in mid-2024 could hamper all RSV vaccine sales, in addition to the CDC's suggestion that the vaccines are expected to confer multiple years of protection making it unnecessary to be vaccinated annually.

Market overview

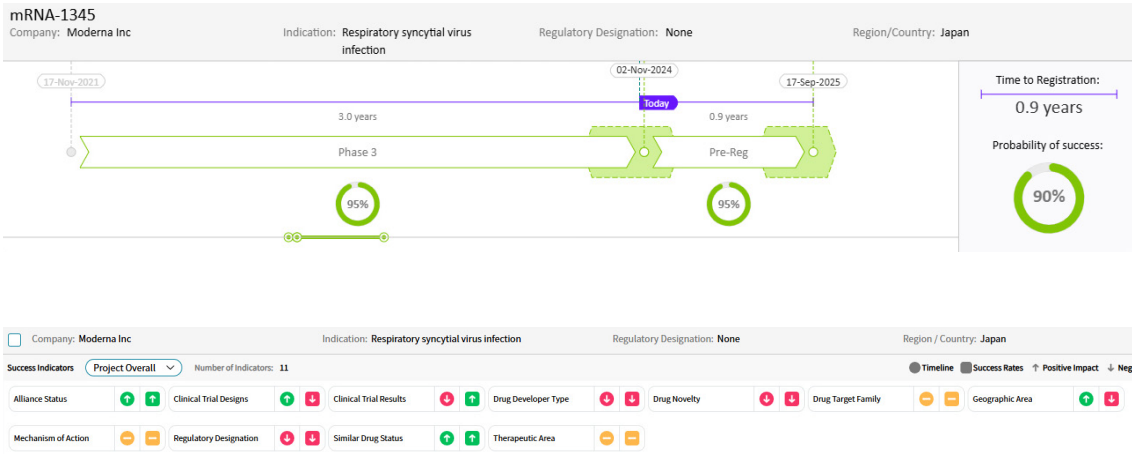
$1.40B

expected sales in the G7 markets in 2030

"Moderna's vaccine is an mRNA vaccine. I doubt it will capture much share because there's so much worry about mRNA vaccines -- unless they figure out a way to combine it with another vaccine to reduce the number of shots."

Infectious disease specialist, United States

Cortellis data indicate there is a 90% probability of success for mRESVIA in Japan.



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

SEL-212

Gout

SEL-212 at a glance

Producers

Sobi

Cartesian Therapeutics Inc/
Selecta Biosciences Inc

Type

ImmTOR™ (nanoparticles encapsulating sirolimus [SEL-110.36]) + pegylated uricase (pegadricase; SEL-037)

Usage

Once-monthly intravenous infusion to treat chronic refractory gout

Impact

19.7m

prevalent cases of chronic gout in the G7 markets in 2023

Review and approval status

March 2024

- Fast track designation: U.S. FDA

July 2024

- Rolling BLA submitted: U.S. FDA

Actual and expected launch:

- **2025:** United States
- **2026:** European Union, Japan

SEL-212 is a novel, once-monthly co-administration of pegylated uricase (pegadricase; SEL-037) with ImmTOR™, an immune tolerance technology designed to inhibit formation of anti-drug antibodies (ADAs).

For this application, the ImmTOR consists of SEL-110.36, an inhibitor of uricase-specific ADA. This could help address the limitation of reduced efficacy and tolerability in the presence of ADAs developed in response to other biologic medicines (e.g., Amgen's KRYSTEXXA®/pegloticase) for chronic gout.

Why is it a drug to watch?

Sobi licensed SEL-212 from Selecta Biosciences Inc (acquired by Cartesian Therapeutics Inc in November 2023) for $100m and is responsible for development, regulatory and commercial activities in all markets except Mainland China. It is expected to be the first drug for treatment-refractory chronic gout in the European and Japanese markets.

SEL-212 was designed to reduce serum urate levels in chronic refractory gout, thereby reducing harmful tissue urate deposits that can result in gout flares and joint deformity when left untreated. Administration involves sequential infusions of ImmTOR (SEL-110.36), followed by SEL-037. Phase 3 results revealed similar efficacy and safety to that of KRYSTEXXA, the main competitor in the treatment of chronic refractory gout. However, SEL-212 has less-frequent dosing and is co-administered with an immunomodulator, whereas KRYSTEXXA can require follow-up administration of methotrexate for immunomodulation when needed.

The rolling BLA submission was based on results from the pivotal phase 3 DISSOLVE I and DISSOLVE II trials:

Both RCTs had the same inclusion criteria and treatment regimen:

- Adults (19-80 years old) with chronic gout refractory to conventional therapies (xanthine oxidase inhibitors [XOIs], uricosurics) and not previously exposed to pegylated uricase-based therapy
- Treatment arms (administered every 28 days for six months)
  - Low-dose SEL-212: 0.1 mg/kg SEL-110.36, followed by SEL-037
  - High-dose SEL-212: 0.15 mg/kg SEL-110.36, followed by SEL-037
  - Placebo

DISSOLVE I (United States); n=112

- Achieved and maintained a reduction in serum uric acid levels <6 mg/dL for at least 80% of the trial duration: 48% vs 56% vs 4%

DISSOLVE II (global); n=153

- Achieved and maintained a reduction in serum uric acid levels <6 mg/dL for at least 80% of the trial duration: 40% vs 46% vs 11%
- In both trials, the active treatment groups experienced mild-to-moderate stomatitis (3.4% vs 9.2%), infusion reactions (4.5% vs 3.4%). Serious TEAEs included anaphylaxis and gout flare (3.4% of all participants receiving active treatment)

How will SEL-212 impact the market for gout?

Major market sales of drugs for acute and chronic gout will increase from $3.6bn in 2023 to $8.6bn in 2033, driven primarily from the launch and uptake of emerging therapies and the increased incidence and prevalence of gout over the forecast period.

At the same time, market value could be constrained by the limited number of assets in late-stage development and the availability of inexpensive generic options, which effectively treat most individuals with gout. Generic options will likely remain the standard of care due to their low price, satisfactory efficacy and physician familiarity.

In the chronic gout market specifically, SEL-212 is expected to drive substantial sales growth because of its anticipated high price, which is expected to be at approximately a 10% premium to KRYSTEXXA, and successful positioning for chronic gout refractory to other treatments.

SEL-212 could also have a competitive edge over KRYSTEXXA, its main competitor, given its similar efficacy and safety profile, less-frequent dosing and co-administration with an immunomodulator. In the first months following launch, KRYSTEXXA achieved sales of $507m, providing an indicator of the potential for SEL-212.

What gaps in treatment does SEL-212 fill?

In the United States, KRYSTEXXA is the only option for individuals whose chronic gout does not respond to standard treatments but is not currently approved in Europe nor Japan, representing a large gap for patients with chronic refractory gout in these markets. Treatment-refractory chronic gout is often painful and debilitating, resulting in several flares per year and potential nodular masses of uric acid crystals (tophi). In markets where KRYSTEXXA is available, SEL-212 is expected to be a welcome option for patients and clinicians given its once-monthly infusion and co-administration of two separate drugs, compared with KRYSTEXXA's biweekly administration and the need to administer it with methotrexate.

What hurdles might it need to overcome to reach blockbuster status?

Despite its potential competitive edge over KRYSTEXXA, uptake of SEL-212 might be limited by the relatively small target population of patients with chronic refractory gout (~2% of individuals with gout)[8] its extremely high price and the expected launch of biosimilar versions of KRYSTEXXA (pegloticase) starting in 2030.

Market overview

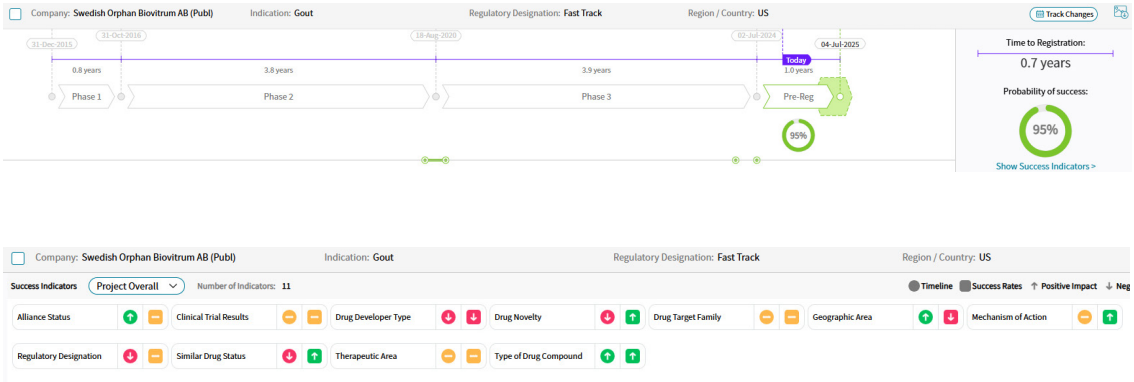
$1.70B

expected sales in the G7 markets in 2030

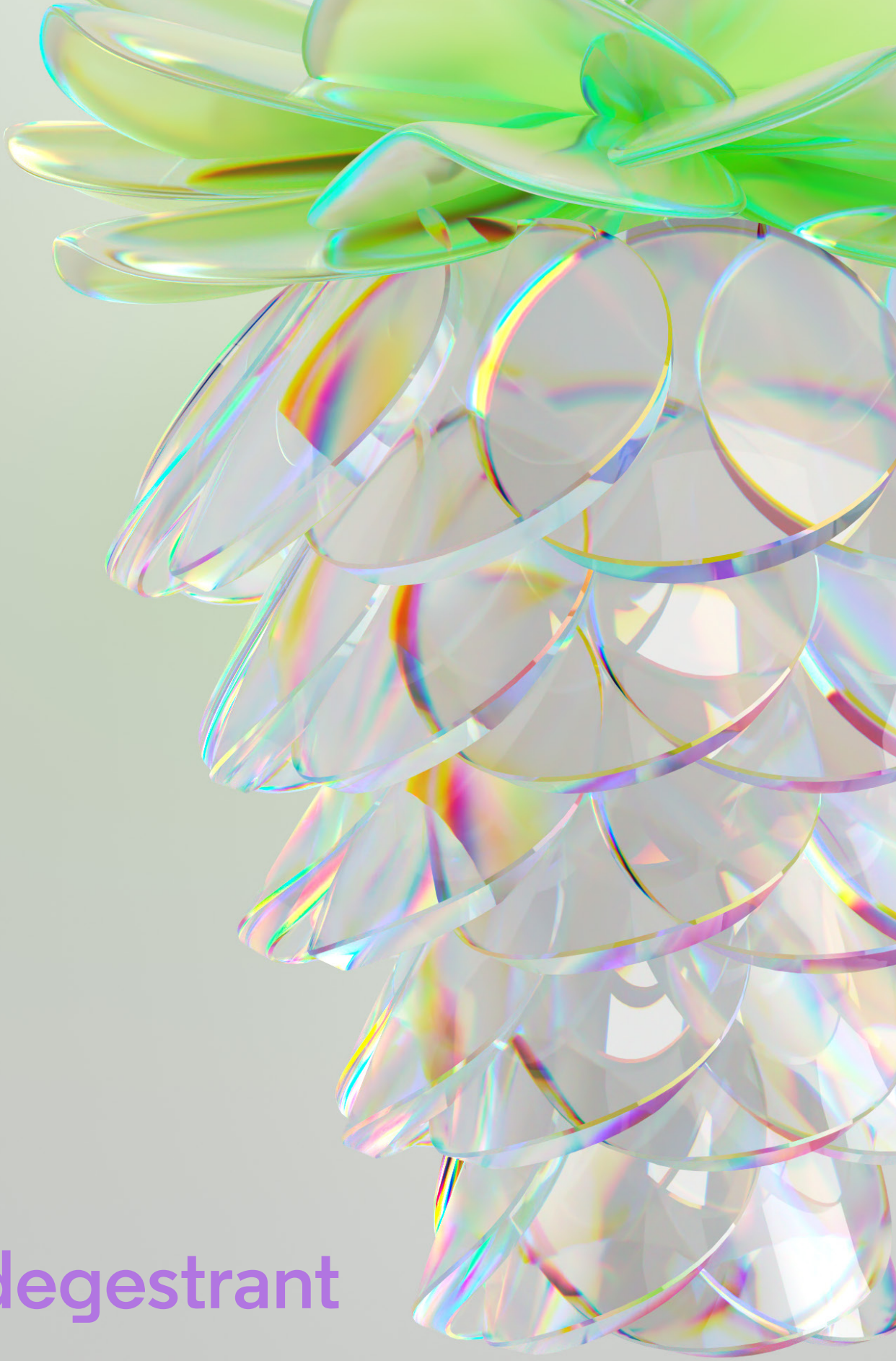
"I would absolutely be very excited to use this agent over KRYSTEXXA. It's non-immunogenic. If it obviates the need for an immunosuppression agent, certainly that's an advantage."

Rheumatologist, United States

Cortellis data indicate there is a 95% probability of success for SEL-212 in the United States.

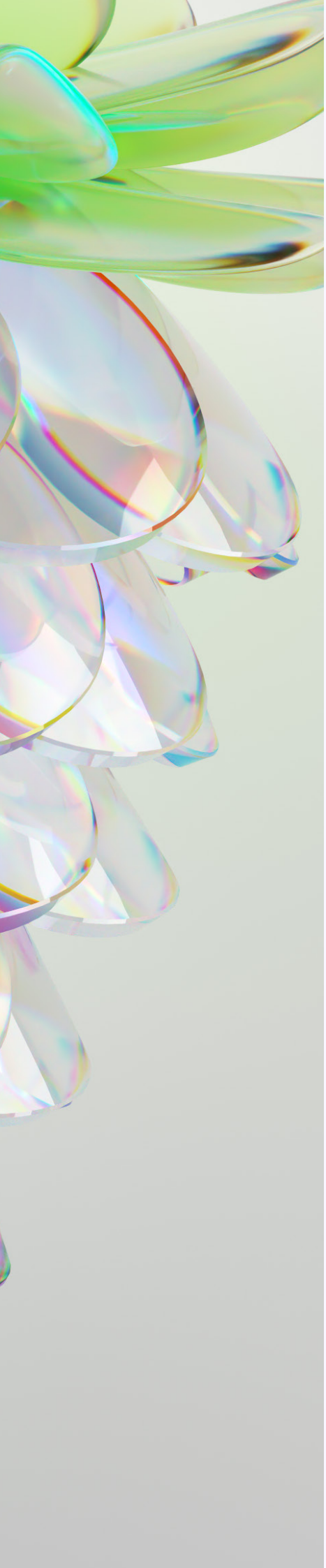


Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.



Vepdegestrant

(ARV-471)
Breast cancer



Vepdegestrant at a glance

Producers

Arvinas Inc

Pfizer Inc

Type

ER PROTAC degrader

Usage

Oral administration to treat adults with estrogen receptor (ER)-positive/HER2-negative locally advanced or metastatic breast cancer

Impact

~90K

new cases of previously untreated (first-line) metastatic HR-positive/HER2-negative breast cancer in the G7 markets in 2024

~115K

new cases of previously treated (second- and third-line) HR-positive/HER2-negative breast cancer in the G7 markets in 2024

Review and approval status

July 2023

- Innovation passport designation via the Innovative Licensing Access Pathway (ILAP): U.K. MHRA

February 2024

- Fast track designation: U.S. FDA

Actual and expected launch:

- **2025:** United States
- **2026:** European Union, Japan
- **2027:** Mainland China

Patents estimated to expire:

- Beginning in **2037**

The product of a global collaboration between Arvinas Inc and Pfizer Inc, vepdegestrant has the potential to become the first PROteolysis Targeting Chimera (PROTAC®) protein degrader to reach the market.

Vepdegestrant is designed to target and degrade the estrogen receptor (ER) protein, and early studies have shown that PROTAC-induced protein degradation is more complete than with oral selective estrogen receptor degraders (SERDs). This promises a potential strategy to overcome endocrine resistance in breast cancer, which could be groundbreaking for this patient population. Label expansions being explored include combination with IBRANCE® (palbociclib; Pfizer Inc).

Why is it a drug to watch?

Vepdegestrant is being developed as potential monotherapy and part of combination therapy for ER-positive/HER2-negative metastatic breast cancer. Vepdegestrant is the first PROTAC therapy to reach phase 3 development in breast cancer where it has shown promising efficacy in the phase 2 VERITAC trial.

Results have been reported from the following trials:

Phase 1b of the VERITAC trial (part C): patients treated with at least one prior line of endocrine therapy and no more than 2 lines of chemotherapy in the metastatic setting:

- Vepdegestrant in combination with IBRANCE
- ITT population (N=46; *ESR1*-mutant and wild-type patients)
  - 87% had received prior treatment with a CDK4/6 inhibitor (78% had received IBRANCE)
  - 80% had received prior fulvestrant
  - 46% had received chemotherapy in the metastatic setting
  - ORR: 42% (47% in the *ESR1*-mutant subgroup, N=29)
  - Median PFS: 11.2 months (13.7 months in the *ESR1*-mutant subgroup)
- Subgroup of patients with no prior CDK4/6 inhibitor treatment:
  - Median PFS: 19.3 months (2 of 6 events)

Phase 2 cohort expansion of the VERITAC trial (part B): patients treated with at least one prior line of endocrine therapy and CDK4/6 inhibitors in the metastatic setting:

- Vepdegestrant monotherapy
- ITT population (N=71; *ESR1*-mutant and wild-type patients with a median number of 3 prior regimens in the metastatic setting)
  - 78.9% had received prior treatment with fulvestrant
  - 45.1% had received prior chemotherapy in the metastatic setting
  - CBR: 38% (51.2% in the *ESR1*-mutant subgroup)
  - Median PFS: 3.7 months (5.7 months in the *ESR1*-mutant subgroup)

- Subgroup of patients (N=8) with no prior fulvestrant or chemotherapy in the metastatic setting
  - CBR: 62.5%
  - Median PFS: 19 months (4 of 8 events)
  - ORR: 29%

The following phase 3 trials are ongoing:

VERITAC-2: patients with metastatic ER-positive/HER2-negative breast cancer who have received prior treatment with CDK4/6 inhibitors and endocrine therapy in the metastatic setting with no more than one additional line of endocrine therapy (second- and third-line metastatic setting)

- Vepdegestrant monotherapy vs fulvestrant
- Dual primary endpoints: PFS in the ITT population and in the *ESR1*-mutant subgroup
- Estimated primary completion: January 2025

VERITAC-3: endocrine-sensitive patients who have not received prior treatment for their metastatic setting nor adjuvant CDK4/6 inhibitors (first-line metastatic setting):

- Vepdegestrant in combination with IBRANCE vs letrozole in combination with IBRANCE
- Primary endpoint: PFS in the ITT population

- Two additional pivotal trials are planned (pending further data and regulatory agreement):
  - Vepdegestrant in combination with atirmociclib in the first-line setting
  - Vepdegestrant in combination with IBRANCE or potentially other CDK4/6 inhibitors in the second- and third-line setting

Several phase 1/1b and phase 2 studies (TACTIVE-K/N/U/E) are also investigating the preliminary efficacy and safety for vepdegestrant in combination with other targeted agents as well as its efficacy in the neoadjuvant setting.

How will vepdegestrant impact the market for breast cancer?

Breast cancer is one of the largest therapy markets in oncology in terms of current dollar value, owing to the large number of diagnosed incident cases, high drug treatment rates and typically long treatment durations.

In 2033, sales are expected to be dominated by two drug classes that will amass sales of approximately $27bn and capture nearly two-thirds of the total market share: HER2-targeted agents and CDK4/6 inhibitors. HR-positive/HER2-negative sales are anticipated to increase from almost $1.4bn in 2023 to $2.5bn in 2033.

Within the class of ER-targeting agents, next-generation drugs are expected to collectively garner $3.1bn in sales in 2033, largely driven by the market entry of vepdegestrant and the oral SERD camizestrant (AstraZeneca). Others that will likely be approved over the next few years include the oral SERD imlunestrant (Eli Lilly and Co), oral selective estrogen receptor modulator (SERM) lasofoxifene (Sermonix Pharmaceuticals Inc) and the complete ER antagonist (CERAN) palazestrant (Olema Pharmaceuticals Inc).

Vepdegestrant is expected to gain its first market approval as a monotherapy for the treatment of patients with endocrine-sensitive metastatic HR-positive/HER2-negative breast cancer who have received at least one prior line of endocrine therapy in the metastatic setting and have had exposure to a CDK4/6 inhibitor (i.e., second- and later-line setting). We expect that the agent will gain a broad label (for ESR1-mutant and non-mutant) and compete for patient share with other emerging ER-targeting drugs forecast to enter the same setting.

In the first-line metastatic HR-positive/HER2-negative setting, we expect approval of vepdegestrant in combination with IBRANCE (Pfizer Inc) in a non-biomarker-restricted population. This regimen will compete with approved CDK4/6-inhibitor based regimens that have standard endocrine therapy (e.g., letrozole) as a backbone.

Label expansions of vepdegestrant, in combination with other targeted therapies for first-line metastatic HR-positive/HER2-negative disease, a larger and thus more lucrative setting, could boost its sales and improve its market share in this segment

What gaps in treatment does vepdegestrant fill?

Following treatment in the metastatic HR-positive/HER2-negative breast cancer setting, a high proportion of patients (~30-40%) develop disease recurrence owing to the acquisition of *ESR1* mutations. The oral SERD ORSERDU® (elacestrant; Menarini Group) is the only therapy in the market with proven efficacy in this subgroup of patients. Vepdegestrant degrades both *ESR1*-mutant and *ESR1*-wildtype, and we expect it to become part of the treatment armamentarium in the post-CDK4/6-inhibitor setting, where currently available therapies show limited efficacy outcomes, especially for patients without mutations that can be targeted. Additionally, its development in combination with CDK4/6 inhibitors in the first-line setting could provide better inhibition of ER-driven tumor survival and proliferation than standard endocrine therapies (e.g., aromatase inhibitors), thereby delaying disease progression.

What hurdles might it need to overcome to reach blockbuster status?

Regulatory approval and launch of multiple ER-targeting agents in the second- and later-line settings could introduce intense competition and therefore constrain uptake of vepdegestrant. Blockbuster status also hinges on successful label expansions for use in the treatment of first-line metastatic disease where it is currently being investigated in combination with IBRANCE (Pfizer Inc).

Market overview

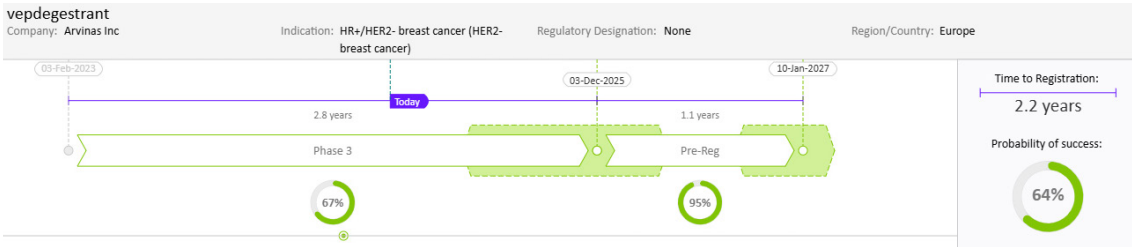
$1.19B

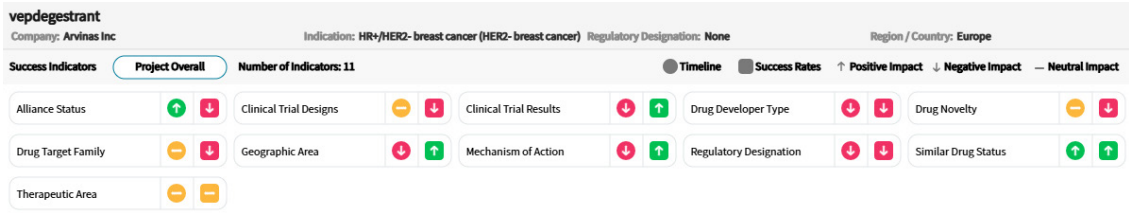
expected sales in the G7 markets in 2030

"It's an unfair comparison [vepdegestrant vs. fulvestrant] because vepdegestrant is not a drug. It's a technology. So, you can even use this technology by combining it and that's potentially very helpful. We will see. It's in an earlier phase of development compared with the oral SERDs, but I think that it will be the next frontier."

Medical oncologist, Italy

Cortellis data indicate there is a 64% probability of success for vepdegestrant in the European Union.



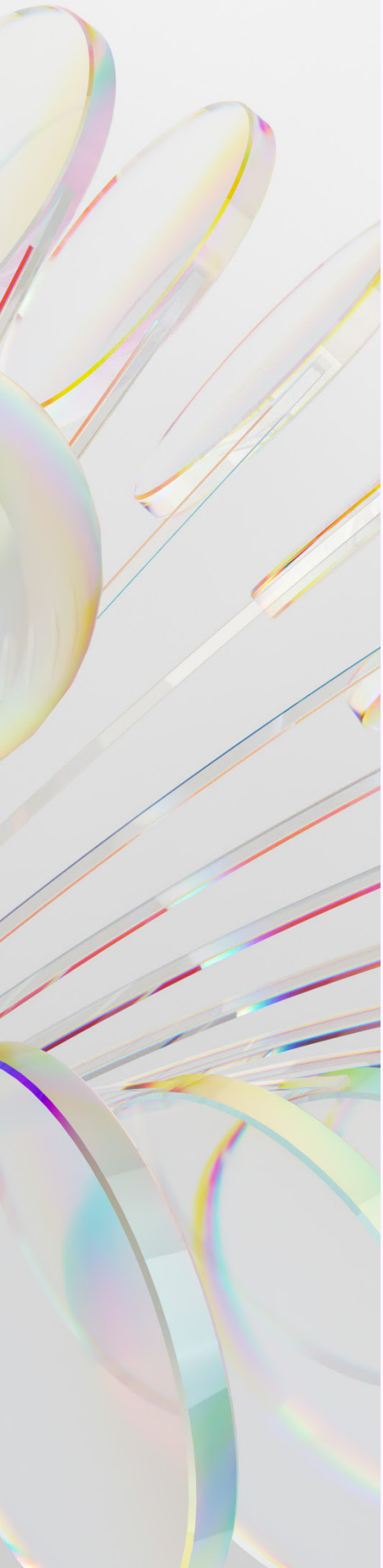


Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

Zanzalintinib

(XL092)

Colorectal cancer, renal cell carcinoma and squamous cell carcinoma of head and neck



Zanzalintinib at a glance

Producers

Exelixis Inc

Type

Tyrosine kinase inhibitor (TKI) targeting VEGF receptors, MET and the TAM kinases (TYRO3, AXL, MER)

Usage

Once-daily oral administration being investigated in non-clear-cell renal cell carcinoma (nccRCC), colorectal cancer (CRC) and squamous cell carcinoma of the head and neck (SCCHN)

Impact

~9K

new cases of previously untreated (first-line) advanced or metastatic nccRCC in the G7 markets in 2024

~131K

new cases of previously treated (third- and later-line) metastatic CRC in the G7 markets in 2024

~57K

new cases of previously untreated (first-line) recurrent or metastatic non-nasopharyngeal SCCHN in the G7 markets in 2024

Review and approval status

Actual and expected launch:

- **2026:** European Union, United States (CRC and nccRCC)
- **2028:** European Union, United States (SCCHN)

Patents estimated to expire:

- Beginning in **2039**

Zanzalintinib is a third-generation oral TKI that inhibits the activity of receptor tyrosine kinases implicated in tumor angiogenesis, metastasis and immunosuppression, including VEGF receptors, MET and the TAM kinases (TYRO3, AXL, MER).

Currently being investigated in phase 3 trials in combination with immune checkpoint inhibitors for nccRCC, CRC and SCCHN. Compared with CABOMETYX® (cabozantinib), the company's flagship medicine that is approved broadly for advanced RCC, zanzalintinib has the potential advantages of being approved specifically for the ncc histology as well as a broader patient population that includes nccRCC, CRC and SCCHN.

Why is it a drug to watch?

Zanzalintinib represents Exelixis Inc's first in-house compound to enter the clinic following its re-initiation of drug discovery activities in 2017 and represents an important component of the company's lifecycle management strategy for CABOMETYX, which generated $1.6bn in revenue in the United States in 2023 and is due to come off patent in the United States in 2031. Exelixis Inc sought to build on its extensive experience with the kinase targeting profile of CABOMETYX while improving characteristics such as its pharmacokinetic half-life.

As such, zanzalintinib has a shorter half-life of approximately one day, which supports once-daily dosing and promises more favorable tolerability. With these characteristics and its promising anti-tumor activity, zanzalintinib is positioned to be a best-in-class VEGF-receptor TKI in a wide range of solid tumors when used as a monotherapy, as well as in combination regimens. Initial investigations of combination therapy involve OPDIVO® (nivolumab; Bristol Myers Squibb) for nccRCC, WELIREG® (belzutifan; Merck) for RCC, TECENTRIQ® (atezolizumab; Genentech, a member of the Roche Group) for CRC and KEYTRUDA® (pembrolizumab; Merck) for SCCHN.

The phase 1b/2 STELLAR-001 trial was a dose-escalation and expansion study of zanzalintinib as monotherapy and combination therapy for inoperable locally advanced or metastatic solid tumors. Within the ccRCC cohort, an ORR of 38% and disease control rate of 88% with single-agent zanzalintinib was achieved in previously treated ccRCC patients after a median 8.3 months.

The following pivotal phase 3 trials are currently underway to confirm and expand upon these findings:

STELLAR-303: adults with microsatellite stable (MSS)/microsatellite instable (MSI)-low metastatic CRC (mCRC) and known *RAS* status who have progressed during or after or are intolerant to standard of care therapy

- Zanzalintinib plus TECENTRIQ vs STIVARGA® (regorafenib; Bayer)
- Primary analysis includes patients with non-liver metastases (NLM) Approximately 350 NLM patients will be enrolled, while enrollment of patients with liver metastases will be capped at approximately 524.
- Primary endpoint: OS in NLM patients
- Estimated primary completion: August 2025
- Estimated study completion: February 2026

STELLAR-304: previously untreated adults with unresectable, advanced or metastatic nccRCC

- Zanzalintinib plus OPDIVO vs SUTENT® (sunitinib; Pfizer Inc)
- Primary endpoints: PFS and ORR
- Estimated primary completion: July 2025
- Estimated study completion: June 2028

STELLAR-305: previously untreated adults with PD-L1-positive recurrent or metastatic SCCHN

- Zanzalintinib plus KEYTRUDA vs placebo plus KEYTRUDA
- Primary endpoints: OS and PFS
- Estimated primary completion: August 2028
- Estimated study completion: March 2029

How will zanzalintinib impact the market for colorectal cancer, renal cell carcinoma and squamous cell carcinoma of the head and neck?

Sales of RCC drug therapies in the G7 markets are expected to increase from $9.0bn in 2023 to $12.7bn in 2033 (3.5% CAGR), heavily shaped by the entry of new combination regimens, including zanzalintinib plus OPDIVO for nccRCC.

The first-line treatment of advanced or metastatic RCC is the largest and therefore most lucrative RCC population, capturing more than 50% of the total RCC market throughout the forecast period. We forecast that sales of the zanzalintinib plus OPDIVO regimen will account for 27% of total RCC sales in this setting in 2033.

Major-market sales of angiogenesis inhibitors for RCC treatment are expected to decline from $4.5bn in 2023 to $3.9bn in 2033, largely as a result of generic erosion. However, the entry of novel anti-angiogenics for nccRCC will somewhat offset this decline, and zanzalintinib is forecast to be the top-selling angiogenesis inhibitor in 2033 for RCC, with major-market sales of over $1.4bn.

Major market sales of CRC drug therapies are expected to increase slightly from $9.6bn in 2023 to $12.0bn in 2033 (2.3% CAGR), driven by anticipated drug approvals and label expansions.

Angiogenesis inhibitors, such as zanzalintinib, and cytotoxic agents are forecasted to dominate the overall CRC market, accounting for 55% of the overall market share in 2033.

Zanzalintinib will likely help boost sales of TECENTRIQ and other immune checkpoint inhibitors when used in combination therapy for mCRC.

G7 sales for SCCHN therapies are also expected to increase from $1.6bn in 2023 to $4.3bn in 2033 (10.6% CAGR), driven mainly by the expected approval of high-cost emerging therapies such as zanzalintinib, which is expected to account for 40% of total sales by 2033.

The first-line treatment of recurrent or metastatic SCCHN represents the bulk of the SCCHN market, accounting for 73% of total market share in 2023. Growth in this setting will also likely be driven by the expected approval of zanzalintinib, which could also boost KEYTRUDA sales and further erode patient shares of doublet and triplet chemotherapy regimens, including the EXTREME regimen.

Collectively, pembrolizumab and zanzalintinib are projected to generate 93% of sales in this setting of first-line treatment of recurrent or metastatic SCCHN in 2033.

What gaps in treatment does zanzalintinib fill?

Approximately 20-25% of patients with RCC have nccRCC, which is a heterogenous group of rare, histologic subtypes with a poor prognosis and limited treatment options. Zanzalintinib could be the first therapy specifically approved for this histology. Patients with SCCHN are often relegated to immunotherapy plus chemotherapy but could benefit from a chemo-free option. Current therapies for mCRC are largely palliative, highlighting a gap in treatments that offer durable benefits in advanced stages. Novel treatment options supported by data from robust clinical trials are needed for all of these indications, and zanzalintinib offers a promising choice for these patients.

What hurdles might it need to overcome to reach blockbuster status?

The aggressive nature of the targeted diseases results in short treatment durations, constraining the sales potential of therapies including zanzalintinib. In addition, combination treatment with zanzalintinib is expected to be significantly more expensive than current standard treatments for the target diseases. This could impact the overall market by potentially limiting patient access and therefore deterring uptake, especially in cost-sensitive regions. Finally, there are strong molecular similarities between zanzalintinib and its predecessor cabozantinib. Sales could be limited by this factor, along with the expected launch of cabozantinib generics in Japan in 2030 and in the U.S. and E.U. in 2031. As a result, zanzalintinib will be competing with cabozantinib in RCC, where cabozantinib has a broad label for advanced disease.

Market overview

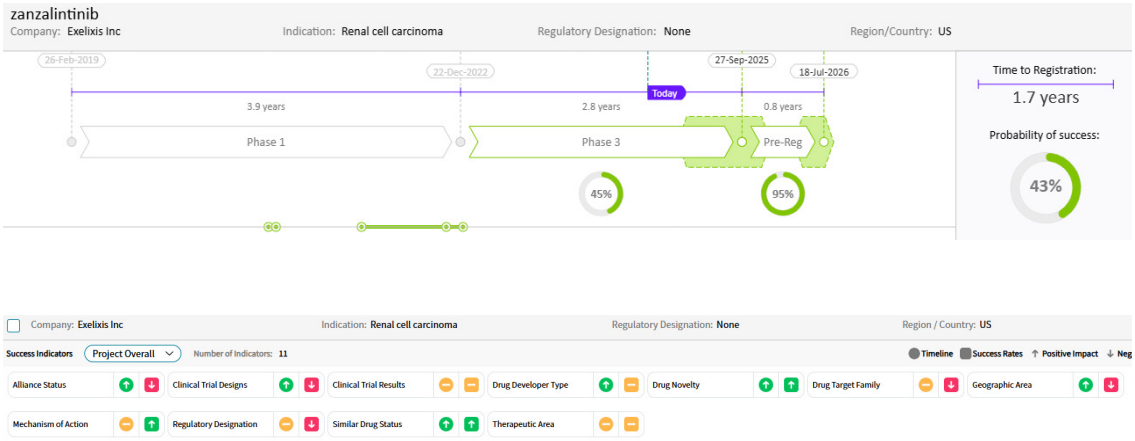
$2.60B

expected sales for CRC, RCC
and SCCHN in the G7 markets in 2030

"The early data with zanzalintinib are encouraging. There are ways you could make cabozantinib better in terms of potency that would be helpful to patients, and zanzalintinib tries to address those. Also, zanzalintinib's half-life is much shorter, so having zanzalintinib available would be an advantage."

Medical oncologist, United States

Cortellis data indicate there is a 43% probability of success for zanzalintinib in the United States.



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of October 31, 2024.

Addressing health priorities in Mainland China

We identified five drugs, including both global and domestically manufactured assets, that are likely to achieve the traditional $1bn blockbuster status by 2030 or have a significant impact for patients in Mainland China.

These drugs reflect the current disease landscape in Mainland China and aim to address the growing prevalence of non-communicable diseases such as obesity, diabetes and cancers.

The rates of overweight and obesity in Mainland China have tripled in the last 20 years.[9] In 2022, an estimated 34.8% of the Mainland Chinese population were overweight, and 14.1% were obese.[10] This equates to ~690m people, approximately double the size of the entire U.S. population, representing significant revenue-generating opportunities from medications for weight loss and its associated complications such as diabetes and CVD. In the same study, prediabetes, dyslipidemia and hypertension affected ~68%, 74% and 58% of the overweight/obese individuals.

The incidences of cancers are also increasing, resulting in high levels of morbidity and mortality. Lung cancers lead in incidence (75.13 cases per 100,000) and as the cause of cancer-related deaths, while breast cancer comes in second for women, at an incidence of 51.71 per 100,000.[11]

+34%

of the Mainland Chinese population were overweight, and 14.1% were obese. (2022)

Andewei

(安得卫; benmelstobart)

Company(s):
Chia Tai Tianqing Pharmaceutical (CTTQ Pharma)

Indication:
Endometrial cancer, ovarian cancer, SCLC, NSCLC, RCC, SCCHN

Initial U.S. approval:
N/A

Initial European approval:
N/A

Initial approval in Mainland China:
2024

2023 global sales ($M):
N/A

Expected 2030 sales in Mainland China ($M):
>700 (primarily from early-stage III locally advanced NSCLC)

Expected patent expiry in Mainland China:
N/A

Why it's a Drug to Watch:
Initially approved in Mainland China for the first-line treatment of extensive-stage SCLC, this drug has demonstrated significant improvements in PFS and OS. It is under NMPA review for metastatic endometrial cancer and expected to receive label expansions for NSCLC, SCCHN, ovarian cancer and RCC in the near future. Encouraging outcomes from recent late-phase clinical trials highlight its potential as a groundbreaking treatment for these difficult-to-treat cancers.

ENHERTU®

(fam-trastuzumab - deruxtecan-nxki)

Company(s):
AstraZeneca and Daiichi Sankyo

Indication:
Breast cancer, gastroesophageal cancer

Initial U.S. approval:
2019

Initial European approval:
2021

Initial approval in Mainland China:
2023

2023 global sales ($M):
2,700

Expected 2030 sales in Mainland China ($M):
>700

Expected patent expiry in Mainland China:
N/A

Why it's a Drug to Watch:
Launched in Mainland China to treat R/R HER2-positive breast cancer, ENHERTU showcased superior clinical safety and efficacy than HERCEPTIN® (trastuzumab; Genentech, a member of the Roche Group), the current standard of care, and was later approved for previously treated HER2-low expressing breast cancer in the same year. It is undergoing multiple late-phase clinical trials across various breast cancer subpopulations, including the underserved triple-negative setting. It is expected to be a game-changer in breast cancer treatment in Mainland China over the next decade.

Mazdutide

Company(s):
Innovent Biologics Inc and Eli Lilly and Co

Indication:
Obesity, type 2 diabetes

Initial U.S. approval:
N/A

Initial European approval:
N/A

Initial approval in Mainland China:
Expected in 2025

2023 global sales ($M):
N/A

Expected 2030 sales in Mainland China ($M):
>1,000 (primarily from type 2 diabetes)

Expected patent expiry in Mainland China:
N/A

Why it's a Drug to Watch:
Two different strengths are being developed for varying degrees of obesity. After 48 weeks, a phase 3 trial showed that 6 mg resulted in an average 14.3% weight reduction (superior to Zepbound® [Eli Lilly and Co] and Wegovy), and a phase 2 trial showed that 9 mg resulted in an average 18.6% weight reduction in obese individuals (BMI ≥30 kg/m²). In type 2 diabetes, 6 mg showed superiority over Trulicity® (Eli Lilly and Co) at managing HbA1c levels. Despite a later entry in these markets, substantial growth is expected over the next 10 years.

Wegovy® (semaglutide)

Company(s):
Novo Nordisk

Indication:
Obesity

Initial U.S. approval:
2021

Initial European approval:
2022

Initial approval in Mainland China:
2024

2023 global sales ($M):
4,500

Expected 2030 sales in Mainland China ($M):
>1,000

Expected patent expiry in Mainland China:
2026

Why it's a Drug to Watch:
A significant commercial opportunity exists with the increasing prevalence of overweight and obesity. Wegovy's timely market entry, compared with other weekly dosed competitors (e.g., tirzepatide from Eli Lilly and Co, CagriSema from Novo Nordisk and mazdutide from Innovent Biologics Inc), and its added cardiovascular benefits position it to gain significant traction. Biosimilar competition is expected as soon as Wegovy goes off-patent in Mainland China in 2026, with more than 10 MAH submissions for semaglutide biosimilars already completed. In addition, off-label use of competitors is expected to constrain market share for Wegovy.

Yidafang

(依达方®; ivonescimab)

Company(s):
Akeso Inc

Indication:
NSCLC

Initial U.S. approval:
N/A

Initial European approval:
N/A

Initial approval in Mainland China:
2024

2023 global sales ($M):
N/A

Expected 2030 sales in Mainland China ($M):
>700

Expected patent expiry in Mainland China:
N/A

Why it's a Drug to Watch:
Initially approved as second-line treatment for EGFR-mutated locally advanced or metastatic non-squamous NSCLC based on positive outcomes in the HARMONi-A clinical trial, it is also undergoing regulatory review for first-line treatment of PD-L1-positive non-squamous NSCLC. It has shown significantly improved PFS and OS compared with pembrolizumab monotherapy as well as greater benefit than KEYTRUDA in a head-to-head monotherapy phase 3 trial. As a first-in-class PD-1/VEGF bispecific antibody, Yidafang will likely revolutionize the first-line treatment landscape, providing patients with a superior, chemotherapy-free treatment alternative and generating $1bn+ in the next decade, driven by its adoption as first-line treatment. It has also been outlicensed to Summit Therapeutics, granting exclusive rights to develop and commercialize it in the U.S., Canada, Europe and Japan, with approvals expected in the U.S. and E.U. in 2026.

Regulatory agencies are prioritizing equitable health access and patient preferences

Life science companies face additional challenges in their path to market due to evolving regulatory and market expectations around incorporating the patient voice, improving patient outcomes and addressing health inequities in medical product development. To demonstrate the value of new products, pharma and biotech companies will increasingly need to furnish epidemiological data, real world data and evidence (RWD/RWE) and patient-reported outcomes (PROs), as well as advanced technologies such as AI/ML to make sense of the volume of incoming information.

Challenges faced by life science companies in the current drug development environment fall largely within the following categories:

Regulatory hurdles: The approval process is already costly and lengthy,[12] and concerns about the safety of innovative therapies could increase regulatory timelines and postmarketing requirements.[13]

Data and evidence generation: Some primary and key secondary endpoints, such as pain or fatigue, will need to be measured using PROs.[14] In addition, RWD will be necessary to demonstrate long-term benefits and safety for regulatory submission as well as evaluation by health technology assessment (HTA) agencies and payers. Data security and privacy will be paramount when handling these data sets.

Market access and reimbursement: Slow pricing and reimbursement decision-making delay the introduction of new products, and innovative pricing models demand additional data to demonstrate real-world performance and outcomes.

Integration into healthcare systems: Education about new therapies and treatment protocols is becoming essential for healthcare provider adoption, and introducing innovative therapies into the healthcare system infrastructure is challenged by the need for new types of patient information.

Complexities of personalized medicine: Clinical trial and marketing strategies will need to incorporate the ability to identify the correct patient population, tailor treatments to individual genetic profiles and build fit-for-purpose clinical outcome assessments (COAs).

Ethical and social considerations: Innovative therapies can encounter public skepticism and ethical concerns. Ensuring equitable access to expensive, cutting-edge therapies requires intentional planning.

With appropriate, early planning, life science companies can seize opportunities to overcome these challenges, such as:

Ensuring a representative population in clinical trials: By ensuring a representative study population, especially those most at risk for the disease of interest, we gain insights into how the disease will perform and its safety risks in real-life applications. Some pharma companies are taking the opportunity to retrospectively assess diversity in their trials to address historical disparity, improve future trial designs and address enrollment challenges.

Using synthetic twin comparator arms: Using AI, statistical analysis of a previous population (i.e., computer-generated datasets mimicking real-world patterns) can be compared with long-term RWE for an active substance.

Exploring alternative study designs: Study designs, such as basket studies, can supplement small patient groups, such as those for a rare disease, in clinical trials.

Designing fit-for-purpose PROs: PROs need to be validated for use in the concept of interest in the context of use. Because each regulator, HTA agency and payer could have different PRO requirements, it is important to identify PROs that will be used early in the planning stages, so consultations with agencies in the target geographies can begin before final selection and validation occur.

Collecting data from digital devices: Using wearables and other digital devices could facilitate the collection of objective data directly from patients, minimizing issues around missing and inconsistently collected data.

Whitepaper: Succeeding with Advanced Therapies in Europe

To stay ahead of the competition, multifaceted approaches are needed, including robust R&D strategies, strong regulatory and market access planning, effective stakeholder engagement and continuous innovation. Read the whitepaper, **Succeeding with Advanced Therapies in Europe**, for strategies to deliver the information expected by regulators and health agencies.

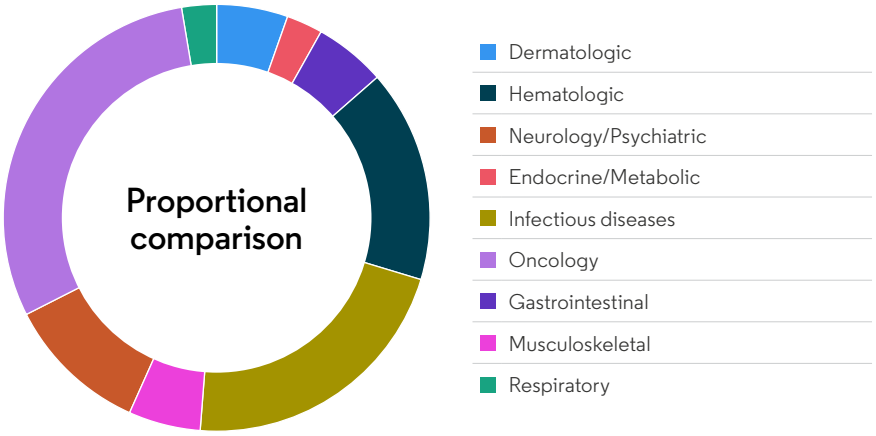
Innovation abounds in 2024 product approvals

In the regulatory space, 2024 was a year of firsts. Patients with Niemann-Pick disease type C (NPC), a very rare, inherited disease that causes damage to the nervous system over time, saw the first drugs approved in the U.S.: AQNEURSA™ (levacetylleucine; IntraBio Inc) and MIPLYFFA™ (arimoclomol; Zevra Therapeutics Inc). For patients with liver scarring due to fatty liver disease, REZDIFFRA™ (resmetirom; Madrigal Pharmaceuticals Inc) entered the U.S. market as their first treatment option, and ACENOBEL® (aceneuramic acid; Nobelpharma Co, Ltd) represents the first drug approved in Japan for *GNE* myopathy, a very rare disease characterized by progressive muscle weakness that typically worsens over time. After more than three decades of research in the area, AMTAGVI™ (lifileucel; Iovance Biotherapeutics Inc) made history as the first cancer treatment using tumor infiltrating lymphocytes (TILs) as well as the first cell therapy approved for a solid tumor, while VYLOY is the first and only anti-claudin 18.2 (CLDN18.2)-targeted therapy approved by any regulatory agency in the world. Many of the drugs listed in Table 1 (p. 96-98) also have the distinction of being first in class, delivered via a new administration route or the first to be approved for an indication in decades.

These trends demonstrate the industry's continuing innovation as well as regulatory agencies' commitment to filling treatment gaps for patient populations with high unmet needs.

These trends demonstrate the industry's continuing innovation as well as regulatory agencies' commitment to filling treatment gaps for patient populations with high unmet needs. In fact, recent FDA decisions against advisory committee recommendations have sparked controversary for granting full approval when the drug has not been completely proven. ELEVIDYS (delandistrogene - moxeparvovec-rokl; Sarepta Therapeutics) was approved by the FDA to treat Duchenne muscular dystrophy in those who are at least 4 years old and have a confirmed mutation in the dystrophin gene despite missing its primary endpoint in a confirmatory trial. Similarly, the FDA approved ADUHELM (aducanumab; Biogen; since withdrawn from the market) for AD against recommendations and without positive demonstration of primary endpoints. In both cases, being able to meet secondary and exploratory endpoints was used as arguments of the benefits of the drugs for patients with significant unmet needs; these benefits were considered to outweigh potential safety risks and high costs.

Figure 1. Indications addressed by novel drug approvals in 2024



Source: Cortellis Regulatory Intelligence

Table 1. Novel drugs with a first approval in 2024 in Australia, Canada, the EU, Japan, Mainland China, the United Kingdom or the United States

Company(s)	Indication(s)	Modality	Country(s)/region(s)
ACENOBEL® (aceneuramic acid)			
Nobelpharma Co, Ltd	*GNE* myopathy	Organic acid	Japan
AKANTIOR® (polihexanide)			
SIFI	Acanthamoeba keratitis	Anti-infective polymer	E.U.
ALYFTREK™ (yanzacaftor/tezacaftor/deutivacaftor)			
Vertex Pharmaceuticals Inc	Cystic fibrosis	Cystic fibrosis transmembrane	U.S.
AMTAGVI (lifileucel)			
Iovance Biotherapeutics Inc	Melanoma	Tumor-infiltrating lymphocyte (TIL) T-cell immunotherapy	U.S.
Anfangning (安方寧; garsorasib)			
Sino Biopharmaceutical Ltd	NSCLC	KRAS G12C inhibitor	Mainland China
ANKTIVA® (nogapendekin alfa inbakicept)			
ImmunityBio	Bladder cancer	Interleukin-15 (IL-15) receptor agonist (to be administered with Bacillus Calmette-Guérin [BCG])	U.S.
AQNEURSA (levacetylleucine)			
IntraBio Inc	NPC	Modified amino acid	U.S.
Attruby™ (acoramidis)			
BridgeBio Pharma Inc	ATTR-related cardiomyopathy (ATTR-CM)	Transthyretin stabilizer	U.S.
AWIQLI (insulin icodec)			
Novo Nordisk	Type 1 and type 2 diabetes (type 2 only in Mainland China)	Long-acting insulin (once-weekly injection)	Australia, Canada, E.U., Japan,Mainland China
BEQVEZ™/DURVEQTIX ® (fidanacogene elaparvovec-dzkt)			
Pfizer Inc	Hemophilia B	AAV-based gene therapy	Canada, E.U., U.S.
BIZENGRI® (zenocutuzumab-zbco)			
Merus N.V.	Pancreatic adenocarcinoma and NSCLC	HER2xHER3 bispecific antibody	U.S.
CAPVAXIVE™ (V-116)			
Merck	Pneumococcal disease and pneumococcal pneumonia	Pneumococcal 21-valent conjugate vaccine	U.S.
CELLDEMIC and INCELLIPAN			
CSL Seqirus	H5N1 infection	Inactivated vaccines	E.U.
COBENFY™ (xanomeline and trospium chloride)			
Bristol Myers Squibb	Schizophrenia	Dual M1/M4 muscarinic acetylcholine receptor agonist	U.S.

CRENESSITY™ (crinecerfont)			
Neurocrine Biosciences Inc	Congenital adrenal hyperplasia (CAH)	Corticotropin-releasing factor type 1 receptor (CRF1) antagonist	U.S.
DATROWAY® (datopotamab deruxtecan)			
Daiichi Sankyo	Breast cancer	TROP2-directed DXd ADC	Japan
DUVYZAT (givinostat)			
Italfarmaco SpA	Duchenne muscular dystrophy	Histone deacetylase (HDAC) inhibitor	U.S.
EMBLAVEO® (aztreonam-avibactam)			
AbbVie and Pfizer Inc	Gram-negative bacterial infections	β-lactam + β-lactamase inhibitor	E.U.
EXBLIFEP® (cefepime + enmetazobactam)			
Allecra Therapeutics	Urinary tract infections (UTIs)	β-lactam + β-lactamase inhibitor	E.U., U.S.
HYMPAVZI™ (marstacimab-hncq)			
Pfizer Inc	Hemophilia A or B	Anti-tissue factor pathway inhibitor (TFPI)	E.U., U.S.
IMDELLTRA™ (tarlatamab-dlle)			
Amgen Inc	Small cell lung cancer (SCLC)	Anti-DLL3 bispecific antibody	U.S.
IQIRVO® (elafibranor)			
Ipsen	Primary biliary cholangitis (PBC)	Peroxisome proliferator-activated receptor (PPAR) agonist	U.S.
Itovebi™ (inavolisib)			
Genentech, a member of the Roche Group	Breast cancer	PI3Kα-specific inhibitor	U.S.
JERAYGO™/TRYVIO™ (aprocitentan)			
Idorsia Ltd	Hypertension	Endothelin receptor antagonist (ERA)	E.U., U.S.
Junshida (君适达®; ongericimab)			
Shanghai Junshi Biosciences Co Ltd	Hypercholesterolemia and dyslipidemia	Anti-PCSK9 mAb	Mainland China
Kisunla™ (donanemab-azbt)			
Eli Lilly and Co	Alzheimer's disease (AD)	Anti-beta-amyloid monoclonal antibody (mAb)	Japan, U.S.
LAZCLUZE™ (lazertinib)			
Johnson & Johnson	NSCLC	Kinase inhibitor	U.S.
LEQSELVI™ (deuruxolitinib)			
Sun Pharmaceutical Industries Inc	Alopecia areata	Selective inhibitor of JAK1 and JAK2	U.S.
Lumisight (pegulicianine) and Lumicell Direct Visualization System (DVS): LumiSystem			
Lumicell Inc	Breast cancer	Fluorescent optical imaging agent	U.S.

MIPLYFFA (arimoclomol)			
Zevra Therapeutics Inc	NPC	Organic cationic transporter 2 (OCT2) inhibitor	U.S.
mRESVIA™ (mRNA-1345)			
Moderna Inc	Respiratory syncytial virus (RSV)	mRNA vaccine	U.S.
Niktimvo™ (axatilimab-csfr)			
Syndax Pharmaceuticals Inc and Incyte Corp	Chronic graft-vs-host disease (GVHD)	Anti-CSF-1R antibody	U.S.
OHTUVAYRE™ (ensifentrine)			
Verona Pharma plc	COPD	Dual inhibitor of phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4)	U.S.
OJEMDA™ (tovorafenib)			
Day One Biopharmaceuticals Inc	Glioma	Type II RAF kinase inhibitor	U.S.
OPSYNVI®/YUVANCI® (macitentan and tadalafil)			
Johnson & Johnson	PAH	Endothelin receptor antagonist (ERA) and phosphodiesterase 5 (PDE5) inhibitor	E.U., Japan, U.S.
Ordspono™ (odronextamab)			
Regeneron Pharmaceuticals Inc	Follicular lymphoma and diffuse large B-cell lymphoma	CD20xCD3 bispecific antibody	E.U.
ORLYNVAH™ (sulopenem etzadroxil and probenecid)			
Iterum Therapeutics plc	UTIs	Penem antibiotic	U.S.
PiaSky® (crovalimab-akkz)			
Genentech, a member of the Roche group	Paroxysmal nocturnal hemoglobinuria (PNH)	Anti-C5 mAb	E.U., Japan, Mainland China, U.S.
PIVYA (pivmecillinam)			
UTILITY therapeutics	UTIs	Antimicrobial	U.S.
RELFYDESS® (relabotulinumtoxinA)			
Galderma	Glabellar and lateral canthal lines	Neuromodulator	Australia, E.U.
Revuforj® (revumenib)			
Syndax Pharmaceuticals	Leukemia	Menin inhibitor	U.S.
REZDIFFRA (resmetirom)			
Madrigal Pharmaceuticals Inc	NASH	Thyroid hormone receptor-beta agonist	U.S.
RYTELO™ (imetelstat)			
Geron Corporation	Myelodysplastic syndromes (MDS)	Oligonucleotide telomerase inhibitor	U.S.

TASFYGO® (tasurgratinib succinate)			
Eisai Co, Ltd	Biliary tract cancer	FGFR-selective tyrosine kinase inhibitor	Japan
Theralugand® (Lutetium-177 chloride)			
Eckert & Ziegler Radiopharma GmbH	Cancers	Labeling of therapeutic radiopharmaceuticals	E.U.
TRYNGOLZA™ (olezarsen)			
Ionis Pharmaceuticals Inc	Familial chylomicronemia syndrome (FCS)	APOC-III-directed antisense oligonucleotide (ASO)	U.S.
UNLOXCYT™ (cosibelimab-ipdl)			
Checkpoint Therapeutics Inc	Cutaneous squamous cell cardinoma (cSCC)	PD-L1-blocking mAb	U.S.
VOYDEYA™ (danicopan)			
AstraZeneca	PNH	Complement factor D inhibitor	E.U., Japan, U.S.
VYLOY™ (zolbetuximab)			
Astellas Pharma Inc	Gastric cancer	Anti-claudin 18.2 (CLDN18.2) mAb	Japan, U.K., U.S.
WINREVAIR™ (sotatercept-csrk)			
Merck	PAH	Activin signaling inhibitor	E.U., U.S.
XOLREMDI™ (mavorixafor)			
X4 Pharmaceuticals Inc	WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis)	CXC chemokine receptor 4 (CXCR4) antagonist	U.S.
ZELSUVMI™ (berdazimer)			
Ligand Pharmaceuticals Inc	Molluscum contagiosum	Nitric oxide	U.S.
Ziihera® (zanidatamab-hrii)			
Jazz Pharmaceuticals plc	Biliary tract cancer	HER2-directed bispecific antibody	U.S.
ZUNVEYL® (benzgalantamine)			
Alpha Cognition Inc	AD	Acetylcholinesterase inhibitor (AChEI)	U.S.

Source: Cortellis Regulatory Intelligence; company websites

Radiopharmaceutical theranostics drive opportunities for personalized oncology medicines

Following the first FDA-approved radiopharmaceutical, iodine-131 (an iodine radioisotope), in 1951 for thyroid cancer, over half a century passed before observing real progress in the area. The next generation of radiopharmaceuticals attached the radioisotope via a linker molecule to a vector (eg, small molecule, peptide, antibody) that binds to the target to deliver radiation with a high degree of specificity and selectivity. The most recently approved radiopharmaceuticals adopt the concept of "theranostics," combining imaging (diagnostic) and therapeutic radiopharmaceuticals that share the same target-binding ligand for the ability to apply a "see it and treat it" approach.

The number of recent $1bn+ M&A and licensing partnerships indicates that the industry believes this area could truly disrupt cancer treatments, by providing greater specificity, biomarker-driven patient management and higher local concentration of radiation with less toxicity to the surrounding normal tissue. In fact, the global radiopharma market is expected to grow 10% over the next decade to $13.67bn by 2032.[15]

Bayer kicked off the modern radiotherapeutic era after its $2.5bn acquisition of Algeta ASA and, with it, XOFIGO®, approved globally for bone metastases in patients with prostate cancer (Table 2). The first approved theranostic followed: LUTATHERA®, approved to treat neuroendocrine tumors, became part of Novartis' radiopharma portfolio when the company acquired Advanced Accelerator Applications (AAA) for $3.9bn. Overall, Novartis is the biggest spender, shelling out approximately $6bn to acquire theranostic expertise and assets, including PLUVICTO®, the first targeted radioligand therapy containing a radioisotope to make it to market, from Endocyte Inc for $2.1bn. In the most recent M&A transaction, AstraZeneca acquired Fusion Pharmaceuticals Inc and its lead phase 2 program, FPI-2265, an actinium-225 based PSMA-targeting radiopharmaceutical for metastatic castration-resistant prostate cancer (mCRPC), for $2.4bn (after Fusion Pharmaceuticals acquired FPI-2265 from RadioMedix Inc for a mere $60m in 2023).[16]

+10%

expected growth of the radiopharma market over the next decade.

Table 2. Radiotherapeutic, including theranostic, approvals globally

Company(s)	Therapeutic area	Year of first approval	Countries/regions
Xofigo® (radium-223 dichloride)			
Bayer	Oncology	2013	Australia, Canada, E.U., Japan, Mainland China, U.K., U.S.
LUTATHERA® (lutetium Lu 177 dotatate)			
Novartis	Oncology	2017	Australia, Canada, E.U., Japan, U.S.
AZEDRA® (iobenguane I 131)			
Progenics Pharmaceuticals Inc (acquired by Lantheus Holdings Inc)	Oncology	2018	U.S. (withdrawn)
PLUVICTO® (lutetium Lu 177 vipivotide tetraxetan)			
Novartis	Oncology	2022	Australia, Canada, E.U., U.K., U.S.

Source: Cortellis Regulatory Intelligence; company websites

As long-standing radiopharmaceutical leaders, Bayer and Novartis have demonstrated the marketability of radiopharmaceuticals, with PLUVICTO nearing blockbuster status ($655m in sales in H1 2024),[17] and paved the way for further research and regulatory approvals in the field. Hot spots of development activity have popped up in Germany, France and Australia. Isotope Technologies Munich SE (ITM) in Germany, Orano Med in France, and Telix Pharmaceuticals and Clarity Pharmaceuticals in Australia represent some of the most active companies in terms of financing, deals and clinical trials activity.

Despite the promising activity in this space, some key challenges facing pharma and biotech moving forward include:

- The ability for treatment facilities to manage radioactive waste material and monitor patients, especially as treatments become more widely available, potentially extending beyond specialized facilities
- Reliable supply of medical isotopes to meet demand, requiring investment in infrastructure and collaborative approaches to accessing nuclear stockpiles
- Just-in-time delivery of radioactive materials with potentially short half-lives to patients who must isolate during treatment, while maintaining quality control and regulatory compliance
- Navigating regulatory challenges across agencies including health regulators and nuclear regulators such as the Nuclear Regulatory Council (NRC) in the U.S., with requirements differing by region, country and even state

Radiopharmaceuticals: The next big disrupter?

For more information on the radiopharmaceutical landscape, visit the eight-part BioWorld series **Radiopharmaceuticals: The next big disrupter?**

The meteoric rise in obesity drugs spurs activity across the life sciences landscape

Since 1990, the prevalence of obesity has more than doubled for adults and quadrupled for adolescents, resulting in 43% of the world's adult population and 20% of children and adolescents (5-19 years) living with overweight or obesity.[18]

In addition to the added morbidity and mortality due to weight-related conditions such as cardiovascular disease, diabetes, cancers and chronic respiratory disorders, the global economic costs of overweight and obesity are estimated to be more than $4 trillion by 2035.[19] Although prescription weight loss treatments, such as XENICAL® (orlistat; CHEPLAPHARM), ALLI (orlistat; Haleon), QSYMIA® (phentermine/topiramate; VIVUS LLC) and CONTRAVE® (naltrexone/bupropion; Currax Pharmaceuticals LLC), have been available since the late 1990s and can produce clinically meaningful weight loss (5%), their side effects are often limiting factors.

The recent improved understanding of weight regulation mechanisms and the role of gut-brain axis on appetite has led to the development of safe and effective entero-pancreatic hormone-based treatments for obesity such as GLP-1 RAs. The market was redefined by the approvals of once-weekly injections of semaglutide (Wegovy; GLP-1) and tirzepatide (Zepbound, GLP-1/GIP dual RA), which are safe, more convenient than previous once-daily GLP-1 injections (liraglutide [Saxenda®]) and result in greater weight loss (i.e., ~15%-22% weight loss vs ~6%).[20,21]

The market for such drugs as well as next-generation medicines is anticipated to grow massively in the coming years, with estimates placing the GLP-1 obesity market alone at $100bn+ by 2030.[21] However, revenue potential could be affected by several factors, including potential direct negotiation under the U.S. Inflation Reduction Act (IRA),[22] private and public payer coverage (at an annual cost of nearly $18,000),[23-25] global supply constraints,[26] a growing gray market of counterfeits,[27,28] direct-to-patient prescription services,[28] increasing competition from emerging assets, expiring patents as early as 2026 and expansion of indications to include cardiovascular disease,[29] obstructive sleep apnea,[30] NASH/MASH, some obesity-related cancers[31] and dementia, including Alzheimer's disease.[32,33] The ripple effects of the latest generation of GLP-1s into other areas of healthcare also remain uncertain. They have the potential to impact medtech, affecting uptake of bariatric surgery, aesthetic procedures and orthopedic surgery,[34] as well as spur significant investment into manufacturing.[35]

43% of the world's adult population and 20% of children and adolescents are living with overweight or obesity.

Table 3. Eli Lilly and Co and Novo Nordisk, the current leaders in this space, reported increased global sales for their weight loss drugs in H1 2024 compared with H1 2023*

Drug	H1 2024 global sales ($m)	Change from H1 2023
Eli Lilly and Co		
Zepbound	1,240 (U.S. only)	N/A (launched in the U.S. in November 2023)
Novo Nordisk		
Saxenda	579.38	+36%
Wegovy	3,122.62	+74%

*Sales of GLP-1s approved to treat diabetes (e.g., Ozempic, Mounjaro) prescribed off-label for obesity not included
Source: Company financial statements[36,37]

Pharma companies wanting to enter the space are looking for candidates to in-license or partnerships for drug discovery. Novo Nordisk continues to invest heavily, currently drawing on its strategic partnership with Flagship Pioneering and companies it founded. According to BioWorld data, the collaboration with Omega Therapeutics Inc, signed in January 2024, is worth up to $532m and uses Omega Therapeutics Inc's platform to develop an epigenomic controller for obesity, which could enhance metabolic activity for weight loss. The second of the obesity-related collaborations sees Novo Nordisk partnering with Metaphore to use the latter's MIMIC™ platform to discover and develop two multitarget GLP-1-based therapeutics for obesity management, a partnership that could be worth $600m (May 2024).

In addition, Rhythm Pharmaceuticals entered into a licensing agreement potentially worth $305m with LG Chem Ltd to develop and commercialize LB-54640, a phase 2 oral small molecule melanocortin-4 receptor (MC4R) agonist, for obesity worldwide. Another multimillion-dollar agreement in 2024 ($211.85m) was that between Metsera Inc and D&D Pharmatech Inc, who extended their previous agreement to include an oral GLP-1/GIP dual RA (DD-14) and an oral amylin agonist (DD-07).

While Eli Lilly and Co has initiated a head-to-head study of Zepbound vs Wegovy, GLP-1 and GLP-1/GIP competitors in clinical trials from other companies include Amgen Inc's GIP/GLP-1 agonist AMG-133, Structure Therapeutics Inc's oral GLP-1 GSBR-1290, Gan & Lee Pharmaceuticals' GLP-1 GZR-18 and Viking Therapeutics Inc's GLP-1/GIP VK-2735.

However, other targets, individually and in combination with GLP-1s, are also being explored in clinical trials. Novo Nordisk just released phase 1 data for oral amycretin, a co-agonist of GLP-1 and amylin (which suppresses gastric emptying and glucagon secretion) receptors, showing a 13.1% reduction in body weight at 12 weeks.[38] GLP-1/glucagon dual RAs are in early phase trials by Innovent Biologics (mazdutide) and Altimmune Inc (pemvidutide). Laekna Inc recently announced its phase 1 trial for its anti-ActRIIA mAb; ActRIIA is a receptor that plays an important role in muscle regeneration and lipid metabolism. Bimagrumab, an anti-activin mAb, is also being evaluated with GLP-1s for its ability to preserve muscle mass, a concern with the currently approved GLP-1s.

Gene editing promises life-changing therapies for people with rare diseases

The landmark approval of CASGEVY (Vertex Pharmaceuticals Inc and CRISPR Therapeutics) at the tail end of 2023 made it the first CRISPR-Cas9 gene-edited cell therapy approved globally. It is currently approved to treat sickle cell disease (SCD) and transfusion-dependent beta-thalassemia (TDT) in the U.S., U.K. and E.U. and is under regulatory review in Canada.[39] As of November 2024, Vertex Pharmaceuticals Inc had activated more than 45 authorized treatment centers (ATCs) globally, and ~35,000 patients were identified as being eligible for CASGEVY treatment in the U.S. and E.U.[39]

Although Vertex Pharmaceuticals Inc has secured reimbursed access in France[39] and the U.K.[40] coverage of the U.S. $2.2m per treatment remains under discussion in other markets. In the U.S., however, the Centers for Medicare & Medicaid Services (CMS) Cell and Gene Therapy (CGT) Access Model could facilitate access to cell and gene therapies, beginning with those for SCD, for individuals on Medicaid, who tend to be of great financial need.[41] In addition to the high cost, competition from other gene therapies for these indications, such as LYFGENIA™ from bluebird bio Inc, could restrict market success for CASGEVY. bluebird bio Inc's existing network of SDC ATCs for ZYNTEGLO™ could benefit LYFGENIA's launch, although the lack of reimbursement for the high costs of ZYNTEGLO and SKYSONA™ in some E.U. countries (and their subsequent withdrawals from those markets) could influence the company's decision around where it will seek regulatory approval and limit competition in non-U.S. markets.

Additional challenges involve the myeloablative conditioning involving high-dose chemotherapy before gene therapy, which renders some patients ineligible for treatment and can result in undesirable side effects such as infertility. Against the background of heated discussions around Medicaid coverage of company-sponsored fertility preservation programs due to antitrust concerns,[42] discovering gentler conditioning approaches is increasing in priority for Vertex Pharmaceuticals Inc[39] and other gene editing companies. To that end, in July 2024, Vertex Pharmaceuticals Inc entered into a $945m agreement with Orum Therapeutics to use Orum Therapeutics' Dual-Precision Targeted Protein Degradation (TPD²®) technology to discover novel targeted conditioning agents.[43] With alternative conditioning regimens, Vertex Pharmaceuticals Inc estimates that the eligible patient population could broaden to more than 150,000 people in the U.S. and Europe.

Other deals announced in 2024 include that between Regeneron Pharmaceuticals Inc and Mammoth Biosciences Inc for a projected $470m to research, develop and commercialize in vivo CRISPR-based gene editing therapies for multiple tissues and cell types. In addition, YolTech Therapeutics granted Salubris Pharmaceuticals Co Ltd an exclusive licensing agreement for a projected $145m to develop and commercialize its proprietary YOLT-101 in Mainland China. A PCSK9-targeting base editing therapeutic, YOLT-101 is designed to be a single-course treatment for three cholesterol-related conditions: heterozygous familial hypercholesterolemia, established atherosclerotic cardiovascular disease and uncontrolled low-density lipoprotein cholesterol (LDL-c).

Numerous gene editing therapies are also currently in clinical development, ranging from early phase 1 to phase 3 as well as long-term (e.g., 10 years) post-infusion follow-up of participants in phase 1 and 1/2 trials.

Table 4: Clinical development status of gene editing therapies in clinical trials started in 2019 to August 20, 2024

Asset	Organization(s)	Indication(s)	Technology	Clinical development phase
Allogeneic CD19-STAR T cell	Chinese PLA General Hospital	B-cell non-Hodgkin' s lymphoma	CRISPR-Cas9	1/2
ATHENA CAR-T	Chinese PLA General Hospital	B-cell non-Hodgkin' s lymphoma	CRISPR-Cas9	1/2
Autologous hematopoietic stem and progenitor cells (HSPCs)	National Institute of Allergy and Infectious Diseases (NIAID)	X-linked chronic granulomatous disease (CGD)	Base editing	I1/2
BD111	BDgene	Refractory herpetic viral keratitis	CRISPR-Cas9	Investigator-initiated trial (IIT)
BD113vVLP	BDgene	Primary open-angle glaucoma (POAG)	CRISPR-Cas9	IIT
BEAM-101	Beam Therapeutics Inc	SCD	Base editing	1/2
BRL-101	BRL Medicine Inc	TDT	CRISPR-Cas9	1/2
BRL-103	BRL Medicine Inc	β-thalassemia	CRISPR-Cas9	1/2
CD33KO-HSPC	University of Pennsylvania	Acute myeloid leukemia (AML)	CRISPR-Cas9	1
CD34+ HSC	German Cancer Research Center	AML	CRISPR-Cas9	1
CISH-inactivated tumor-infiltrating lymphocytes (TIL)	Intima Bioscience Inc	Colon cancer, gall bladder cancer, gastrointestinal cancer, lung cancers, pancreatic cancer	CRISPR-Cas9	1/2
CRISPR_SCD001	University of California, San Francisco	SCD	CRISPR-Cas9	1/2
CS-101	Children's Hospital of Fudan University, CorrectSequence Therapeutics Co Ltd, First Affiliated Hospital of Guangxi Medical University	β-thalassemia	Base editing	1
CASGEVY	Vertex Pharmaceuticals Inc, CRISPR Therapeutics	SCD, TDT	CRISPR-Cas9	3
CTX110	CRISPR Therapeutics	B-cell malignancies	CRISPR-Cas9	1/2
CTX112	CRISPR Therapeutics	B-cell malignancies	CRISPR-Cas9	1/2
CTX120	CRISPR Therapeutics	Multiple myeloma	CRISPR-Cas9	1

Company(s)	Indication(s)	Modality	Country(s)/region(s)	Clinical development phase
CTX130	CRISPR Therapeutics	Renal cell carcinoma, T-cell lymphoma	CRISPR-Cas9	1
CTX131	CRISPR Therapeutics	Hematologic malignancies, solid tumors	CRISPR-Cas9	1/2
EBT-101	Excision BioTherapeutics Inc	HIV-1	CRISPR-Cas9	1
ECUR-506	iECURE Inc	Neonatal onset OTC deficiency	ARCUS® meganuclease	1/2
EDIT-101	Editas Medicine Inc	Lebers congenital amaurosis	CRISPR-Cas9	1/2
EDIT-301	Editas Medicine Inc	SCD, TDT	SLEEK™ (SeLection by Essential-gene Exon Knock-in) gene editing	1/2
GEN6050X	Peking Union Medical College Hospital	Duchenne muscular dystrophy (DMD)	Base editing	1
GPH101	Kamau Therapeutics Inc	SCD	CRISPR-Cas9	1/2
HG202	HuidaGene Therapeutics	Neovascular age-related macular degeneration (nAMD)	CRISPR-Cas13	1
NTLA-2001	Intellia Therapeutics Inc	Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) and ATTR-related cardiomyopathy (ATTR-CM)	CRISPR-Cas9	3
NTLA-2002	Intellia Therapeutics Inc	Hereditary angioedema	CRISPR-Cas9	1/2
SB-318	Sangamo Therapeutics Inc	Mucopolysaccharidosis type II (MPS II)	Zinc-finger nuclease (ZFN)	Long-term follow-up of phase 1/2 participants
SB-913	Sangamo Therapeutics Inc	MPS II	ZFN	Long-term follow-up of phase 1/2 participants
SB-FIX	Sangamo Therapeutics Inc	Hemophilia B	ZFN	Long-term follow-up of phase 1/2 participants
VERVE-101	Verve Therapeutics	Heterozygous familial hypercholesterolemia (HeFH), atherosclerotic cardiovascular disease (ASCVD) and uncontrolled hypercholesterolemia	Base editing	Long-term follow-up of phase 1 participants
VERVE-102	Verve Therapeutics	HeFH, premature coronary artery disease (CAD)	Base editing	1
ZVS203e	Peking University Third Hospital	Retinitis pigmentosa	CRISPR-Cas9	1

Source: Cortellis Clinical Trials Intelligence

Key takeaways for industry executives

01 AI/ML are having an impact across the innovation cycle.

AI and machine learning (ML) continue to impact drug discovery, development and commercialization. While the use of AI to identify promising molecules or repurpose existing drugs has generated much of the buzz so far, ML has potential uses throughout the innovation cycle. One particularly promising emerging opportunity involves applying ML to large sets of anonymized patient data to aid in the diagnosis of rare diseases. Another involves using ML and real-world data (RWD) to maximize the efficiency of clinical trials.

02 Work with regulators to seize the opportunities presented by big data.

Leveraging these advanced technologies effectively requires close collaboration between researchers, healthcare providers and technology experts, along with an understanding of the regulatory challenges associated with technology-driven systems. This collaboration is fostering opportunities to streamline innovation through the use of patient-reported outcomes in conjunction with RWD and ML.

03 Tackle drug shortages and access bottlenecks with expertise and emerging technologies.

While drug shortages due to supply chain bottlenecks and other manufacturing issues have eased since the height of the COVID-19 pandemic, they continue to bedevil categories like obesity and weight loss, where meeting the demand for revolutionary GLP-1 drugs has proven difficult, and they shadow emerging technologies like radiopharmaceuticals with its complicated supply chain. Ensuring that patients realize the benefits of these medicines requires improving manufacturing processes to ensure scale and cost effectiveness (another area where AI and ML can help). It also requires making the economic case for expensive new treatments so that patients can access them. Engineers and behavioral economists will hold essential roles in the emerging innovation paradigm.

Abbreviations and acronyms

AAA: Advanced Accelerator Applications

AAV: adeno-associated virus

ABR: annualized bleeding rate

AChEI: acetylcholinesterase inhibitor

ACIP: Advisory Committee on Immunization Practices

AD: Alzheimer's disease

ADA: anti-drug antibody

AE: adverse event

AI: artificial intelligence

ALT: alanine aminotransferase

AML: acute myeloid leukemia

ASCVD: atherosclerotic cardiovascular disease

ASO: antisense oligonucleotide

AST: aspartate aminotransferase

AT-DR: antithrombin-based dosing regimen

ATC: authorized treatment center

ATTRv-PN: transthyretin amyloidosis with polyneuropathy

BBB: blood-brain barrier

BCG: Bacillus Calmette-Guérin

BiTE: bispecific T-cell engager

BLA: Biologics License Application

CAD: coronary artery disease

CAGR: compound annual growth rate

CBR: clinical benefit rate

CDC: Centers for Disease Control and Prevention

CERAN: complete estrogen receptor antagonist

CFTR: cystic fibrosis transmembrane conductance regulator

CGD: chronic granulomatous disease

CGI-S: Clinical Global Impression-Severity

CGM: continuous glucose monitoring

CGT: Cell and Gene Therapy

CIAS: cognitive impairment associated with schizophrenia

CLDN18.2: claudin 18.2

CMS: Centers for Medicare & Medicaid Services

COA: clinical outcome assessment

COPD: chronic obstructive pulmonary disease

CR: complete response

CRC: colorectal cancer

CRL: complete response letter

CRS: cytokine release syndrome

CVD: cardiovascular disease

DCR: disease control rate

DLL3: Delta-like ligand-3

DMD: Duchenne muscular dystrophy

DOR: duration of response

EASI: Eczema Area and Severity Index

EASI-75: 75% improvement in the Eczema Area and Severity Index

EMA: European Medicines Agency

ER: estrogen receptor

ERA: endothelin receptor antagonist

ES-SCLC: extensive-stage small cell lung cancer

FCS: familial chylomicronemia syndrome

FDA: Food and Drug Administration

FDC: fixed dose combination

FGFR: fibroblast growth factor receptor

GAIN: Generating Antibiotic Incentives Now

GIP: glucose-dependent insulinotropic polypeptide

GLP: glucagon-like peptide

GVHD: graft-vs-host disease

HDAC: histone deacetylase

HeFH: heterozygous familial hypercholesterolemia

HER2: human epidermal growth factor receptor 2

hMPV: human metapneumovirus

HR: hormone receptor

HSPC: hematopoietic stem and progenitor cell

HTA: health technology assessment

ICANS: immune effector cell-associated neurotoxicity syndrome

IGA: Investigator's Global Assessment

IIT: investigator-initiated trial

IL: interleukin

ILAP: Innovative Licensing Access Pathway

IMD: invasive meningococcal disease

IRA: Inflation Reduction Act

ITM: Isotope Technologies Munich SE

ITT: intention-to-treat

IV: intravenous

JAK: Janus kinase

KOL: key opinion leader

LDL-c: low-density lipoprotein cholesterol

LNP: lipid nanoparticle

LRTD: lower respiratory tract disease

LS-SCLC: limited-stage small cell lung cancer

M&A: merger and acquisition

MAA: marketing authorisation application

mAb: monoclonal antibody

MAH: Marketing Authorization Holder

MASH: metabolic dysfunction-associated steatohepatitis

MC4R: melanocortin-4 receptor

mCRC: metastatic colorectal cancer

MDS: myelodysplastic syndrome

MenB: meningococcal group B

MHRA: Medicines and Healthcare products Regulatory Agency

ML: machine learning

MMSE: Mini-Mental State Examination

MOA: mechanism of action

MPS: mucopolysaccharidosis

MSI: microsatellite instable

MSS: microsatellite stable

nAMD: neovascular age-related macular degeneration

NASH: non-alcoholic steatohepatitis

nccRCC: non-clear-cell renal cell carcinoma

NDA: new drug application

NIAID: National Institute of Allergy and Infectious Diseases

NLM: non-liver metastases

NMPA: National Medical Products Administration

NPC: Niemann-Pick disease type C

NPI-C: H+D: Neuropsychiatric Inventory-Clinician: Hallucinations and Delusions

NRC: Nuclear Regulatory Council

OCT2: organic cationic transporter 2

OMV: outer membrane vesicle

ORR: objective response rate

OS: overall survival

OTC: over-the-counter

PAH: pulmonary arterial hypertension

PANSS: Positive and Negative Syndrome Scale

PBC: primary biliary cholangitis

PDE: phosphodiesterase

PFS: progression-free survival

PIV-3: parainfluenza virus type 3

PMDA: Pharmaceuticals and Medical Devices Agency

PNH: paroxysmal nocturnal hemoglobinuria

PNRS: Pruritus Numeric Rating Scale

POAG: primary open-angle glaucoma

PR: partial response

PRO: patient-reported outcome

PROTAC: PROteolysis Targeting Chimera

PSMA: prostate-specific membrane antigen

R&D: research and development

RA: receptor agonist

RCC: renal cell carcinoma

RCT: randomized controlled trial

RSV: respiratory syncytial virus

RWD: real-world data

RWE: real-world evidence

SAE: serious adverse event

SC: subcutaneous

SCCHN: squamous cell carcinoma of head and neck

SCD: sickle cell disease

SCLC: small cell lung cancer

SERD: selective estrogen receptor degrader

SERM: selective estrogen receptor modulator

siRNA: small interfering RNA

sNDA: supplemental new drug application

T1DM: type 1 diabetes mellitus

T2DM: type 2 diabetes mellitus

TCS: topical corticosteroid

TDT: transfusion-dependent beta-thalassemia

TEAE: treatment-emergent adverse event

TFPI: tissue factor pathway inhibitor

TIL: tumor-infiltrating lymphocyte

TKI: tyrosine kinase inhibitor

TZD: thiazolidinedione

UTI: urinary tract infection

XOI: xanthine oxidase inhibitor

WCLC: World Conference on Lung Cancer

WHIM: warts, hypogammaglobulinemia, infections and myelokathexis

WHO: World Health Organization

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