Drugs to Watch 2024

New frontiers in medicine

Clarivate™

New technologies fueling medical breakthroughs

The year 2024 is shaping up to be the best of times and the worst of times for the pharma industry. New modalities, underpinned by scientific breakthroughs in the past decade, are achieving clinical successes and providing treatments for patients with previously unmet medical needs. Meanwhile, externalities such as government initiatives to contain healthcare costs, the sustained high cost of capital and global geopolitical disputes are putting a brake on investor appetites for the sector.

In this 2024 edition of Drugs to Watch, we highlight some of the trends that will be consequential to the discovery, development and delivery of new medicines, and spotlight drugs and drug candidates that will achieve important milestones in the coming years as they establish themselves as either blockbuster or breakthrough medicines.

Last year, we flagged 15 molecules as Drugs to Watch. Of these, 12 have been approved and have either been launched or are on the launchpad. Arguably, the most successful to date from last year's list is Bristol Myers Squibb's SOTYKTU™, a tyrosine kinase 2 inhibitor to treat moderate-to-severe plaque psoriasis. Company reports indicate a strong early start, with sales of $107M in the first nine months of 2023. Bristol Myers Squibb believes it already has approximately 10% of patients in plans and is looking to broaden formulary coverage in 2024.

Some innovative meds still struggle

One area that has attracted a lot of media attention in recent years has been the emergence of potentially disease-modifying drugs to treat Alzheimer's disease. In the 2023 edition of Drugs to Watch, we identified two such drugs, though they have taken different paths. Eisai's beta amyloid-targeting drug LEQEMBI® was first approved in January 2023 via accelerated pathway and was then awarded full approval in June 2023. Eisai has reported patient uptake in line with their expectations, and this is forecast to rise in 2024. Less successful was Lilly's donanemab, which received a Complete Response Letter (CRL) from the Food and Drug Administration (FDA) on its submission for accelerated approval. Although the company had recruited the correct number of patients, the speed of amyloid plaque reduction meant that many patients stopped taking the drug just after six months. Lilly has submitted a traditional approval application and is expecting action from the FDA in early 2024.

In the 2023 list, we also saw examples of next-generation medicines such as bispecific antibodies and gene therapies. The bispecific antibody we spotlighted was Johnson and Johnson's TECVAYLI®, a first-in-class treatment for patients with multiple myeloma. Johnson and Johnson has said it has been encouraged by the early success of the product and expects to begin disclosing actual sales in the first quarter of 2024. On the other hand, BioMarin's ROCTAVIAN™ gene therapy for the treatment of hemophilia A has had a lackluster start, achieving sales of just $0.8M in the third quarter of 2023. Nevertheless, the company says it has made progress on key reimbursement negotiations and is expecting that price negotiations with the German and Italian authorities will have been resolved by the end of 2023. Moreover, in the United States, BioMarin has been building a reimbursement network, setting the stage for meaningful uptake in 2024.

New platforms for medical innovation are coming online

These examples show just how challenging drug launches can be. Looking back at some of our 2022 picks, however, we can see how quickly sales can ramp up to blockbuster status. The standout performer of our Drugs to Watch 2022 cohort is Lilly's Mounjaro® for treating type 2 diabetes. In 2022, the drug achieved sales of $482.5M, but in the first nine months of 2023, that had jumped to $2.96B and seems on course to soar even further. Other big winners were Roche's eye drug VABYSMO™, which achieved sales of CHF1.6B in the first nine months of 2023 and, with new indications added to the label, is on an upward trend. Similarly, TEZSPIRE®, a treatment for severe asthma jointly developed by Amgen and AstraZeneca, achieved sales of $170M in 2022 and ramped up sales of $390M in the first nine months of 2023. Another of the 2022 cohort worth highlighting is Alnylam® Pharmaceuticals' RNAi drug AMVUTTRA®, which is approved for the treatment of polyneuropathy of hereditary transthyretin amyloidosis (hATTR) in adults. RNAi is another of the next-generation platforms that will shape the treatment of patients in the coming years. Initially held up by manufacturing issues at the contract manufacturing organization hired to make the drug, AMVUTTRA achieved sales of $382.6M in the first nine months of 2023 – $289M coming from the U.S. market alone. However, in response to the Inflation Reduction Act (IRA), Alnylam said it would not pursue a phase 3 trial of the drug to treat Stargadt's disease because, if it were approved, Alnylam would lose single orphan exemption from Medicare price negotiation for AMVUTTRA.

New technology platforms that are likely to achieve significant proof of concept in 2024 include CRISPR-Cas9 gene-editing as well as artificial intelligence (AI)/machine learning (ML) tool applications in drug discovery, clinical development and commercial launch. In the long run, the latter technologies hold enormous potential to help drugmakers cut costs and shorten innovation cycles, enabling the delivery of more innovative drugs to patients faster going forward.

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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 $1 billion annual sales milestone).

To identify this year's **Drugs to Watch** 2024 list, we drew from expertise from over 160 Clarivate analysts covering hundreds of diseases, drugs and markets and eleven 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 2023** were selected for analysis, including drugs launched for a new indication that could be particularly impactful on the industry; drugs launched prior to 2023 were excluded.
- The dataset was then filtered for drugs that had total **forecast sales of $1 billion or more** in 2029.
- 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 13 Drugs to Watch in 2024:

Aflibercept (high dose) ▼ |

Budesonide ▼ |

Datopotamab deruxtecan ▼ |

Efanesoctocog alfa ▼ |

Ensifentrine ▼ |

Exagamglogene autotemcel and lovotibeglogene autotemcel ▼ |

Mirikizumab ▼ |

Niraparib + abiraterone ▼ |

RSVpreF and RSVpreF3 ▼ |

Talquetamab ▼ |

Zolbetuximab ▼ |

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 impact of AI and gene editing on drug discovery and development, how the Inflation Reduction Act is influencing research strategies, the biosimilar landscape and how real world data (RWD) is informing clinical trials. Please note that Clarivate analysts generated the data shown in this report on January 3, 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.

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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. behavior so clients can optimize their market access strategy and determine how to best position their brand to specific stakeholders.

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Drugs to Watch 2024

01. Aflibercept

High dose; EYLEA® HD

For individuals with wet age-related macular degeneration (AMD), diabetic macular edema (DME) or diabetic retinopathy (DR) whose treatment choices include invasive, burdensome administration that limits treatment uptake, high-dose aflibercept offers less-frequent administration while achieving similar efficacy and safety as the current standard of care (aflibercept 2 mg/EYLEA dosed every 8 weeks or LUCENTIS® from Genentech dosed every 4 weeks)

More convenient for patients and clinicians alike, the 12- and 16-week dosing helps meet a significant unmet need for these patient populations.

Why is it a drug to watch?

The approval of high-dose aflibercept (8 mg; EYLEA HD) by the U.S. Food and Drug Administration (FDA) was based on positive results from the pivotal phase 3 PULSAR (wet AMD) and PHOTON (DME) studies. Both studies met their primary endpoints with EYLEA HD (administered every 12 or 16 weeks after three initial monthly doses), demonstrating non-inferiority to EYLEA (dosed every 8 weeks following the loading phase) in visual acuity gains from baseline at week 48 while providing a similar safety profile.

The real benefit is expected from the need for fewer injections to reach equivalent visual acuity gains and anatomical features as EYLEA without compromising safety, therefore reducing the treatment burden for patients and healthcare providers. Compelling trial results through two years reinforce the ability of EYLEA HD to prolong treatment intervals of at least 12 weeks to a meaningful proportion of patients:

- **PULSAR for wet AMD (96 weeks):**
  - 88% were on the ≥12-week dosing interval
  - 71% were on the ≥16-week dosing interval
  - 47% met the extension criteria for a ≥20-week dosing interval
  - 28% met the extension criteria for a 24-week dosing interval
- **PHOTON for DME (96 weeks):**
  - 89% were on the ≥12-week dosing interval
  - 83% were on the ≥16-week dosing interval
  - 43% met the extension criteria for a ≥20-week dosing interval
  - 27% met the extension criteria for a 24-week dosing interval

New frontiers in medicine

Reducing the treatment burden

Aflibercept at a glance

Producers

Bayer and Regeneron Pharmaceuticals Inc

Type

VEGF inhibitor

Usage

Intravitreal (IVT) administration to treat wet AMD, DME and DR

Also being studied to treat macular edema secondary to retinal vein occlusion (RVO) as well as macular telangiectasia type 1

Impact

2.55M
people in the G7 markets expected to be drug-treated for wet AMD by 2032

2.0M
people with DME in the G7 markets expected to be drug-treated by 2032

~130K
people with severe non-proliferative DR and proliferative DR in the G7 countries expected to receive drug treatment by 2032

Review and approval status

February 2023
– sNDA/sBLA accepted: EMA

March 2023
– NDA accepted: Japan PMDA

August 2023
– sNDA/sBLA accepted: Mainland China NMPA

For patients with wet AMD,DME or DR
– Approved U.S. FDA

Actual and expected launch
– 2023: United States
– 2024: Europe, Japan
– 2025: Mainland China

Patents estimated to expire
– Beginning in 2039

How will high-dose aflibercept impact the market for wet AMD, DME and DR?

- The prevalences of wet AMD, DME and diabetic retinopathy are expected to continue increasing with the aging population and greater diabetes burden in the population.
- EYLEA HD's uptake is expected to be challenged by other agents currently approved or in active late-phase development:
  - Vabysmo™ (Roche) for wet AMD and DME
  - Aflibercept biosimilars for wet AMD, DME and DR
  - OCS-01 (Oculis) for DME
  - To a lesser extent:

    LYTENAVA™ (ONS-5010; Outlook Therapeutics) for wet AMD

    ABBV-RGX-314 gene therapy (AbbVie and REGENXBIO Inc) for wet AMD and DR
- VEGF inhibitors will likely remain the treatment mainstay for wet AMD, DME and DR during this decade and will generate the majority of major-market (U.S., EU5 and Japan) sales.
- Clarivate analysts anticipate that EYLEA HD will capture meaningful patient share and become one of the biggest drivers of growth in the wet AMD and DR/DME market.

What gaps in treatment does high-dose aflibercept fill?

The biggest unmet need for patients with DME or wet AMD has been clinically superior therapies with more convenient delivery profiles than available treatments. The frequency and time requirement of clinic visits take a toll on patient and caregiver quality of life and can be particularly burdensome for the working-age population and patients who cannot drive. High-dose aflibercept affords extended dosing intervals while offering favorable safety and efficacy profiles, greatly reducing the administrative and follow-up burden of treatment on patients, caregivers and healthcare providers.

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

The launch of biosimilar versions of aflibercept are expected to erode the patient share of the EYLEA franchise, including EYLEA HD. Clarivate experts expect that, by 2032, approximately 45% of U.S. patients with drug-treated wet AMD receiving aflibercept will receive EYLEA HD while 34% will receive an aflibercept biosimilar. Moreover, they expect that 43% of U.S. patients with wet AMD will receive a competing, newly launched therapy (including biosimilars) by 2032. Novel therapies in development include treatments promising even longer dosing intervals than EYLEA HD and gene therapies that could require a single IVT injection, which would greatly reduce the burden of treatment. Furthermore, EYLEA HD will have to compete with Vabysmo, its biggest rival currently on the market. With a novel mechanism of action, Vabysmo became the first injectable drug allowing administration to up to 16 weeks while providing a safety and efficacy profile consistent with that of EYLEA. Vabysmo experienced rapid uptake shortly after its launch in early 2022, which will have a negative impact on the blockbuster status of EYLEA HD.

Market overview

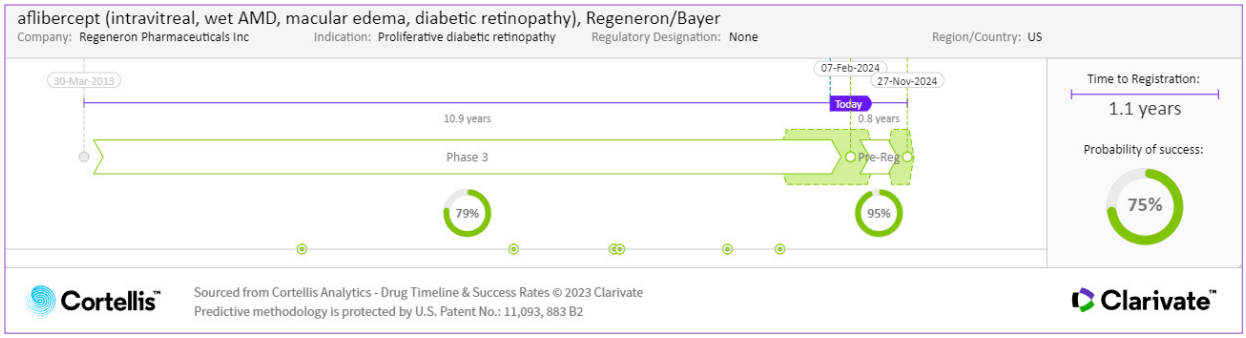
$1.77B

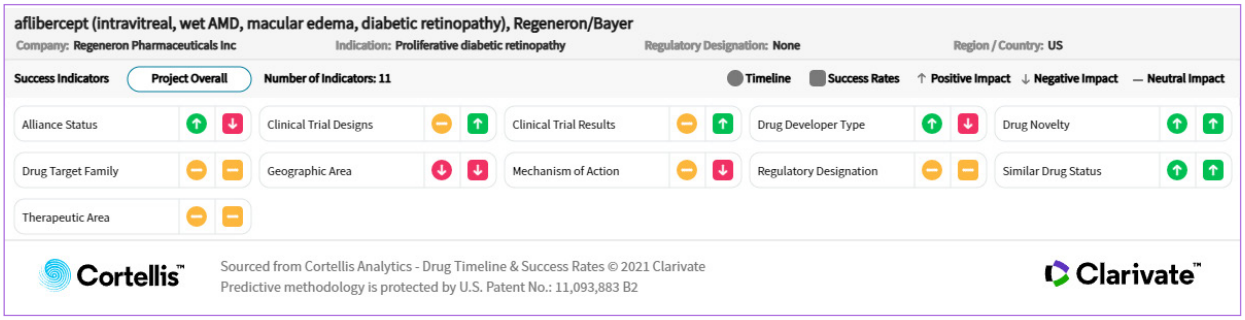
expected sales for wet AMD in the G7 markets for 2029

"I would like to try Eylea HD, especially in patients with stabilization of the disease, in order to simplify the life of patients."

Retinal specialist, Italy

Cortellis data indicate there is a 75% probability of success for diabetic retinopathy in the United States.





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

02. Budesonide

TARPEYO®/Kinpeygo®/Nefecon

TARPEYO®/Kinpeygo® (developed under the project name Nefecon) is a second-generation, synthetic, non-halogenated form of the corticosteroid budesonide. The delayed release formulation of budesonide has shown greater efficacy for protein reduction and slowing the decline in kidney function in primary immunoglobulin A (IgA) as well as a much better safety profile than conventional corticosteroids. As such, it will likely experience high uptake for high-risk patients.

Calliditas Therapeutics AB has partnered with STADA Arzneimittel AG to commercialize Kinpeygo in Europe and with Everest Medicines to commercialize TARPEYO in Mainland China, Hong Kong, Macau, Taiwan, South Korea and Singapore.

Why is it a drug to watch?

With its modified targeted drug release technology, this second-generation synthetic nonhalogenated form of budesonide provides superior safety and efficacy compared with first-generation corticosteroids. The 4-mg delayed-release capsule is enteric-coated so it remains intact until it reaches the ileum where it targets the mucosal B cells, including Peyer's patches, responsible for the IgA-causing complexes. Because of the absorption characteristics, it may result in fewer side effects than other corticosteroids despite prolonged use.

Submissions for regulatory approval have been based on data from the phase 3, placebo-controlled NefIgArd clinical trial. The study was conducted with adult patients with primary IgA nephropathy who were at risk of progressing to end-stage renal disease (ESRD) despite maximum tolerated treatment with optimized renin-angiotensin system (RAS) blockade. Budesonide treatment lasted nine months, followed by a 15-month observational follow-up period off the study drug.

- The results demonstrated slowed progression of IgA nephropathy with budesonide:
  - 34% reduction in proteinuria (urine protein-to-creatinine ratio [UPCR]) at nine months with budesonide, compared with 5% with placebo
  - Greater reductions in UPCR with budesonide continued at two years
  - Significantly greater reduction in eGFR with budesonide vs placebo at nine months and two years

Budesonide at a glance

Producers

Calliditas Therapeutics AB, Everest Medicines and STADA Arzneimittel AG

Type

Delayed release corticosteroid formulation

Usage

Daily oral administration to reduce proteinuria in adults with IgA nephropathy at risk of rapid disease progression

Also being evaluated to treat autoimmune hepatitis (AIH) and primary biliary cholangitis

Impact

~500K

diagnosed prevalent adult cases of IgA nephropathy in the G7 markets in 2023

Review and approval status

November 2016
– Orphan drug designation: EMA

November 2020
– Breakthrough therapy designation: Mainland China NMPA

December 2021
– Accelerated approval granted: U.S. FDA

July 2022
– CMA granted: EMA

November 2022
– NDA accepted: Mainland China NMPA

February 2023
For adult patients with IgA neuropathy at risk of rapid disease progression (UPCR ≥1.5 g/g)
– CMA granted: U.K. MHRA

June 2023
– sNDA accepted: U.S. FDA

August 2023
– Priority review granted: U.S. FDA

September 2023
– MAA filed: EMA

October 2023
– MAA filed: U.K. MHRA

December 20, 2023
– Approved: U.S. FDA

Actual and expected launch
– 2021: United States
– 2022: European Union, United Kingdom
– 2024: Mainland China

Patents estimated to expire
– Beginning in 2028

How will budesonide impact the market for IgA nephropathy/Berger's disease?

- The IgA nephropathy market is poised for robust growth, primarily due to the emergence of various therapies targeting the disease at different stages in its pathogenesis.
- Before the approval of TARPEYO/Kinpeygo, IgA nephropathy treatment was based only on supportive therapy, which included long-standing genericized therapies such as renin-angiotensin-aldosterone system (RAAS) inhibitors, diuretics, corticosteroids and immunosuppressants.
- TARPEYO/Kinpeygo will likely be used primarily with high-risk patients, in preference to general corticosteroids.

What gaps in treatment does budesonide fill?

IgA nephropathy is a rare, progressive kidney disorder that can lead to end-stage renal disease requiring dialysis or a kidney transplant. IgA nephropathy generally progresses slowly, and treatment is primarily directed at managing symptoms, minimizing kidney failure and improving patient quality of life through multidisciplinary supportive care. Clinicians are looking for a more holistic approach that takes into account all of these aims (i.e., reduce protein levels and improve kidney function and therefore quality of life). Therefore, effective, safe and well-tolerated drugs that protect kidney function or slow the progressive decline in GFR are needed. Because of its better efficacy and safety, budesonide will likely provide physicians with an alternative option to conventional corticosteroids.

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

The extremely high price of TARPEYO/Kinpeygo will likely constrain its use, especially since nephrologists are reluctant to prescribe expensive therapies unless they are shown to be significantly more effective. In addition, other potential competitors that specifically treat IgA nephropathy have already been approved or are in late-stage development, which could make it a crowded market.

9mth

Budesonide treatment cycle, followed by a 15 month observational follow-up period off the study drug.

34%

reduction in proteinuria at nine months with budesonide, compared with 5% with placebo.

Market overview

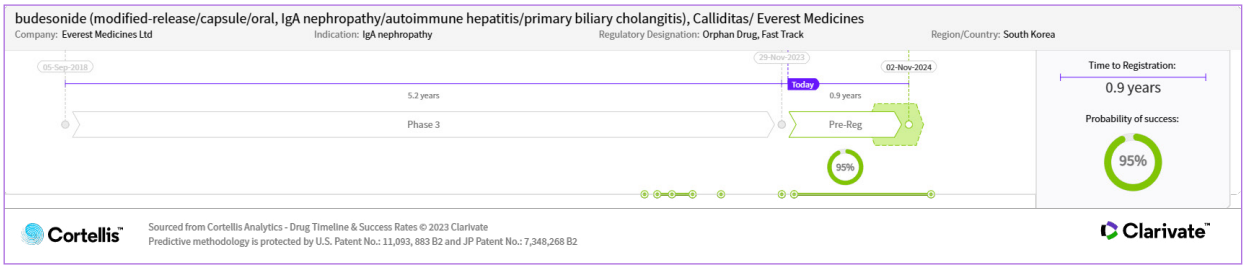
$0.73B

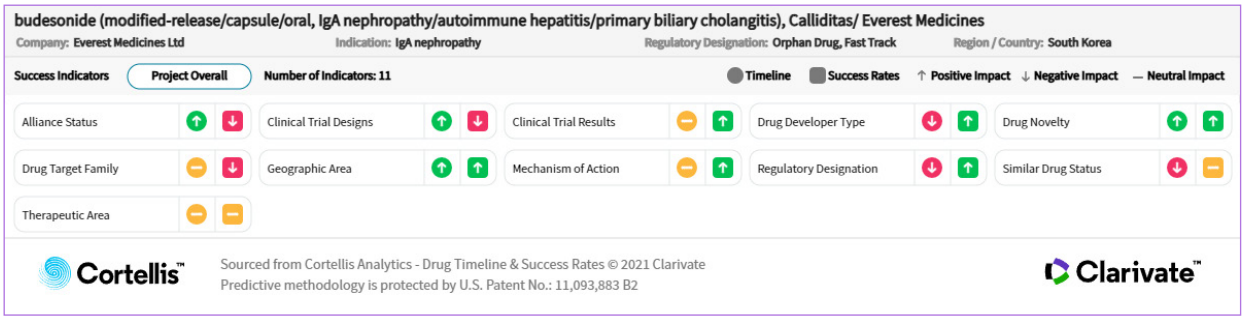
expected sales in 2029

"We are excited about using this drug because we are aware of the very interesting results from the clinical trials and because we are already using corticosteroids. Also, this drug has fewer side effects than traditional corticosteroids, so we have placed an order with the local pharmacy so that we can start replacing some of the patients who are on corticosteroids with Kinpeygo."

Nephrologist, Italy

Cortellis data indicate there is a 95% probability of success for IgA neuropathy in South Korea.





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

03. Datopotamab deruxtecan

Dato-DXd

With the potential to become the best-in-class TROP2-targeted antibody drug conjugate (ADC), datopotamab deruxtecan is set to be second to market (after TRODELVY®; Gilead Sciences Inc) for both HR-positive/HER2-negative and triple-negative breast cancer, and to enter the non-small cell lung cancer (NSCLC) market.

The collaboration between AstraZeneca and Daiichi Sankyo combines the former's strategic focus on NSCLC and breast cancers and investment in ADCs with the latter's proprietary DXd ADC technology.

Label expansions for datopotamab deruxtecan, either as monotherapy or in combination with IMFINZI® (AstraZeneca), are expected in various triple-negative breast cancer populations, including in the early-stage and first-line metastatic settings.

In NSCLC, we expect that datopotamab deruxtecan will gain initial approval for previously treated metastatic NSCLC without actionable genomic alterations. The ADC could earn a label expansion for first-line treatment (in combination with IMFINZI and chemotherapy) if the phase 3 AVANZAR trial is positive.

Why is it a drug to watch?

TROP2 is highly expressed (>80%) on epithelial cancer cells, including NSCLC, with limited expression in healthy human tissues, making it an attractive target.

Positive results were reported from two pivotal phase 3 trials, one each for HR-positive/HER-negative breast cancer and NSCLC:

- TROPION-Breast01 compared datopotamab deruxtecan with the investigator's choice of chemotherapy in patients with inoperable or metastatic HR-positive/HER2-low or negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer previously treated with endocrine-based therapy and one or two lines of chemotherapy:
  - 37% reduction in the risk of disease progression or death (vs chemotherapy)
  - Median progression-free survival (PFS) of 6.9 months (vs 4.9 months with chemotherapy)
  - 36.4% objective response rate (ORR; vs 22.9% with chemotherapy)
  - Assessment of overall survival (OS; dual primary endpoint) ongoing
  - Grade 3 or higher treatment-related adverse events (TRAEs) in 21% of patients (vs 45% with chemotherapy)

Datopotamab deruxtecan at a glance

Producers

AstraZeneca
and Daiichi Sankyo

Type

TROP2-directed ADC

Usage

Intravenous administration every 3 weeks to treat metastatic NSCLC or metastatic HR-positive/HER2-negative breast cancer

Also being evaluated to treat ovarian cancer, pancreatic cancer, prostate cancer, SCLC, colorectal cancer, bladder cancer, gastric cancer, biliary cancer, cervical cancer, endometrial cancer, transitional cell carcinoma of the urothelium, HER2-negative gastroesophageal cancer, esophageal cancer and squamous cell carcinoma

Impact

~168K
new cases of previously treated metastatic HR-positive/HER2-negative breast cancer in the G7 markets in 2023

~86K
new cases of early-stage and previously untreated metastatic triple-negative breast cancer in the G7 markets in 2023

~329K
new cases of previously treated metastatic NSCLC in the G7 markets in 2023

Review and approval status

HR-positive/HER-negative breast cancer

Expected launch
- 2024: Europe, Japan, United Kingdom, United States
- 2027: Mainland China

NSCLC

Expected launch
- 2024: European Union, Japan, United States

- TROPION-Lung01 compared datopotamab deruxtecan with docetaxel in patients with metastatic NSCLC treated with at least one prior line of therapy (including immunotherapy, chemotherapy and, if applicable, a targeted therapy for driver mutations):
  - 25% reduction in the risk of disease progression or death (vs docetaxel)
  - Median PFS of 4.4 months (vs 3.7 months with docetaxel)
  - 26% ORR (vs 13% with docetaxel)
  - Assessment of OS ongoing
  - Grade 3 or higher TRAEs in 25% of patients (vs 41% with chemotherapy)

AstraZeneca is also researching a potential diagnostic test to help identify patients most likely to benefit from treatment with datopotamab deruxtecan.

In addition, the following phase 3 trials are evaluating potential label expansions for datopotamabdatopotamab deruxtecan):

- TROPION-Breast02: datopotamabdatopotamab deruxtecan compared with the investigator's choice of chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer who are not candidates for PD-1/PD-L1 inhibitor therapy
- TROPION-Breast03: datopotamab deruxtecan plus durvalumab compared with the investigator's choice of chemotherapy in patients with early (stage I-III) triple-negative breast cancer with residual invasive disease after neoadjuvant therapy
- TROPION-Breast04: datopotamab deruxtecan plus durvalumab followed by adjuvant durvalumab with/without chemotherapy compared with pembrolizumab plus chemotherapy followed by pembrolizumab with/without chemotherapy in patients with previously untreated triple-negative or HR-low/HR2-negative breast cancer
- TROPION-Breast05: datopotamab deruxtecan with/without durvalumab compared with the investigator's choice of chemotherapy plus pembrolizumab in patients with PD-L1-positive locally recurrent inoperable or metastatic triple-negative breast cancer
- AVANZAR: datopotamab deruxtecan plus durvalumab and carboplatin for first-line treatment of patients with advanced NSCLC without actionable genomic alterations

25%

reduction in the risk of disease progression or death offered by datopotamab deruxtecan versus docetaxel.

How will datopotamab deruxtecan impact the market for breast cancer and NSCLC

HR-positive/HER-negative breast cancer

- HR-positive/HER-negative breast cancer is the most common subtype, accounting for around 60-75% of all cases.
- Datopotamab deruxtecan is expected to garner most uptake in the third- and later-line settings for the treatment of patients who have acquired resistance to endocrine therapy and have received at least one chemotherapy line for their metastatic disease. In such a setting, datopotamab deruxtecan will compete with TRODELVY for the treatment of patients who are not eligible to receive ENHERTU® (Daiichi Sankyo; i.e., non-HER2-low patients, who represent ~40% of the population).

Triple-negative breast cancer

- Datopotamab deruxtecan will be positioned both in the early and the metastatic triple-negative breast cancer settings. Its approval is expected to take patient share from current treatment with immunotherapy and chemotherapy.
- Datopotamab deruxtecan will face fierce competition from TRODELVY in both settings.

NSCLC

- For NSCLC, datopotamab deruxtecan is entering one of the busiest drug development pipelines that includes established drug classes (e.g., EGFR inhibitors, immune checkpoint inhibitors, angiogenesis inhibitors) as well as novel therapies (e.g., CD73-, NKG2A-, HER3- and TROP2-targeting agents).
- Datopotamab deruxtecan is initially positioned as a new therapy for patients with metastatic NSCLC who fail at least immunotherapy and chemotherapy, a setting with high unmet need and a lack of clear sequencing options. In that regard, offering an effective treatment with a novel mechanism of action would be attractive to prescribers.

What gaps in treatment does datopotamab deruxtecan fill?

Sequential chemotherapy regimens are widely utilized for management of endocrine-resistant metastatic HR-positive/HER-negative disease, but an unmet need remains in this setting, as chemotherapy is associated with low response rates and toxicity. Datopotamab deruxtecan has been shown to provide both improved efficacy and safety compared with chemotherapy.

There is high unmet need for improved treatment options in the triple-negative breast cancer setting due to the limited efficacy of current therapies in the metastatic setting and the high recurrence rate following curative treatment in the early stage. Datopotamab deruxtecan — as monotherapy or in combination with immunotherapy — is expected to improve the outcome of patients with this subtype of breast cancer.

Substantial unmet treatment needs also still exist for NSCLC, including effective therapies for previously treated metastatic NSCLC. The NSCLC treatment algorithm is rapidly evolving, as agents approved in later lines of therapy seek and gain label expansions for first-line use. Although this improves patient responses in the first-line setting, it depletes the options available when these patients experience progression, creating an urgent need for more treatment options in later lines of therapy.

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

Datopotamab deruxtecan is likely to face stiff competition from various agents in both the HR-positive/HER-negative breast cancer and the NSCLC segments.

For HR-positive/HER-negative breast cancer, major hurdles in uptake and thus sales potential include competition from established earlier-to-market therapies (e.g., endocrine therapies, aromatase inhibitors, oral selective estrogen receptor degraders [SERDs]) and emerging novel therapies (e.g., other TROP2 inhibitors, immune checkpoint inhibitors, PARP inhibitors, vaccines). Multiple novel drug classes are being developed for metastatic HR-positive/HER-negative breast cancer with the aim of tackling endocrine resistance. These novel agents, including novel PI3K/AKT/mTOR inhibitors and ER-targeted therapies, could push the use of ADCs, including datopotamab deruxtecan, to later lines of treatment. In addition, the efficacy of sequential use of ADCs (e.g., use of datopotamab deruxtecan following treatment with ENHERTU) is uncertain and could potentially hamper the use of TROP2-agents after treatment with ENHERTU. The market entry of multiple agents creates a growing need to optimize treatment sequencing across lines of therapy, and physicians may experience challenges determining the best treatment sequence following first-line therapy.

In triple-negative breast cancer, datopotamab deruxtecan is expected to face fierce competition from TRODELVY, which has the advantage of being the first of its class to market.

For NSCLC, similar competition from entrenched therapies (e.g., immune checkpoint inhibitors, monoclonal antibodies) and emerging therapies (e.g., antibody-drug conjugates) will need to be overcome. In first-line metastatic NSCLC, treatment choices are increasingly fragmented depending on biomarker status, and combined immunochemotherapy is a standard of care for patients without driver mutations. The addition of datopotamab deruxtecan to existing combinations will need to demonstrate convincing efficacy improvements (and a favorable benefit-risk profile) if it is to get a slice of this fiercely competitive but lucrative market segment.

60-75%

of all cases are HR-positive /HER-negative breast cancer, making it the most common subtype.

Market overview

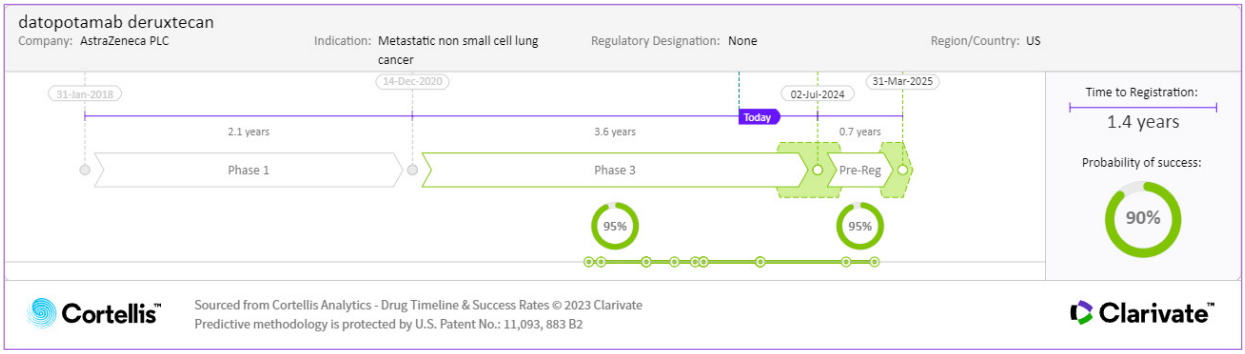
$2.70B

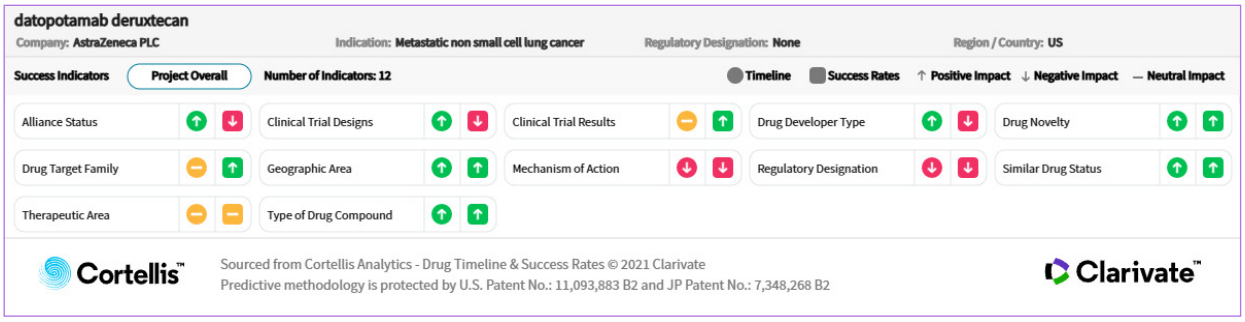
expected sales in 2029
(for breast cancer and NSCLC combined)

"TROP2 is a new target in NSCLC and the data that I know of are really promising. At the moment, TROP2 expression is not a prerequisite for using these targeted agents, but still, they seem to work. I'm really very interested in seeing more data on them."

Medical oncologist, Germany

Cortellis data indicate there is a 90% probability of success for metastatic NSCLC in the United States.





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

04. Efanesoctocog alfa

ALTUVIIIO™ / BIVV001

Efanesoctocog alfa is the first once-weekly factor VIII (FVIII) replacement intravenous infusion therapy, which will help reduce the burden associated with the injection frequency of other currently available FVIII therapies. For patients reluctant to receive novel therapies, such as mAbs or gene therapy, efanesoctocog alfa will likely be an appealing option.

Clinicians also view efanesoctocog alfa favorably given the attainable FVIIII levels, injection frequency and safety profile demonstrated in clinical trials to date.

Sanofi has development and commercialization rights for efanesoctocog alfa in the United States, whereas Sobi is responsible for developing and marketing the drug in Europe and other markets.

Why is it a drug to watch?

To potentially extend its time in circulation, efanesoctocog alfa adds a region of von Willebrand factor and XTEN® polypeptides to the innovative Fc fusion technology. It is the only therapy that has been shown to break through the von Willebrand factor ceiling, which is believed to impose a half-life limitation on current FVIII therapies. The result is the first FVIII replacement therapy that is administered only once a week, reducing the treatment burden.

The U.S. FDA approval was primarily based on data from the pivotal phase 3 XTEND-1 study conducted over a period of 52 weeks with adult and adolescent (>12 years) patients with severe hemophilia A who had been previously treated with either a FVIII prophylaxis treatment or FVIII on-demand therapy. Patients who were on FVIII prophylaxis pre-study received efanesoctocog alfa for routine prophylaxis (arm A). Patients who received on-demand treatment with FVIII pre-study were assigned to receive on-demand efanesoctocog alfa treatment for 26 weeks, followed by routine prophylaxis once weekly for 26 weeks (arm B). The study results for once weekly efanesoctocog alfa prophylaxis included the following:

- Median annualized bleeding rates (ABRs) of 0, 21.1 and 0 in arm A, B (on-demand) and B (prophylaxis), respectively
- Mean ABRs of 0.7, 21.4 and 0.7 in arms A, B (on-demand) and B (prophylaxis), respectively
- In arm A, a 77% reduction in ABR, based on an intra-patient comparison with prior factor prophylaxis
- >40 IU/dL mean FVIII activity for the majority of the week, with 15 IU/dL at day 7
- For all participants with target joints at baseline, resolution of all target joints after 12 months of prophylactic treatment with efanesoctocog alfa
- Improved patient-reported physical health and pain intensity
- No signs of FVIII inhibitor development in the study

New frontiers in medicine

Reducing burden of treatment for hemophilia A patients

Efanesoctocog alfa at a glance

Producers

Sanofi (Bioverativ Therapeutics Inc) and Swedish Orphan Biovitrum AB

Type

Recombinant FVIII replacement therapy

Usage

Once weekly intravenous infusion for routine prophylaxis to prevent bleeding, on-demand treatment for control of bleeding episodes, and perioperative management of bleeding in adults and children with hemophilia A

Impact

~45K

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

Review and approval status

August 2017
- Orphan Drug designation granted: U.S. FDA

June 2019
- Orphan Drug designation granted: EMA

February 2021
- Fast Track designation granted: U.S. FDA

July 2021
- Breakthrough therapy designation granted: Mainland China

June 2022
- Breakthrough therapy designation granted: U.S. FDA

February 2023
For adult and pediatric patients with hemophilia A
- Approved: U.S. FDA

May 2023
- Marketing authorization application (MAA) accepted: EMA

September 2023
For adult and pediatric patients with hemophilia A
- Approved: Japan MHLW

Actual and expected launch
- 2023: Japan, United States
- 2024: European Union
- 2028: Mainland China

Patents estimated to expire
- Beginning in 2032

The phase 3 XTEND-Kids study was also conducted over 52 weeks with previously treated children (<12 years) with severe hemophilia A and found the following for once weekly efanesoctocog alfa prophylaxis:

- Median and mean ABR of 0 and 0.89, respectively
- No signs of FVIII inhibitor development

Ongoing studies include the following:

- XTEND-ed: extension study to evaluate the long-term efficacy and safety
- FREEDOM: phase 3b European trial with patients with severe hemophilia A aged 12 years and older who are currently on prophylactic therapy
- Prospective, observational, longitudinal cohort study to describe the real-world effectiveness, safety and treatment use of efanesoctocog alfa in patients with hemophilia A treated per standard of care in the United States and Japan

How will efanesoctocog alfa impact the market for hemophilia A?

- The hemophilia A treatment landscape is becoming increasingly crowded.
- Despite the development of treatment burden-reducing therapies with subcutaneous administration, a sizable percentage of patients who do well on FVIII replacement therapy will likely continue with the treatment. These patients may have good venous access, become accustomed to lifelong IV infusions or very few bleeds.
- Even with alternative treatment options, some breakthrough bleeds are inevitable. These, as well as postsurgical management and trauma-related bleeds, will continue to require treatment with FVIII.
- The hemophilia A patient population is aging because the expected median survival time of hemophilia patients in the G7 countries is approaching background life expectancy. In addition to an increased number of treatable patients and longer overall treatment duration, the older hemophilia A patient population will undergo more major surgeries during which they may require hemostatic interventions, such as continuous FVIII infusions.
- Because factor replacement therapies are dosed based on patient weight, proportionate increases in weight per age will drive the increase in per-unit consumption of drugs, ultimately contributing to sales growth.

What gaps in treatment does efanesoctocog alfa fill?

A primary goal in the treatment of hemophilia A is to prevent bleeding, particularly bleeding into the joints, which is associated with permanent joint damage. Another important outcome is better quality of life. However, the dosing frequency and route of administration for current FVIII replacement therapies are burdensome and contribute to suboptimal compliance rates. As the first once-weekly FVIII replacement infusion therapy, efanesoctocog alfa could improve patient convenience, reduce the treatment burden and enhance treatment compliance.

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

Treating hemophilia is expensive, especially for patients with severe bleeding tendencies, and both clinicians and payers are asking for precise quantification of the value of a treatment regimen. As a lower-cost subcutaneously administered treatment option that is currently available for patients, HEMLIBRA® (Genentech) continues to constrain the value of the market with its increasing adoption. Although also likely to be costly initially, emerging gene therapies could be curative and reduce the need for invasive standard treatments, such as FVIII replacement therapy.

Market overview

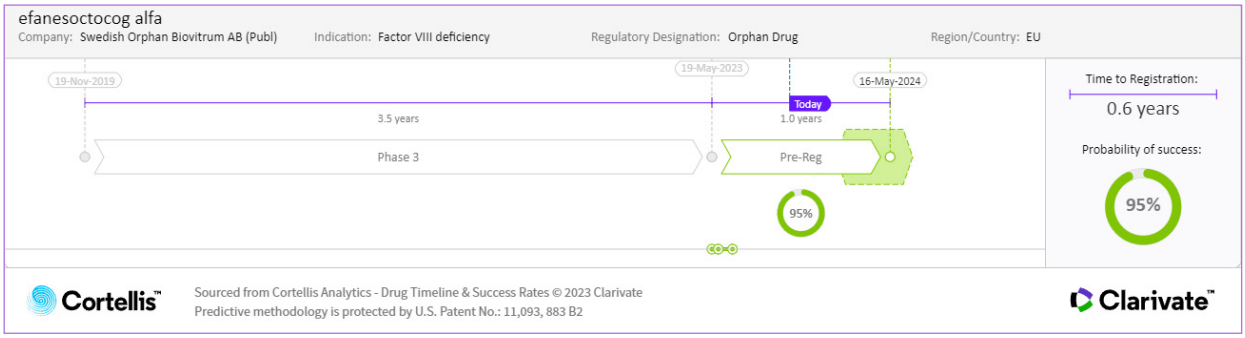
$1.77B

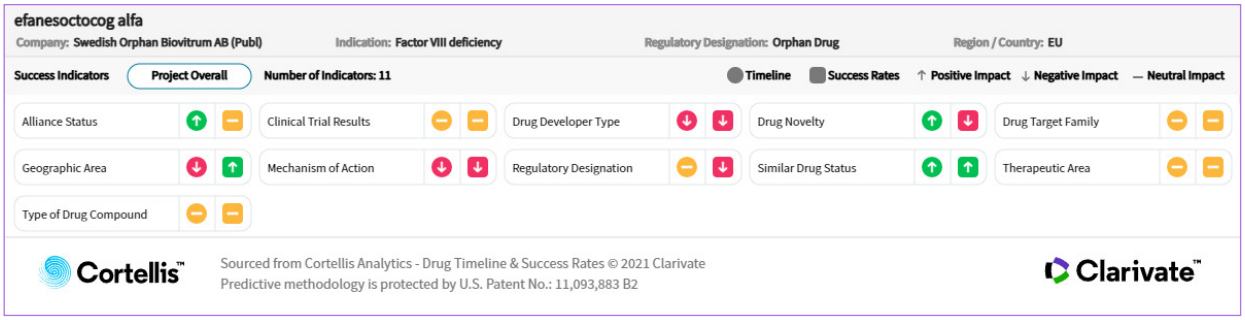
expected sales in 2029

"BIVV001 will certainly take a lot of market share from the FVIII product because it can be infused every week or 10 days, instead of every other day or twice a week, which is a big advantage. So, the only thing I am sure of is that the currently available SHL or EHL will probably disappear with the advent of BIVV001."

Hematologist, France

Cortellis data indicate there is a 95% probability of success for efanesoctocog alfa in the European Union.





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

05. Ensifentrine

RPL554

Ensifentrine is an inhaled dual phosphodiesterase (PDE)3 and PDE4 inhibitor that is expected to reduce exacerbations in moderate to severe COPD without the systemic side effects of current PDE inhibitors that are delivered orally. If approved, it would be the first in class as well as the first novel mechanism that has become available for maintenance COPD treatment in more than 10 years.

The clinical and safety profile of ensifentrine makes it a promising addition to the limited treatment class options available for this patient population.

Why is it a drug to watch?

Ensifentrine is a novel, potent and selective dual inhibitor of PDE3 and PDE4 that combines bronchodilator and nonsteroidal anti-inflammatory activities in one compound. It also promotes ciliary function, which could potentially improve sputum-associated symptoms. The FDA submission was based on positive results from two phase 3 trials (ENHANCE-1 and ENHANCE-2) that evaluated the efficacy and safety of nebulized ensifentrine as monotherapy or as an add-on to a long-acting muscarinic antagonist or long-acting beta-agonist in patients aged 40 years to 80 years with moderate to severe COPD.

The findings showed the following:

- 36-42% reduction in the rate and risk of COPD exacerbations over 24 weeks
- 87-94 mL placebo-corrected change from baseline in average FEV1 area under the curve 0 to 12 hours post dose at week 12
- Statistically (ENHANCE-1) or clinically (ENHANCE-1 and ENHANCE-2) significant improvements in quality of life
- Improvements were consistent across subgroups, including gender, age, smoking status, COPD severity, background medication, inhaled corticosteroids use, chronic bronchitis and geographic region.

New frontiers in medicine

A promising new treatment option for COPD

Ensifentrine at a glance

Producers

Verona Pharma

Type

Dual inhibitor of PDE3 and PDE4

Usage

Nebulized formulation administered twice daily for maintenance treatment of COPD

Also being evaluated to treat asthma, cystic fibrosis and idiopathic pulmonary fibrosis

Impact

~28K

diagnosed prevalent cases in the G7 markets in 2023

Review and approval status

September 2023
– NDA accepted: U.S. FDA

June 26, 2024
– PDUFA date

Expected launch
– 2024: Japan, United States
– 2025: European Union

How will ensifentrine impact the market for COPD?

- Maintenance therapies will be the primary growth driver of the COPD market.
- Although biologics will capture less than 1% of COPD patients, they could generate combined sales of more than $3.4 billion, contributing to nearly 14.2% of the COPD market in 2032.
- However, novel emerging therapies, such as ensifentrine, that address daily symptoms, minimize exacerbations and improve quality of life will likely contribute significantly to the COPD market toward the end of the forecast period (depending on approval).
- Ensifentrine is in the most advanced stage of development of all novel drugs including biologics, and it will most likely be used as an add-on to a long-acting bronchodilator therapy.

$3.4B+

combined sales could be generated by biologics even though they will capture less than 1% of COPD patients.

What gaps in treatment does ensifentrine fill?

Individuals with COPD rely on inhaled maintenance therapies (e.g., bronchodilators and inhaled corticosteroids [ICS]) for long-term control of symptoms and exacerbations. However, limited treatment options remain available, and patients can experience unpleasant systemic effects. The dual inhibition of PDE3/4 following inhaled ensifentrine administration directly to the lungs maximizes local effects in the lung (bronchodilation and anti-inflammatory effects) and minimizes the possibility of the side effects experienced with orally delivered PDE inhibitors.

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

Ensifentrine offers an incremental benefit and does not represent a transformative treatment paradigm, which could limit uptake. The initial release in only a nebulized form might also be seen as a disadvantage for some patients who prefer a more portable inhaler (dry powder or metered dose). Inhalers are smaller, and patients have already been exposed to them through other treatments. The need to learn how to use, clean and maintain a nebulizer plus the twice-daily administration at home could be a major hurdle. Therefore, in its nebulized form, ensifentrine might be limited to hospital-bound or the most elderly patients.

Market overview

$500-750M

expected sales in 2029

"Neutrophilic inflammation is the most dominant pathway in COPD and is often poorly responsive to steroids. Ensifentrine is a drug that is very effective against neutrophils as well, so that is a potentially important way of reducing the major inflammatory component of COPD"

Pulmonologist, United Kingdom

06/07. Exagamglogene autotemcel and lovotibeglogene autotemcel

Exa-cel/CASGEVY™ and Lovo-cel/LYFGENIA™

Both exagamglogene autotemcel and lovotibeglogene autotemcel have the potential to be transformative for a patient population with debilitating, life-altering diseases that have limited symptomatic and no curative treatments currently available.

With only a one-time administration, these therapies aim to treat the underlying cause of sickle cell disease (SDC) and transfusion-dependent beta-thalassemia and result in patients being transfusion-independent or vaso-occlusive crises (VOC)-free, with significant improvement in quality of life and physical performance.

Why are they drugs to watch?

Inherited blood disorders, SCD and beta-thalassemia cause severe pain, organ damage and shortened life span. With only a one-time administration, these therapies aim to treat the underlying cause of SDC and transfusion-dependent beta-thalassemia and result in patients being transfusion-independent or vaso-occlusive crises (VOC)-free, with significant improvement in quality of life and physical performance. The enthusiasm for gene therapies in this space is based not only on the potential curative effect but also concerns about the effectiveness of other current treatments, their accessibility and their side effects. In its recent evaluation of SCD treatments, the Institute for Clinical and Economic Review (ICER) considered both treatments to potentially provide a substantial net health benefit compared with standard of care, given the severity of disease and the rate of treatment success and despite uncertainties around durability and harms.

Exagamglogene autotemcel

Exagamglogene autotemcel is the first treatment to emerge from the joint research program between Vertex and CRISPR Therapeutics that started in 2015 to focus on using CRISPR/Cas9 to discover and develop potential new treatments aimed at the underlying genetic causes of human disease. ICER rated exagamglogene autotemcel, compared with standard of care, as "Comparable or Better."

U.S. FDA approval and other submissions to regulatory agencies were based on data from two pivotal phase 1/2/3 studies, which showed the following:

- CLIMB-111:
  - Patients aged 12 years to 35 years with transfusion-dependent beta-thalassemia characterized by recurrent VOCs
  - 88.9% with independence from transfusion for at least 12 consecutive months
  - 20.5-month mean duration of independence from transfusion (maximum 40.7 months)

New frontiers in medicine

The first disease-modifying therapies for sickle cell disease and beta-thalassemia

Lovotibeglogene autotemcel at a glance

Producers

Bluebird bio

Type

Ex vivo lentiviral-based HBB gene stimulator

Usage

One-time intravenous infusion following myeloablative conditioning chemotherapy to treat severe SCD

Review and approval status

October 2018
For patients with transfusion-dependent beta-thalassemia and a non-β^0/β^0 genotype
– MAA accepted: EMA

September 2020
For patients with SCD
– PRIME designation: EMA

June 2023
For patients with SCD
– BLA accepted: U.S. FDA

December 20, 2023
For patients with SCD
– Approved: U.S. FDA

Expected launch
– 2024: European Union, United States

Exagamglogene autotemcel at a glance

Producers

CRISPR Therapeutics and Vertex Pharmaceuticals Inc

Type

Ex vivo CRISPR/Cas9 gene-edited therapy

Usage

Intravenous infusion as part of an autologous hematopoietic stem cell transplant (HSCT) following myeloablative conditioning chemotherapy to treat severe SCD and transfusion-dependent beta-thalassemia

Review and approval status

January 2019
For patients with SCD
– Fast Track designation: U.S. FDA

April 2019
For patients with transfusion-dependent beta-thalassemia
– Fast Track designation: U.S. FDA

October 2019
For patients with transfusion-dependent beta-thalassemia
– Orphan drug status: EMA

January 2020
For patients with SCD
– Orphan drug status: EMA

April 2020
For patients with transfusion-dependent beta-thalassemia
– Orphan drug status: U.S. FDA

May 2020
For patients with SCD
– Orphan drug status: U.S. FDA

For patients with transfusion-dependent beta-thalassemia
– Regenerative medicine advanced therapy (RMAT) designation: U.S. FDA

September 2020
For patients with SCD
– PRIME status: EMA

October 2020
For patients with transfusion-dependent beta-thalassemia
– Rare pediatric disease designation: U.S. FDA

April 2021
For patients with transfusion-dependent beta-thalassemia
– PRIME status: EMA

January 2023
For patients with SCD
– MAAs validated: EMA and U.K. MHRA

April 2023
For patients with SCD
– BLA accepted: U.S. FDA

For patients with transfusion-dependent beta-thalassemia
– BLA submitted: U.S. FDA

August 2023
For patients with SCD
– Priority review granted: U.S. FDA

October 2019
For patients ≥12 years old with SCD with recurrent vaso-occlusive crises (VOCs) or transfusion-dependent beta-thalassemia for whom a human leukocyte antigen-matched related hematopoietic stem cell donor is not available
– CMA: U.K. MHRA

December 8, 2023
For patients >12 years old with SCD with recurrent VOCs
– Approved: U.S. FDA

March 30, 2023
Transfusion-dependent beta-thalassemia
– PDUFA date

Expected launch:
For patients with SCD or transfusion-dependent beta-thalassemia
Actual and expected launch:
– 2023: United Kingdom, United States
– 2024: European Union

Patents estimated to expire
– Beginning in 2033

  - 9 g/dL mean weighted hemoglobin
  - Increase in total hemoglobin from an average of 8.9 g/dL to an average of 16.9 g/dL
  - Increase in fetal hemoglobin (HbF) from an average of 67.4% to an average of 99.6%
- CLIMB-121:
  - Patients aged 12 years to 35 years with SDC characterized by recurrent VOCs
  - 94.1% VOC-free for at least 12 consecutive months
  - 18.7-month mean duration of being VOC-free (maximum 36.5 months)
  - 100% with no VOC-related hospitalizations for at least 12 consecutive months
  - Increase in total hemoglobin from an average of 11 g/dL to an average of 15.9 g/dL
  - Increase in fetal hemoglobin (HbF) from an average of 39.6% to an average of 49.6%

100%

with no VOC-related hopitalizations for at least 12 consecutive months.

Minimum clinically important difference (MCID) met for the mean change in baseline EuroQoL Visual Analog Scale (EQ VAS), the functional assessment of cancer therapy — general (FACT-G), and the bone marrow transplantation subscale of the FACT scale (BMT) scores at month six, which were sustained throughout 18 months of follow-up

The safety profile in both trials has been generally consistent with myeloablative conditioning with busulfan and HSCT, and potential off-target effects have not been detected.

In addition, the following phase 3 trials are ongoing:

- CLIMB-141: patients aged 2 years to 11 years with transfusion-dependent beta-thalassemia characterized by recurrent VOCs
- CLIMB-151: patients aged 2 years to 11 years with SCD characterized by recurrent VOCs
- CLIMB-161: to support expansion of the company's manufacturing footprint after initial potential approval and launch; patients aged 12 years to 35 years with either transfusion-dependent beta-thalassemia or SCD characterized by recurrent VOCs

Participants in the CLIMB-111, 121, 151 and 161 trials have also been asked to continue in CLIMB-131, a long-term follow-up trial of up to 15 years for continued safety and efficacy evaluations.

Lovotibeglogene autotemcel

Approval of lovotibeglogene autotemcel results from more than a decade of work in gene therapy by bluebird bio and represents the company's third ex vivo gene therapy approved by the FDA for a rare genetic disease and second FDA approval for an inherited hemoglobin disorder. Lovotibeglogene autotemcel is considered the most deeply studied gene therapy in

development for these diseases, and ICER rated lovotibeglogene autotemcel, compared with standard of care, as "Incremental or Better."

Regulatory approvals and submissions were based on data from the pivotal phase 1/2 HGB-206, which showed the following:

- Patients aged 12 years to 50 years with severe SCD and at least four severe VOCs in the 24 months prior to enrollment, an intolerance to hydroxyurea or VOC despite hydroxyurea treatment and matched HLA-identical sibling hematopoietic cell donor (Group C: hematopoietic stem cells collected from peripheral blood after mobilization with plerixafor)
- 88.2% VOC-free for a median 35.8 months of follow-up (min-max: 20.2-61 months)
- Adolescent patients: 100% VOC-free during the 6-18-month enrollment period
- Increase in total hemoglobin from a median of 8.5 g/dL to >11 g/dL at 18 months of follow-up
- Improvement in the following quality of life measures: PRO Measurement Information System-57, pain intensity numeric rating scale and EuroQoL-5D-3L Health Utility Index

In addition, the following phase 3 trial is ongoing:

- HGB-210: patients aged 2 years to 50 years with severe SCD

Participants in the HGB-205, 206 and 210 trials have also been asked to continue in LTF-307, a long-term follow-up trial of up to 13 years for continued safety and efficacy evaluations.

How will exagamglogene autotemcel and lovotibeglogene autotemcel impact the market for SCD and beta-thalassemia?

Challenging conditions to treat, SCD and beta-thalassemia have had few new treatments become available, with the approval of ENDARI (Emmaus Medical Inc) in 2017 representing the first in 20 years.

- Representing the first curative treatments to become available, exagamglogene autotemcel and lovotibeglogene autotemcel have the potential to pave the way for future disease-modifying drugs.
- The high cost and limited eligible patient population of both therapies might constrain uptake.
- However, ICER estimated that both therapies could reduce healthcare costs associated with both diseases: up to $11,600 per VOC that is averted due to therapy when compared with standard of care

What gaps in treatment do these treatments fill?

Although some medications are available to help manage symptoms, many patients with SCD and transfusion-dependent beta-thalassemia require lifelong monthly blood transfusions, and therefore frequent hospital visits, to prevent extreme pain crises, minimize organ damage, improve quality of life and provide the ability to complete daily tasks. However, regular transfusions require long-term chelation therapy to avoid serious health complications such as heart and liver disease that result from iron overload. Few other treatment options except analgesia have been available. Although HSCT is a potentially curative treatment for SCD, many people do not have a compatible sibling-matched donor, graft-versus-host disease (GVHD) is a serious risk and the risks of HSCT increase with age. Therefore, a significant unmet need for disease-modifying drugs and curative therapies still exists.

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

For SCD and transfusion-dependent beta-thalassemia, multidisciplinary care is required, but this is often hampered by inadequate physician education as well as poor care coordination. ICER reported that additional factors that could represent barriers to access include systemic racism, poverty and insurance systems that have not been designed to coordinate coverage for patients with chronic conditions affecting multiple systems. Furthermore, generalizability of the reported efficacy and safety results outside of the clinical trial setting remains unknown.

Exagamglogene autotemcel will likely be restricted to patients with severe disease initially, the infrastructure for stem cell transplantation (i.e., authorized treatment centers [ATCs]) might not be broadly available at first and the therapy might be cost-prohibitive for many who are eligible. Another concern is the loss of fertility because this therapy will require pre-treatment ablative therapy, and coverage of oocyte/sperm cryopreservation is often limited, which could also limit uptake.

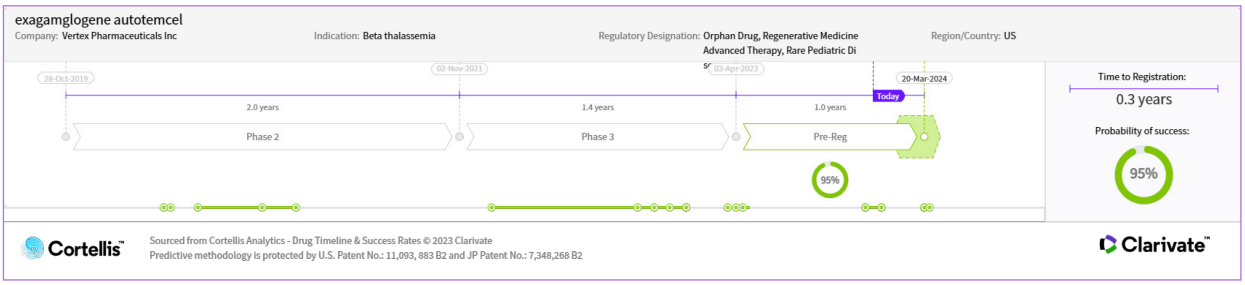
Lovotibeglogene autotemcel uptake could be hampered by the black box label for hematologic malignancy, which requires lifelong monitoring, as well as the high cost, which has been estimated to be higher at launch than that of exagamglogene autotemcel. Treatment access is also limited to Qualified Treatment Centers (QTCs), which receive specialized training to administer complex gene therapies.

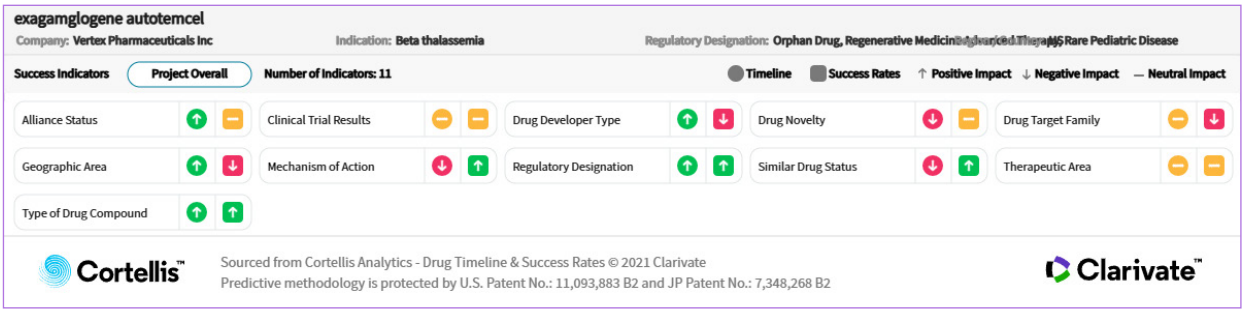
Market overview

$1.32B

expected sales of exagamglogene autotemcel in 2029

Cortellis data indicate there is a 95% probability of approval of exagamglogene autotemcel for beta-thalassemia in the United States.





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

08. Mirikizumab

Omvoh™/ LY-3074828

Mirikizumab, a monoclonal antibody (mAb) targeting the p19 subunit of IL-23, was approved as first-in-class therapy for ulcerative colitis by the EMA and the U.S. FDA and will likely be the third in the class approved for Crohn's disease. Included in Drugs to Watch 2023, a delayed U.S. launch due to manufacturing concerns by the U.S. FDA means that it remains a drug to watch for 2024.

Part of a set of emerging therapies with novel mechanisms of action, it will contribute to the growing market share held by these therapies and potentially more efficacious and long-lasting treatment options for patients.

Why is it a drug to watch?

Results from the phase 3 VIVID-1 study (vs ustekinumab or placebo) with patients 15 to 80 years old with moderate to severe Crohn's disease will be used to support regulatory submissions. The study met the co-primary and all major secondary endpoints at week 52 compared with placebo:

- Co-primary endpoint: 45.4% of mirikizumab group (vs 19.6% of placebo group) achieved clinical response at 12 weeks and clinical remission at 52 weeks on the Crohn's Disease Activity Index (CDAI)
- Co-primary endpoint: 38.0% of mirikizumab group (vs 9.0% of placebo group) achieved clinical response at 12 weeks and endoscopic response at 52 weeks on the Simple Endoscopic Score — Crohn's Disease (SES-CD)

Ongoing phase 3 studies include:

- VIVID-2: long-term extension study to evaluate efficacy and safety
- AMAY: evaluating mirikizumab in pediatric participants (aged 2-17 years)

Positive results from the phase 3 LUCENT 1 induction study (vs placebo) with patients with moderate to severe ulcerative colitis were used to support the regulatory approvals. The study showed improvement as early as four weeks and, at 12 weeks, met its primary and all key secondary endpoints of:

- Clinical remission (64% of the mirikizumab group vs 43% of the placebo group)
- Clinical response (24% of the mirikizumab group vs 15% of the placebo group)
- Endoscopic remission
- Symptomatic remission
- Reduced bowel urgency
- Improvement in endoscopic histologic inflammation

Mirikizumab at a glance

Producers

Eli Lilly and Company

Type

Humanized IgG4
anti-human IL-23p19 mAb

Usage

Induction dose consisting of an intravenous infusion at weeks 0, 4 and 8, followed by maintenance doses every month by subcutaneous injection to treat Crohn's disease and moderately to severely active ulcerative colitis

Impact

Crohn's disease

~1.8M

diagnosed prevalent cases in the G7 markets in 2021

Ulcerative disease

~2.3M

diagnosed prevalent cases in the G7 markets in 2021

Review and approval status

Crohn's disease

Expected launch
– 2025: European Union, Japan, United States
– 2026: United Kingdom

Ulcerative colitis

March 2022
– BLA submission: U.S. FDA

March 2023
For adult patients with moderately to severely active ulcerative colitis not well controlled with standard therapy
– Approved: Japan PMDA

April 2023
For issues related to the proposed manufacturing
– CRL: U.S. FDA

May 2023
For adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to or were intolerant to either conventional therapy or a biologic treatment
– Approved: EMA

June 2023
For adult patients with moderately to severely active ulcerative colitis
– Approved: U.K. MHRA

October 2023
For adult patients with moderately to severely active ulcerative colitis
– Approved: U.S. FDA

Actual and expected launch
– 2023: European Union, Japan, United Kingdom, United States

Patents estimated to expire
– Beginning in 2034

The phase 3 LUCENT-2 study followed LUCENT-1 participants for one year and showed:

- Nearly two-thirds of participants maintained clinical remission at one year and nearly all participants with clinical remission at one year were not taking corticosteroids for at least three months prior to the end of maintenance treatment.
- These results were regardless of previous failure to TNF inhibitors, tofacitinib or other biologics.

Ongoing studies include:

- LUCENT-3: long-term extension study to evaluate efficacy and safety
- LUCENT-URGE: phase 3 study to evaluate the effect of mirikizumab on bowel urgency in patients with moderately to severely active ulcerative colitis
- SHINE-1: phase 2 study evaluating mirikizumab in pediatric participants (aged 2-17 years)

How will mirikizumab impact the market for Crohn's disease and ulcerative colitis

- Because treatments for Crohn's disease and ulcerative colitis vary significantly in potency, onset of action, side effect profile and route of administration, symptom severity and remission status contribute to drug selection.
- Growth in the market for both diseases is most likely driven by increasing uptake of ENTYVIO® and STELARA® and approval and uptake of premium-priced emerging therapies, including mirikizumab.
- Entry of the biosimilar ustekinumab could temper sales of competing therapies.
- Several novel agents, including mirikizumab, are launching for both diseases within the next couple of years, making competition fierce and the market increasingly fragmented.

Crohn's disease

- Mirikizumab is potentially the third IL-23 inhibitor launching for Crohn's disease.
- Emerging therapies, including mirikizumab, will most likely be used for patients refractory to TNF-βnhibitors or who have failed multiple biological agents.
- There is significant commercial opportunity to treat patients refractory to TNF-βnhibitors given they fail to achieve treatment goals in a large proportion of patients.

Ulcerative colitis

- Mirikizumab launched as first in its class for ulcerative colitis but is likely to be followed closely by two other IL-23 inhibitors, risankizumab (SKYRIZI®; AbbVie) and guselkemab (TREMFYA®; Janssen Pharmaceuticals, Inc., Johnson & Johnson Company).
- Targeted therapies, such as mirikizumab, are typically only used to treat moderate-to-severe disease.
- There is potential for approval in the pediatric population, which will expand the overall patient population, differentiate mirikizumab from other in-class competitors and help fill the gap in targeted therapies for this population.

"We do not have any head-to-head trial data for Mirikizumab. We need more cohorts and more experience with the drug to use it ahead of Stelara."

Gastroenterologist, United States

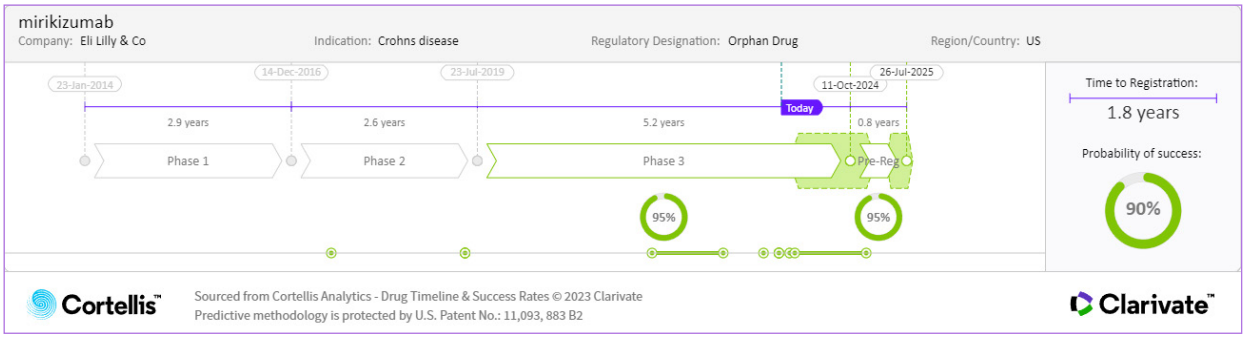
What gaps in treatment does mirikizumab fill?

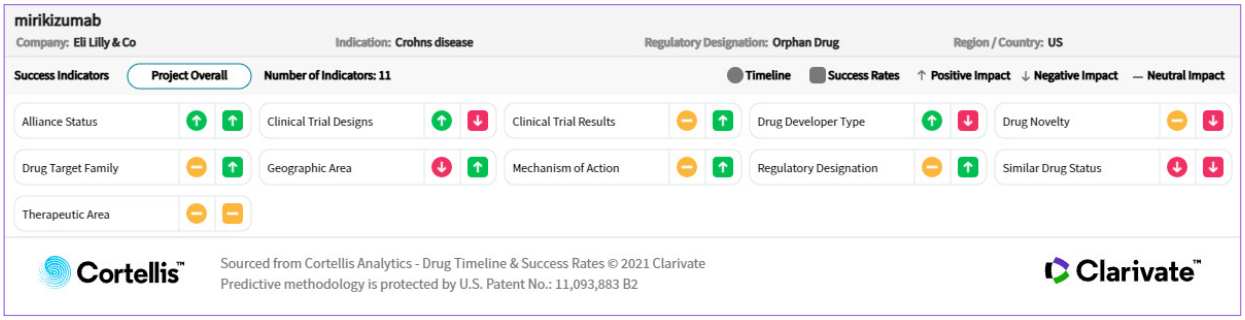
Both Crohn's disease and ulcerative colitis are characterized by intermittent disease courses, with acute flares followed by periods of remission. Patients risk hospitalization and the need for surgical intervention, in addition to experiencing poorer quality of life. Neither disease has a cure, so pharmacotherapy aims to induce remission of acute flairs, maintain remission (without corticosteroids) and improve quality of life. Mirikizumab has a favorable safety profile that will likely help uptake by physicians and patients, especially for a patient population with few effective long-term treatment options. Treatment gaps that mirikizumab could help fill include sustainable long-term remission (many patients lose response to biologics) and therapies with alternative mechanisms of action for patients intolerant or resistant to TNF-βnhibitors.

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

The later market entry of mirikizumab, after STELARA and other IL-23 inhibitors, for both Crohn's disease and ulcerative colitis, will likely restrain its uptake. Regarding STELARA, gastroenterologists will have had 7-9 years of clinical experience prescribing it and, at least initially, new IL-23 inhibitors are unlikely to steal significant patient share and could be used primarily as later-line therapies. In addition, the launch of biosimilar ustekinumab, which is expected in 2024, could encroach on the use of all IL-23 inhibitors. Mirikizumab will be one of many therapeutic options in an increasingly crowded space

Cortellis data indicate there is a 90% probability of success for Crohn's disease in the United States.





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

09. Niraparib + abiraterone acetate

AKEEGA™

This is the first and only dual action (or fixed-dose combination [FDC]) tablet combining a PARP inhibitor (niraparib) and a next-generation hormonal therapy (abiraterone acetate). Its ability to serve as a treatment for patients with deleterious or suspected deleterious BRCA-mutated, metastatic castration-resistant prostate cancer (mCRPC), should help to fulfill the need for more effective treatments. BRCA-positive mCPRC disease tends to be more aggressive; ~10-15% of patients with mCRPC harbor BRCA gene mutations.

The approvals in both the United States and European Union represent the third prostate cancer treatment by Johnson & Johnson Innovative Medicine to reach this milestone and highlight the importance of reliable predictive biomarkers for precision treatment of patients. In August 2023, Foundation Medicine Inc received approval from the U.S. FDA for FoundationOne®CDx to be used as a companion diagnostic for niraparib + abiraterone acetate.

Why is it a drug to watch?

The development of niraparib + abiraterone acetate used an inventive and smart life cycle management strategy (especially considering generics are available for abiraterone). It has a competitive edge given the very good efficacy as well as the positive physician opinion and desire to prescribe it. As an FDC in a single tablet, it is a convenient alternative.

U.S. FDA and EMA approvals were based on the results of a large phase 3 clinical trial (MAGNITUDE) conducted with patients with mCRPC (with or without homologous recombination repair [HRR]-associated gene alterations) who received niraparib + abiraterone acetate plus prednisone, whose outcomes were compared with those of patients who received placebo + abiraterone plus prednisone.

The findings included the following:

- Median radiographic progression free survival (rPFS) in the BRCA1/2 subgroup of 19.5 months (vs 10.9 months with placebo + abiraterone)
- Median rPFS in the full HRR+ cohort of 16.7 months (vs 13.7 months with placebo + abiraterone)
- Manageable safety profile, with no new safety signals that affected the benefit-risk profile

The results also highlighted the importance of testing for HRR status before initiating niraparib + abiraterone acetate to identify who will gain the most benefit from the therapy and to balance with the potential additional toxicity of combination therapy.

New frontiers in medicine

A leap forward in the treatment of an aggressive prostate cancer

Niraparib + abiraterone acetate at a glance

Producers

Johnson & Johnson Innovative Medicine

Type

PARP inhibitor and hormone therapy

Usage

Once daily oral administration in combination with prednisone or prednisolone to treat BRCA-positive mCRPC

Also being evaluated for metastatic, hormone-sensitive prostate cancer (mHSPC) with HRR gene mutations

Impact

~76K
new cases of previously untreated mCRPC

~110K
new cases of rmHSPC in the G7 markets in 2023

Review and approval status

April 2022
– MAA filed: EMA

Febrary 2023
– NDA filed: U.S. FDA

April 2023
For patients with BRCA-positive mCRPC, to be used in combination with prednisone
– Approved: EMA

August 2023
For patients with deleterious or suspected deleterious BRCA-positive mCRPC, as detected by an FDA-approved test
– Approved: U.S. FDA

Actual and expected launch
– 2023: European Union, United States

How will niraparib + abiraterone acetate impact the market for prostate cancer?

- Hormonal therapy is the cornerstone of drug treatment in all patient populations and will remain the dominant drug class, including novel hormonal therapies (e.g., abiraterone, enzalutamide) expecting to hold approximately 50% of the total prostate cancer market by 2032.
- However, treatment is becoming increasingly diversified with the approval of novel targeted agents such as PARP inhibitors and prostate-specific membrane antigen (PSMA)-targeted radioligands.
- The late-phase pipeline spans a wide range of drug classes and novel therapies (e.g., PARP inhibitors, kinase inhibitors, PSMA-targeted radioligands, angiogenesis inhibitors).
- Niraparib + abiraterone acetate will be the sales-leading emerging agent, earning major-market sales of $2.9 billion in 2032. Due to long treatment durations and the premium price of niraparib + abiraterone acetate, 75% of those sales will come from the mHSPC setting.
- Although other PARP inhibitor + hormonal therapy combinations (e.g., Lynparza + abiraterone from AstraZeneca and MSD) are available, they are "open" combinations (i.e., two drugs administered as separate tablets with different dosing schedules).

What gaps in treatment does niraparib + abiraterone acetate fill?

When treated with current standard of care, mCRPC remains an incurable disease, and patients with BRCA-positive mCRPC are more likely to have aggressive disease, experience poor outcomes and have shorter survival times. Drugs with novel MOAs are needed to provide more effective treatment options. PARP inhibitors have the potential to partially satisfy this unmet need, and targeted therapies with predictive biomarkers will help ensure that patients are matched to the most effective MOA. Compared with earlier-to-market PARP + hormonal agent combinations for this molecularly defined subset of patients, niraparib + abiraterone acetate provides a convenient dosing schedule (once-daily dose).

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

Niraparib + abiraterone acetate is likely to face stiff competition from other PARP inhibitor and hormone therapy combinations. Lynparza in combination with abiraterone acetate has the first-to-market advantage in the first line mCRPC with BRCA mutation segment. Lynparza also has greater physician familiarity due to its earlier approval as monotherapy in later-line settings. Another competitor, TALZENNA® (Pfizer Inc) in combination with XTANDI® (Pfizer Inc and Astellas Pharma Inc), has a broader label that also extends to patients with other HRR mutations. Additionally, some oncologists will prefer the dosing flexibility and cost saving offered by "open combinations" over FDCs.

Market overview

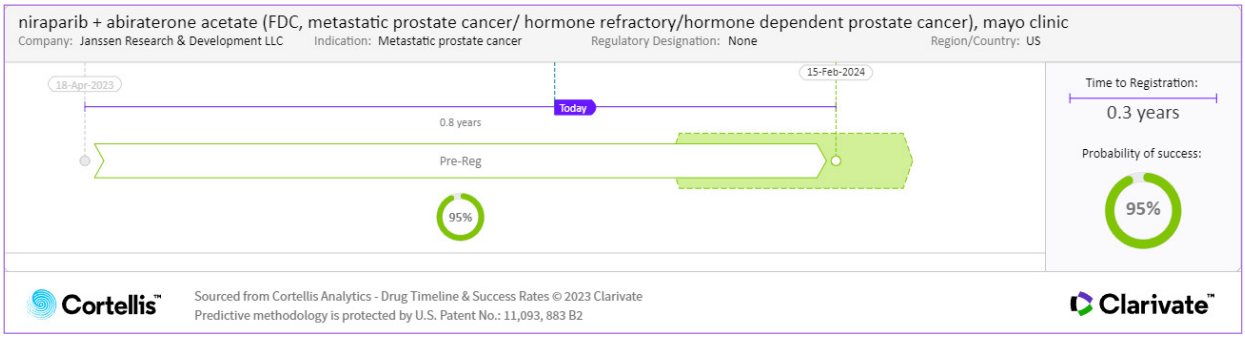
$2.7B

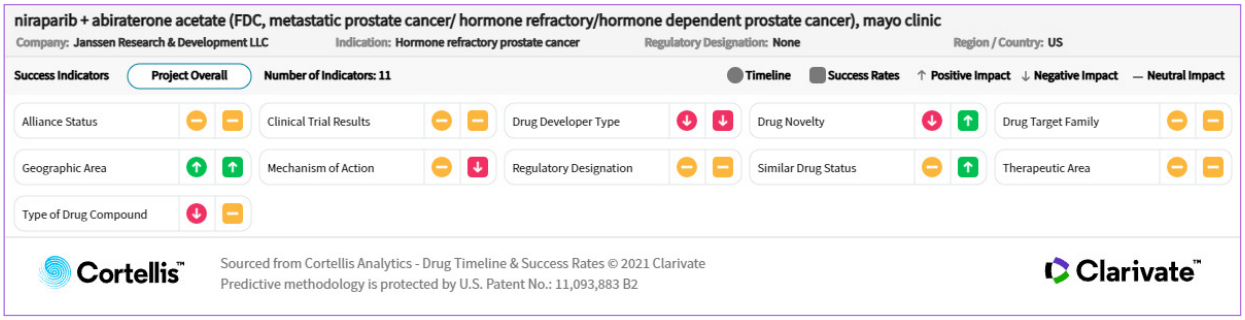
expected sales in 2029

"Novel hormone therapy plus a PARP inhibitor is the right way going forward for patients with BRCA mutations. A combination tablet is more convenient because you're looking at a group of patients who are often on a lot of other medications as well. A fixed-dose combination will simplify their medication."

Medical Oncologist, United Kingdom

Cortellis data indicate there is a 95% probability of success for niraparib + abiraterone acetate in the United States.





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

10/11. RSVpreF and RSVpreF3

ABRYSVO™/ PF-06928316
and AREXVY/ GSK-3844766A

Respiratory syncytial virus (RSV) infections continue to be a public health concern, particularly for infants and older adults (65 years and older). A common upper respiratory infection that can result in hospitalizations in severe cases, RSV infection tends to be seasonal and present with symptoms similar to those of influenza and COVID-19.

The occurrence of all three infectious diseases at the same time of year contributes to what public health experts call a "triple-demic," with an associated increase in healthcare burden particularly for the most vulnerable groups. The first approvals of RSV vaccines (RSVpreF and RSVpreF3) targeted at infants and older adults mark a significant public health milestone.

Why is it a drug to watch?

The phase 3 results for both vaccines validate 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. In addition, these results bode well for the phase 3 trial results of other assets in late-stage development, which will help support the public health initiative to reduce the RSV-related disease burden.

RSVPreF (ABRYSVO)

The regulatory approvals for use with pregnant individuals were based on the data from the pivotal phase 3 MATISSE (MATernal Immunization Study for Safety and Efficacy) trial that followed infants for up to 2 years:

- 81.8% vaccine efficacy at 90 days after birth
- 69.4% vaccine efficacy at 180 days after birth

For use with older adults, the regulatory approvals were based on data from the phase 3 RENOIR study, during which participants were followed for the RSV season as defined for the region:

- 66.7% vaccine efficacy when RSV-LRTD was defined by two or more symptoms
- 85.7% vaccine efficacy when RSV-LRTD was defined by three or more symptoms

The approval in the United States was followed by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) official recommendation in June 2023 for the use of the vaccine in adults 60 years of age and older and in September 2023 for the use of the vaccine in pregnant individuals at 32 through 36 weeks gestational age.

ABRYSVO at a glance

Producers

Pfizer Inc

Type

Recombinant bivalent RSV prefusion F (RSVpreF)

Usage

Single-dose, 0.5-mL intramuscular injection for active immunization:

- To prevent lower respiratory tract disease (LRTD) caused by RSV in individuals ≥60 years old
- For pregnant individuals (32-36 weeks gestational age) to prevent LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age

Impact

1.2%

Projected vaccine-eligible pediatric population in the U.S. in 2025

2.3%

Vaccine-eligible adults in the U.S. in 2023

Review and approval status

July 2020
- Fast Track designation: U.S. FDA

March 2022
- Breakthrough therapy designation: U.S. FDA

April 2023
- Application accepted: Health Canada

For the prevention of LRTD caused by RSV in individuals 60 years of age or older

May 2023
- Approved: U.S. FDA

August 2023
- Approved: EMA

For pregnant individuals (32-36 weeks gestational age) to prevent LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age

August 2023
- Approved: U.S. FDA, EMA

Actual and expected launch
- 2023: European Union, United States

AREXVY at a glance

Producers

GSK plc

Type

Recombinant subunit RSVPreF glycoprotein antigen combined with GSK's proprietary AS01E adjuvant

Usage

Single-dose, 0.5-mL intramuscular injection for active immunization to prevent LRTD caused by RSV in individuals ≥60 years old

Impact

12

per 1,000: RSV maternal and pediatric-eligible population in the U.S.

Review and approval status

February 2020
– Fast Track designation: U.S. FDA

For the prevention of LRTD caused by RSV in individuals 60 years of age and older

May 2023
– Approved: U.S. FDA

June 2023
– Approved: EMA

July 2023
– Approved: U.K. MHRA

August 2023
– Approved: Health Canada

September 2023
– Approved: Japan PMDA

Actual and expected launch
– 2023: Canada, European Union, Japan, United Kingdom, United States

RSVPreF3 (AREXVY)

The regulatory approvals for use with older adults were based on data from the pivotal phase 3 AReSVi-006 (Adult Respiratory Syncytial Virus) trial:

- 82.6% vaccine efficacy against RSV-LRTD
- 94.6% vaccine efficacy against RSV-LRTD in older adults with at least one underlying medical condition of interest, such as certain cardiorespiratory and endocrine-metabolic conditions
- 94.1% vaccine efficacy against severe RSV-LRTD, defined as an RSV-associated LRTD episode preventing normal, everyday activities

Preliminary results from the phase 3 clinical trial evaluating AREXVY for adults aged 50 to 59 years were published in October 2023, showing that the vaccine elicited an immune response in that study population that was non-inferior to that observed in adults aged 60 years and older.

$10B

potential market value for RSV vaccines and prophylaxis in the next five years.

How will these vaccines impact the RSV market?

- As the first vaccine entries into an area of great unmet need, ABRYSVO and AREXVY have a competitive advantage. However, the landscape looks to become increasingly crowded, and within five years, the RSV vaccine and prophylaxis market could reach $10 billion.
- ABRYSVO has the advantage of a broader population that includes both older adults and pregnant individuals.
- AREXVY has gained approval in more of the major markets than ABRYSVO.
- Beyfortus™ (nirsevimab-alip; Sanofi, AstraZeneca), an MAb, is the only approved asset against RSV for children up to 2 years old (U.S. and E.U.) and offers greater flexibility in dosing than the vaccines.
- Other candidates in clinical development include the following:
  - ADV-110 (Beijing Advaccine Biotechnology Co Ltd): Recombinant protein vaccine for RSV
  - BLB-201 (Blue Lake Biotechnology and CyanVac LLC): Recombinant viral vector vaccine for RSV
  - CodaVax-RSV (Codagenix Inc): aLive-attenuated viral vaccine for RSV
  - D46/NS2/N/deltaM2-2-Hindill (NIAID): Recombinant viral vector vaccine for RSV
  - DS-Cav1 (NIAID): Protein subunit vaccine for RSV
  - ITV-RSV-DeltaG (Intravacc): Live-attenuated viral vaccine for RSV

- IVX-A12 (Icosavax): Virus-like particle and protein subunit vaccine for human metapneumovirus and RSV
- MV-012-968 (Meissa Vaccines): Live-attenuated vaccine for RSV
- MVA-BN RSV (Bavarian Nordic): Recombinant viral vector vaccine for RSV
- mRNA-1045 (Moderna Inc): mRNA vaccine for influenza and RSV
- mRNA-1172 (Moderna Inc and Merck): Modified mRNA-based vaccine for RSV
- mRNA-1230 (Moderna Inc): mRNA vaccine for SARS-CoV2, influenza and RSV
- mRNA-1345 (Moderna Inc): RNA vaccine for RSV
- RSV 6120/deltaNS2/1030s (NIAID): cLive-attenuated viral vaccine for RSV
- RSV-276 (NIAID): Live-attenuated viral vaccine for RSV
- RSV-F (Novavax): Protein subunit vaccine for RSV
- RSVdeltaNS2/delta1313/1314L (NIAID): 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.

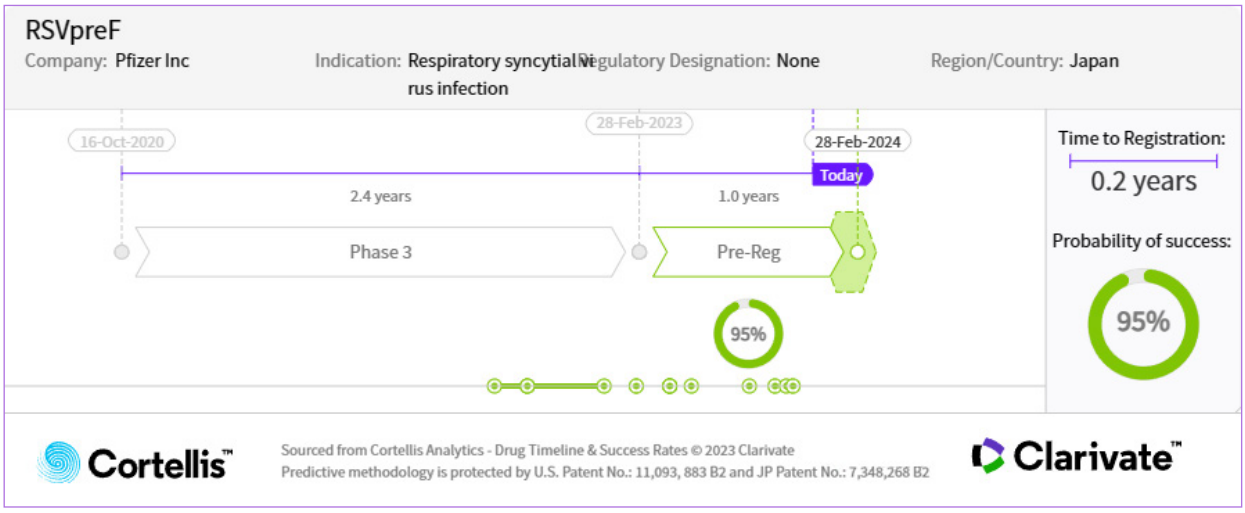
What gaps in care do these vaccines fill?

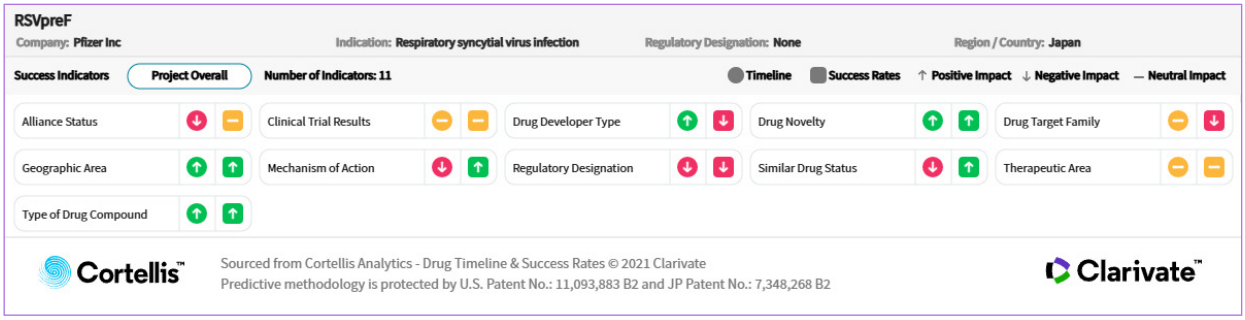
The search for an effective vaccine against RSV, a common, contagious virus, began in the mid-1960s but remained unsuccessful until the 2010s when focus shifted to the RSV F protein. Seasonal hospitalizations due to serious respiratory illness caused by RSV continue to be a public health issue, particularly 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 at times when other infectious disease outbreaks are prevalent.

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

Although these two vaccines were the first approved, other vaccines are in late-stage development, and Beyfortus has also been approved for use in this setting. In addition to this competition, the lag in insurance coverage in the United States during the first season in which the vaccines are available and lingering vaccine hesitancy from the COVID-19 pandemic could limit uptake.

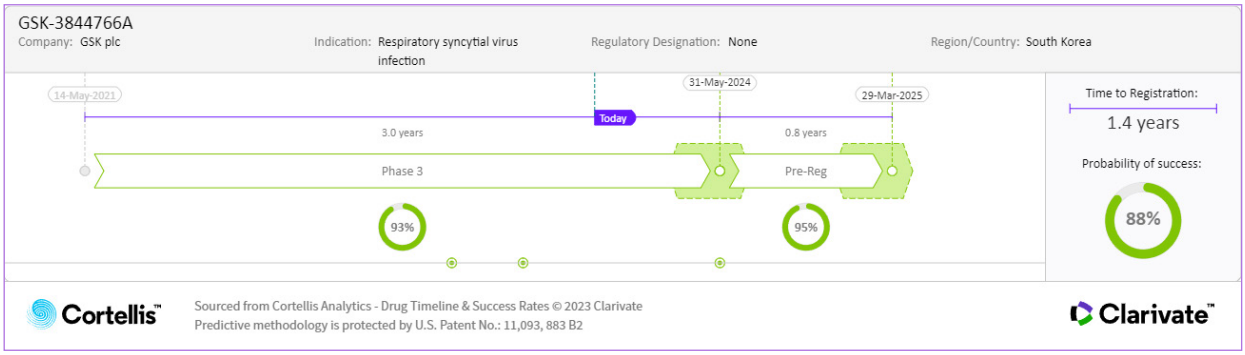
Cortellis data indicate there is a 95% probability of success for ABRYSVO in Japan.

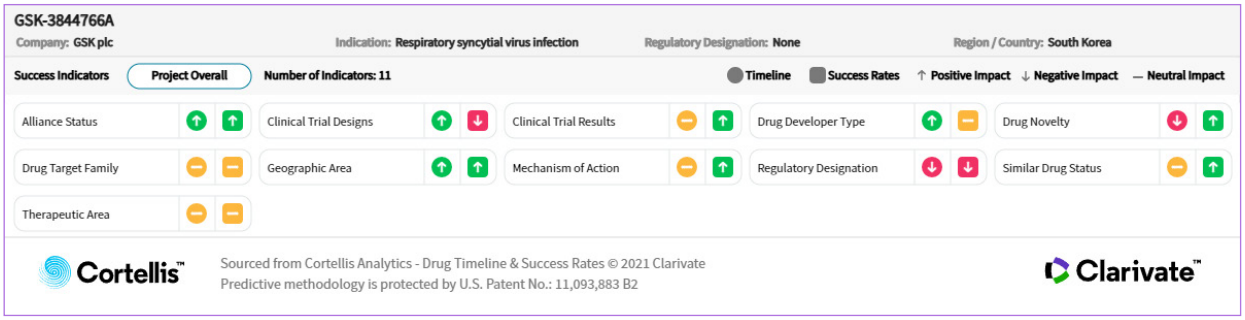




Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

Cortellis data indicate there is an 88% probability of success for AREXVY in South Korea.





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

Drugs to Watch 2024

12. Talquetamab

TALVEY™

After receiving conditional and accelerated approval from the EC and FDA, respectively, talquetamab became the first-in-class bispecific antibody targeted to CD3 and GPRC5D to treat multiple myeloma.

It was approved based on the pivotal phase 1/2 MonumenTAL-1 trial for heavily pretreated patients with relapsed or refractory (R/R) multiple myeloma. Ongoing phase 3 trials are expected to provide confirmation of clinical benefit in talquetamab's approved setting and lead to label expansions in other multiple myeloma patient populations, including in combination with other approved agents (such as DARZALEX®, Johnson & Johnson Innovative Medicine). Talquetamab is poised as an important addition to the treatment armamentarium for this incurable, often-relapsing disease.

Why is it a drug to watch?

With the approval of talquetamab, Johnson & Johnson Innovative Medicine adds to its portfolio dedicated to addressing unmet needs for patients with multiple myeloma, with five innovative therapies including two bispecific antibodies. Talquetamab is an off-the-shelf, first-in-class, T-cell engaging, bispecific antibody targeted to CD3 and GPRC5D that is being investigated to treat multiple myeloma.

Positive results have been reported from the pivotal phase 1/2 MonumenTAL-1 study conducted with patients who had previously received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. One-third of patients also received prior BCMA-targeted therapy. The study results showed the following:

- Biweekly dose after a median follow-up of nearly six months from first response:
  - 73.6% overall response rate (ORR)
  - 58% very good partial response (VGPR) rate and 33% complete response (CR) rate
  - ~85% of responders maintained response for at least nine months
- Weekly dose after a median follow-up of nearly 14 months from first response:
  - 73.0% overall response rate (ORR)
  - 57% very good partial response (VGPR) rate and 35% complete response (CR) rate
  - Median duration of response (DOR) of 9.5 months

New frontiers in medicine

A ground-breaking bispecific antibody for multiple myeloma

Talquetamab at a glance

Producers

Johnson & Johnson Innovative Medicine

Type

Bispecific antibody targeted to CD3 and GPRC5D

Usage

Weekly or biweekly subcutaneous administration to treat R/R multiple myeloma

Impact

~105K

R/R cases in the G7 markets in 2023

Review and approval status

January 2021
- PRIME designation: EMA

May 2021
- Orphan drug designation: U.S. FDA

August 2021
- Orphan drug designation: EMA

June 2022
- Approved: U.S. FD

August 2023
- Breakthrough therapy designation: U.S. FDA

August 2023
For patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 mAb
- Accelerated approval: U.S. FDA

For patients with relapsed or refractory multiple myeloma who had received at least three prior therapies including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb and had demonstrated disease progression on the last therapy
- CMA: EMA

Actual and expected launch
- 2023: European Union, United States
- 2025: Japan

Patents estimated to expire
- Beginning in 2037

MonumenTAL-3 is an ongoing phase 3 clinical trial evaluating talquetamab plus daratumumab with or without pomalidomide plus dexamethasone (compared with daratumumab plus pomalidomide and dexamethasone) in R/R multiple myeloma after at least one prior line of therapy.

How will talquetamab impact the market for multiple myeloma?

Multiple myeloma is one of the largest therapy markets in oncology owing to treatment being dominated by combination regimens comprising premium-priced small molecule and biologic drugs. High treatment rates, many potential lines of treatment for R/R disease and long treatment durations for some regimens drive the large size of this market.

- The multiple myeloma market is expected to experience 5.9% annual growth in the major markets over the 2022-2032 period, driven by label expansions of currently approved therapies in combination with existing standards of care.
- Bispecific antibodies will reach major-market sales of $6.9 billion by 2032.
- Compared with the BCMA-directed bispecific T-cell engagers TECVAYLI™ (teclistamab; Johnson & Johnson Innovative Medicine) and ELREXFIO™ (elranatamab; Pfizer), talquetamab targets GPRC5D, providing an effective treatment option for patients who progressed on a prior BCMA-based treatment. Further, talquetamab has a more flexible dosing advantage than TECVAYLI.
- Expected label expansions for bispecific antibodies, including talquetamab, in combination with DARZALEX, with or without lenalidomide plus dexamethasone, will contribute nearly $4.5 billion in sales by 2032.
- As a subcutaneous-administered, off-the-shelf product, talquetamab is positioned at a competitive advantage over current and emerging CAR T-cell therapies in the R/R setting.
- Talquetamab has shown activity in patients with and without prior exposure to BCMA-targeted therapies (e.g., CARVYKTI™ [Johnson & Johnson Innovative Medicine and Legend Biotech] and TECVAYLI); therefore, patients who have received prior BCMA-targeted therapies are not precluded from being eligible for talquetamab.

What gaps in treatment does talquetamab fill?

A large proportion of patients with multiple myeloma relapse and requires subsequent therapy. In addition, remissions become shorter as the disease progresses with each new line of therapy. Talquetamab has been approved to treat patients in this difficult-to-treat setting where most, if not all, treatment options have been exhausted, helping to fill a remaining unmet need for more efficacious therapies. As an off-the-shelf product, it also has an advantage over patient-specific CAR T-cell therapies, and it provides an option for patients who have progressed on an anti-BCMA therapy.

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

Uptake could be hampered by the black box label for life-threatening or fatal cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity (ICANS). Therefore, talquetamab is only available via the TECVAYLI and TALVEY Risk Evaluation and Mitigation Strategy (REMS), in which prescribers must be certified. In addition, it may face stiff competition from other bispecific therapies.

Market overview

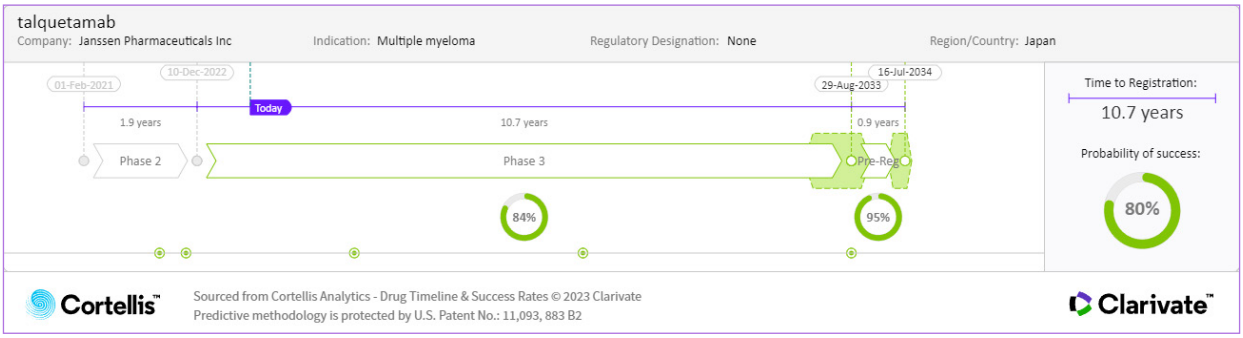
$850M

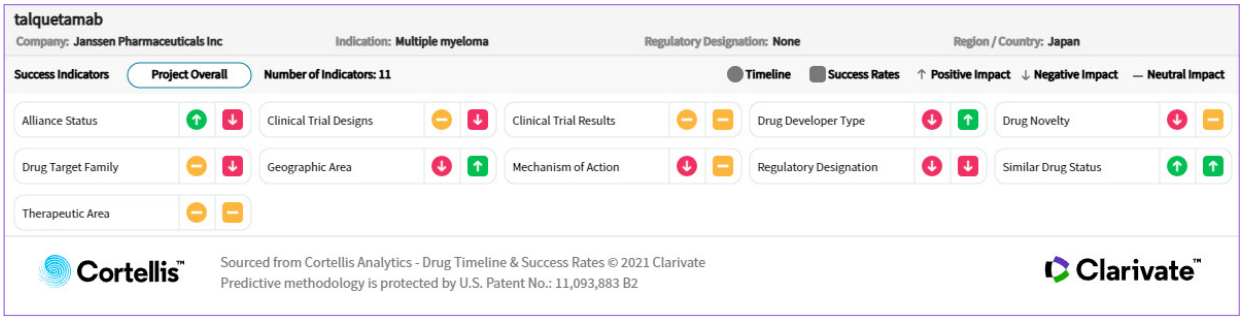
expected sales in 2029

"I'm really excited about talquetamab, and it's key it's targeting GPRC5D and not BCMA. Talquetamab data look strong, including inpatients who previously have been treated with BCMA therapies. However, we all will need to learn how to support our patients through some of the unique toxicities that talquetamab has, particularly the taste changes, to make sure that we can get this very effective therapy into patients without detrimentally affecting their quality of life."

Hematologist-oncologist, United States

Cortellis data indicate there is an 80% probability of success for Talquetamab in Japan.





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

13. Zolbetuximab

IMAB362

Metastatic HER2-negative gastric and gastroesophageal junction (GEJ) adenocarcinoma is notoriously difficult to treat and has a significant unmet need for new efficacious treatments.

In contrast to HER2-positive disease (for which HER2-targetxed agents such as trastuzumab [Genentech] and ENHERTU® [Daiichi Sankyo] are available), targeted treatment options are more limited for HER2-negative patients.

Zolbetuximab would address some of that unmet need as a first-in-class claudin 18.2 (CLDN18.2) inhibitor in oncology as well as first-line metastatic HER2-negative gastric or GEJ adenocarcinoma. CLDN18.2 was found to be highly expressed in ~38% of HER2-negative gastric cancer patients in two phase 3 trials (SPOTLIGHT and GLOW). Zolbetuximab also has the potential to treat pancreatic cancer, in which 50% of cases have CLDN18.2 expression.

Why is it a drug to watch?

Claudin 18.2 (CLDN18.2) has emerged as an exciting target to treat gastric cancers because alterations in claudin expression can affect signaling pathways and help promote tumors. Zolbetuximab is poised to be the first-in-class CLDN18.2 inhibitor to enter the oncology market and to offer a much-needed biomarker-driven option for first-line treatment of metastatic HER2-negative gastric or GEJ adenocarcinoma. Regulatory submissions were based on the positive results from two phase 3 trials conducted in previously untreated CLDN18.2-positive, HER2-negative, unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma:

- SPOTLIGHT: first-line zolbetuximab plus mFOLFOX6 (combination chemotherapy with oxaliplatin, leucovorin and fluorouracil) vs placebo plus mFOLFOX6
  - 24.9% reduction in the risk of progression or death (vs control)
  - Median progression-free survival (PFS) of 10.6 months (vs 8.7 months with control)
  - 25.0% reduction in the risk of death (vs control)
  - Median overall survival (OS) of 18.2 months (vs 15.5 months with control)
- GLOW: first-line zolbetuximab plus CAPOX (combination chemotherapy with capecitabine and oxaliplatin) vs placebo plus CAPOX
  - 31.3% reduction in the risk of progression or death (vs control)
  - Median PFS of 8.2 months (vs 6.8 months with control)
  - 22.9% reduction in the risk of death (vs control)
  - Median OS of 14.4 months (vs 12.2 months with control)

The incidence of serious treatment-emergent adverse events (TEAEs) in both studies was similar between the groups and consistent with previous studies.

New frontiers in medicine

Promise for difficult-to-treat cancers

Zolbetuximab at a glance

Producers

Astellas Pharma Inc

Type

CLDN18.2-targeted mAb

Usage

Intravenous infusion every three weeks to treat HER2-negative, CLDN18.2-positive unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma

Also being investigated to treat pancreatic cancer

Impact

~88K

new cases of previously untreated metastatic HER2-negative gastric or GEJ adenocarcinoma in the G7 markets in 2023

Review and approval status

November 2010
- Orphan drug designation: EMA

November 2012
- Orphan drug designation: U.S. FDA

September 2022
- Fast Track designation: U.S. FDA

June 2023
- MAA accepted: EMA
- BLA filed: Japan PMDA

July 2023
- Priority Review granted: U.S. FDA
- BLA accepted: Mainland China NMPA

January 12, 2024
- PDUFA date

Expected launch
- 2024: United States

Patents estimated to expire
- Beginning in 2032

How will zolbetuximab impact the market for gastric and GEJ adenocarcinomas?

- There are approximately one million new cases of gastric cancer diagnosed annually worldwide, representing a sizable market.
- Approximately 75% of all gastric cancer diagnoses are in Asia, and Japan is a significant market in this setting.
- The treatment of gastric cancer remains largely dominated by non-targeted therapies, and platinum/fluoropyrimidine-based chemotherapy regimens remain the standard of care.
- The first-line metastatic HER2-negative gastric and GEJ adenocarcinoma drug-treatable patient population is the largest in gastroesophageal cancer, yet HER2-negative patients have fewer treatment options than their HER2-positive counterparts. Therefore, a large commercial opportunity exists for novel agents in the HER2-negative setting.
- Zolbetuximab is being evaluated in combination with chemotherapies already commonly used in gastric and GEJ cancer (mFOLFOX6, CAPOX). The demonstration of clear and unequivocal (albeit numerically modest) OS improvements over chemotherapy alone in the two phase 3 trials would likely support rapid uptake for appropriate patients.
- Immunohistochemistry testing for CLDN18.2 will be needed to treat with zolbetuximab, but ~38% of gastric cancer patients could be eligible, which would translate into a sizeable market opportunity.

What gaps in treatment does zolbetuximab fill?

Early-stage gastric cancer symptoms frequently overlap with more common stomach-related conditions. As result, gastric cancer is often diagnosed in the advanced or metastatic stage when it has spread to other body tissues or organs. The five-year relative survival rate for patients at the metastatic stage is 6.6%. Despite approvals of targeted therapies and immunotherapies, improving survival in gastric cancer remains a critical unmet need as few patients survive more than 2 years after initiation of front-line therapy. In addition, metastatic HER2-negative gastric or GEJ adenocarcinoma is notoriously difficult to treat. CLDN18.2 has emerged as a promising target for treating gastric cancers, and zolbetuximab could be an important new option in the largely untapped HER2-negative gastric and GEJ adenocarcinoma market segment.

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

- The uptake of zolbetuximab will hinge upon wide adoption of CLDN18.2 testing, a biomarker that is not yet integral to diagnostic workups, in routine clinical practice. Increased awareness and education on CLDN18.2 testing will help mitigate this risk.
- Several other therapies targeting CLDN18.2 are in clinical development, a few of which were acquired in blockbuster deals. Some of these candidates offer a different modality than mAbs like zolbetuximab, such as antibody-drug conjugates or bispecific agents. If approved, these therapies would be unwelcome competitors for zolbetuximab:
  - TST-001 (osemitamab; Transcenta Therapeutics Co Ltd)
  - ASKB-589 (AskGene Pharma Inc)
  - CMG901 (AstraZeneca)
  - SYSA-1801 (EO-3021; Elevation Oncology Inc)
  - TJ-CD4B (ABL111; I-Mab)
  - TPX-4589 (LM-302; Turning Point Therapeutics)

Market overview

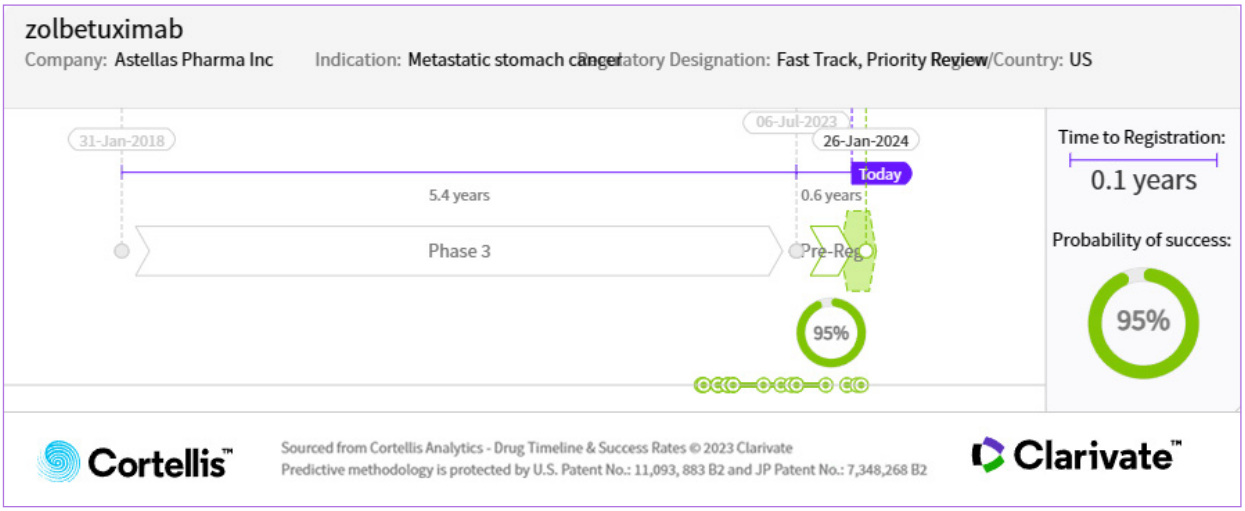
$1.14B

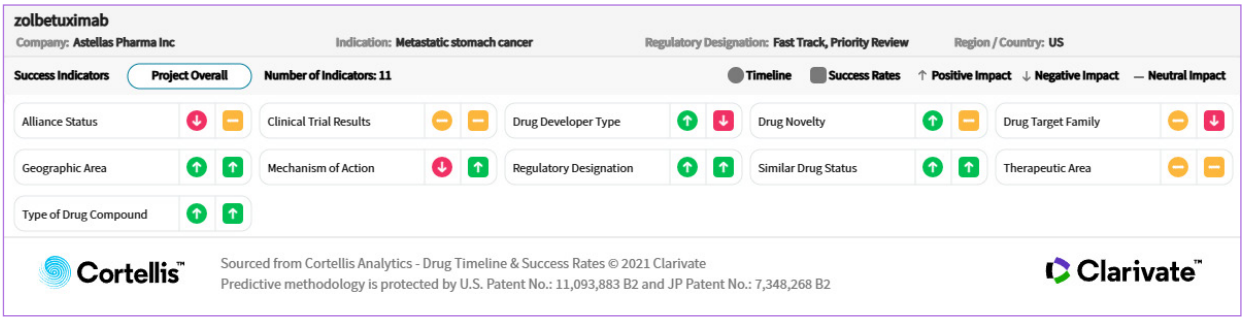
expected sales in G7 countries for 2029

"The zolbetuximab data are the best I've seen over the last years for gastric cancer, because there's a substantial unmet need for HER2-negative patients. Testing for claudin 18.2 will become standard and we will be able to improve response and survival outcomes in this patient population."

Medical Oncologist, Italy

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





Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rates Prediction current as of November 3, 2023

Drugs to Watch 2024

The growing chronic disease market in Mainland China

We identified seven drugs, including both global and domestically manufactured assets, that are likely to achieve the traditional $1 billion blockbuster status by 2029 or to have a significant impact for patients in Mainland China.

Including a Mainland China approach within the market plan can extend revenue-generating opportunities due to large patient populations and the high unmet need for better treatment options for both acute and chronic conditions. The majority of this year's selected drugs target non-communicable diseases, a focus of the Healthy China 2030 initiative.

→ The growing chronic disease market in Mainland China

Drug	Company(s)	Indication	Initial U.S. approval	Initial European approval	Initial approval In Mainland China	2022 global sales ($M)	Expected 2029 sales in Mainland China ($M)	Expected patent expiry in Mainland China	Why it's a Drug to Watch
Cadonilimab (开坦尼®/ AK104)	Akeso Inc	Cervical cancer	N/A	N/A	2022	546	400-500		First-in-class PD-1/ CTLA-4 bispecific antibody approved for relapsed or metastatic cervical cancer (R/M CC) patients who progressed on or after platinum-based chemotherapy; potential to address the unmet need for safer immune checkpoint inhibitor (ICI) combinations; blocks two targets and can be used in lower doses; label expansion actively sought for hepatocellular carcinoma (HCC; Phase 3) and gastric cancer (Phase 3); also in Phase 2 development for NSCLC
Dupilumab (DUPIXENT®)	Sanofi and Regeneron Pharma Inc	Atopic dermatitis (AD)	2019	2017	2020	8,900	1,500	2029	IL-4/IL-13 receptor agonist; first-to-market biologic with an impressive clinical profile; will be available to a highly underserved moderate-to-severe AD patient population in Mainland China; approved across age groups including adults, adolescents and children aged 6 years and older; also has regulatory approvals in one or more countries globally for asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis and prurigo nodularis

| Cont'd ▼ |

Drug	Company(s)	Indication	Initial U.S. approval	Initial European approval	Initial approval In Mainland China	2022 global sales ($M)	Expected 2029 sales in Mainland China ($M)	Expected patent expiry in Mainland China	Why it's a Drug to Watch
Rimegepant (Nurtec® ODT /VYDURA®)	Pfizer Inc	Migraine	2020	2022	2023	213	300–350		CGRP receptor antagonist; first and only antimigraine therapy with dual efficacy in both the acute and prophylactic settings; considering the long-standing unmet need for more effective treatment options for migraineurs in Mainland China, made available in the Lecheng pilot zone in April 2023; formal approval anticipated in 2024
Semaglutide (Ozempic®/ Wegovy®)	Novo Nordisk	Type 2 diabetes mellitus (T2DM)/ obesity	2017/ 2021	2018/ 2022	2021	9,500 (both Ozempic and Wegovy)	1,000 (both Ozempic and Wegovy)	2026	GLP-1 receptor agonist; more convenient dosing combined with a superior clinical profile compared with other GLP-1s — major contributor to semaglutide's success in T2DM; further boost for value proposition in Mainland China expected from the anticipated label expansion in obesity and NASH
Tenofovir amibufenamide (Hengmu®)	Hansoh Pharma	Chronic hepatitis B virus (HBV) infection	N/A	N/A	2021	?	500		Nucleotide reverse transcriptase inhibitor and first second-generation oral anti-HBV drug developed in Mainland China; suitable treatment option for HBV patients who are resistant to first- and second-generation tenofovir drugs; likely to address the large burden of HBV in Mainland China; despite being the latter entrant in this segment, likely to register a modest uptake in this market, owing to its recent inclusion in the NRDL and strong clinical profile compared with traditional nucleoside analogue therapies
Tirzepatide (Mounjaro®)	Eli Lilly & Co	Type 2 diabetes mellitus (T2DM) and obesity	2022	2022	Expected in 2024	483	700		First-of-its-kind dual GLP-1/GIP receptor agonist; per clinical data available to date, higher weight loss with tirzepatide than with semaglutide; considering the sheer size of the patient population and anticipated growth in drug treatment rates in obesity, likely to garner substantial commercial value in the next five years
Upadacitinib (RINVOQ®)	AbbVie	AD and rheumatoid arthritis (RA)	2019	2020	2022	2,522	500-550		Highly selective oral JAK1 inhibitor; superior efficacy compared with other competing JAK inhibitors and patient share–leading biologics including HUMIRA® (RA) and DUPIXENT (AD); also has regulatory approvals in one or more countries globally for psoriatic arthritis, ankylosing spondylitis, axial spondyloarthropathy and ulcerative colitis

Drugs to Watch 2024

Trends to watch

AI/gene editing

Gene editing and AI/ML have arrived. Gene editing and artificial intelligence (AI)/machine learning (ML) are poised to have a significant impact on the biopharma industry's ability to create innovative medicines in 2024.

With the first approvals of a medicine designed using the CRISPR-Cas9 gene-editing platform, all eyes will be on how pharma companies look to use it and other gene-editing approaches to enable the development of highly targeted therapies, improve the drug discovery process and offer new avenues for treating previously untreatable diseases.

500+

AI/ML-related clinical trials were conducted in 2022.

Gene editing has the potential to streamline the drug discovery process by enabling researchers to create more accurate disease models. Pharmaceutical companies will be able to design drugs that directly address the underlying genetic causes of diseases, potentially leading to more effective and personalized treatments while minimizing off-target effects and so improving the safety profile of drugs.

Pharma companies looking to harness gene editing will, however, need to strategically manage their intellectual property portfolios to ensure they have the freedom to operate and stay competitive in the rapidly evolving landscape. Moreover, concerns about accessibility and affordability of therapies developed using gene editing technologies will need to be addressed.

Similarly, AI and ML are poised to have a transformative impact on pharma in various ways. AI and ML algorithms can analyze biological and genetic data to identify potential drug targets more efficiently and create personalized treatment options based on an individual's genetic makeup. AI/ML can also help identify existing drugs that may be repurposed for new therapeutic indications, saving time and resources, as well as predict the success or failure of drug candidates by reviewing complex datasets, leading to more informed decision-making. The first drug candidates designed using AI/ML tools are already in phase 2 testing.

There is already a strong body of evidence highlighting AI/ML's power to help healthcare professionals make more accurate and timely decisions, especially helping in medical imaging interpretation, helping to identify and diagnose diseases more accurately. Moreover, AI will have an increasing role in analyzing large volumes of data to detect and predict adverse events associated with drugs, improving patient safety, as well as identifying potential safety signals from diverse data sources, facilitating early intervention and risk mitigation.

Beyond discovery and development, AI/ML also has a role in clinical trial optimization efforts as well as improving supply chain management. AI/ML can be used to improve patient recruitment for clinical trials by identifying suitable candidates based on specific criteria, thus accelerating the trial process, while ML algorithms can review clinical trial data in real time, detecting patterns or potential issues that might not be apparent through traditional methods. AI can be used to optimize manufacturing processes, leading to improved efficiency, reduced costs and better quality control, while ML algorithms can enhance supply chain efficiency by predicting demand, optimizing inventory and minimizing disruptions.

With the increasing role of real world data and evidence, AI will be able to analyze such datasets to provide valuable insights into the effectiveness and safety of drugs in a broader population as well as assisting in market access strategies by analyzing market dynamics, pricing trends and patient outcomes.

Pharma companies are investing heavily to either develop their in-house capabilities or access the necessary skillsets through external partners. To harness the full potential of AI/ML, it is essential that pharma companies pay careful attention to data collection, preprocessing and curation to ensure that the datasets used for training are diverse, representative and of high quality, while staying abreast of the fast-evolving regulatory landscape surrounding the use of these technologies.

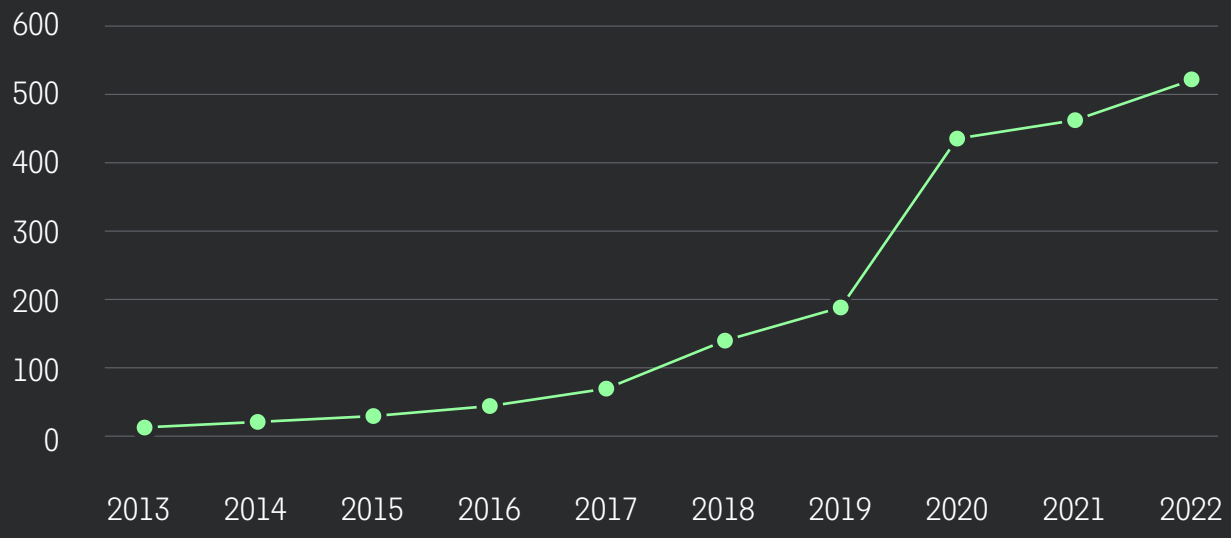
2024

will see a significant impact by gene editing and artificial intelligence machine learning on the biopharma industry's ability to create innovative medicines.

1st

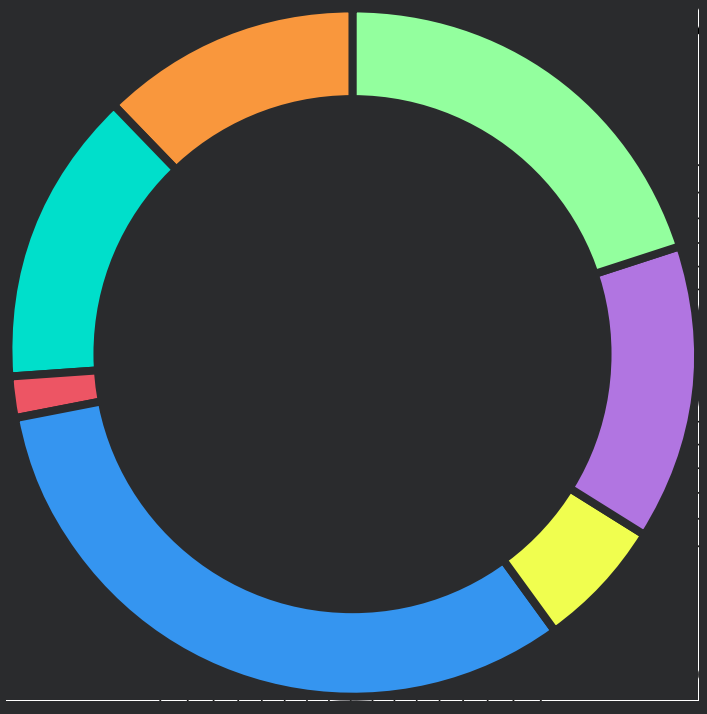
approvals of a medicine designed using the CRISPR-Cas9 gene-editing platform will highlight how pharma companies could use this process to improve overall drug discovery and targeted treatments.

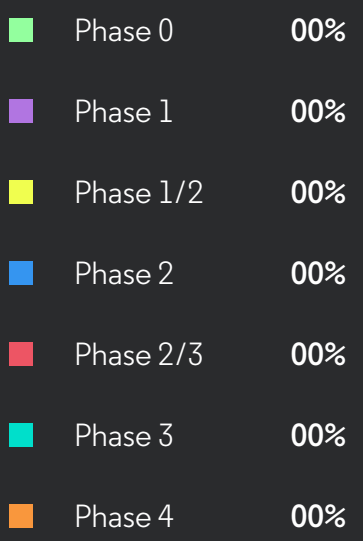
AI/ML-related clinical trails have increased year-on-year globally



Source: Cortellis Clinical Trials Intelligence™

Early-phase trials (phase 0-2) represent the majority of AI/ML-related clinical development from 2013 to 2022





Source: Cortellis Clinical Trials Intelligence™

Inflation Reduction Act

The impact of the IRA scrambles market entry and portfolio strategies.

The Inflation Reduction Act (IRA) — panned by some industry figures as the "Innovation Reduction Act" — has been in effect since the spring of last year, but it is likely to be years, if not decades, before its true impact on biopharma R&D is known. However, we are already seeing some possible unintended consequences, with companies including Lilly and Alnylam® Pharmaceuticals blaming R&D program cancellations on the law.

In Alnylam Pharmaceuticals' case, development of a treatment for Stargardt disease, an eye disorder affecting 7 in 100,000 people across the major mature markets, was shelved due to a provision in the law that exempts treatments for a single rare disease — but one alone – from possible government price negotiations. The Alnylam Pharmaceuticals treatment, AMVUTTRA®, is already indicated for transthyretin amyloidosis (ATTR) in the U.S.

The law has prompted a broad rethink on market entry and portfolio strategies, devaluing the common strategy of seeking an initial market entry on a fast-tracked orphan indication and potentially disincentivizing small molecule drug development due to a tight window for negotiation-free sales.

The regulatory sea change comes at a high stakes moment for pharmas, many of which face substantial patent expiries in the coming years, and at a time of global economic uncertainty. The old crutch of taking hefty year-over-year price hikes in the U.S. to compensate for a lull in the innovation cycle is now a non-starter. To compensate, pharmas will need to become more efficient, emulating the tech industry's fail fast approach and moving go/no go decision-making earlier in the innovation cycle.

→ Initial drugs selected for Medicare price negotiations

Drug name	Commonly treated conditions	Total part D Gross covered prescription drug costs from June 2022 – May 2023	Number of Medicare part D enrollees who used the drug from June 2022 – May 2023
Eliquis	Prevention and treatment of blood clots	$16,482,621,000	3,706,000
Jardiance	Diabetes; Heart failure	$7,057,707,000	1,573,000
Xarelto	Prevention and treatment of blood clots; reduction of risk for patients with coronary or peripheral artery disease	$6,031,393,000	1,337,000
Januvia	Diabetes	$4,087,081,000	869,000
Farxiga	Diabetes; Heart failure; Chronic kidney disease	$3,268,329,000	799,000
Entresto	Heart failure	$2,884,877,000	587,000
Enbrel	Rheumatoid arthritis; Psoriasis: Psoriatic arthritis	$2,791,105,000	48,000
Imbruvica	Blood cancers	$2,663,560,000	20,000
Stelara	Psoriasis; Psoriatic arthritis; Crohn's disease; Ulcerative colitis	$2,638,929,000	22,000
Fiasp; Fiasp FlexTouch; Fiasp Penfill; NovoLog; NovoLog FlexPen; Novolog PenFill	Diabetes	$2,576,586,000	777,000

Notes:

Numbers are rounded to the nearest thousands.

For the time period between June 1, 2022 and May 31, 2023 which is the time period used to determine which drugs were eligible for negotiation, about 8,247,000 people with Medicare Part D coverage used these drugs to treat a variety of conditions, such as cardiovascular disease, diabetes, autoimmune diseases, and cancer. The selected drugs accounted for $50.5 billion in total part D gross covered prescription drug costs, or about 20% of the total part D gross covered prescription drug costs during that time period.

Source: Centers for Medicare and Medicaid Services

Humira/biosimilars

The biosimilars marketplace faces growing pains. HUMIRA sales decline, market share holds on

Loss of exclusivity in the United States for AbbVie's HUMIRA (adalimumab) was one of the trends to watch identified in the 2023 edition of Drugs to Watch. Since the U.S. patent expiry at the end of January 2023, eight adalimumab biosimilars have launched (see table), two of which — Boehringer Ingelheim's CYLTEZO® (adalimumab-adbm) and Pfizer's ABRILADA™ (adalimumab-afzb) — carry interchangeable status, while others may still be undergoing review.

The impact of the U.S. patent expiry on Humira's sales has been stark. AbbVie reported that Humira sales in the United States for the first nine months of 2023 slumped 31% to $9.42B. With international sales also dropping 18% to $1.68B (international patents had expired earlier), the company reported total sales for the first nine months at $11.1Bbn, a 29% decline year-on-year. Amgen, the first out of the traps to launch an adalimumab biosimilar onto the U.S. market, reported nine-month U.S. sales of $93M, alongside international sales for the same period at $373M million.

Nevertheless, although AbbVie's revenues from Humira have tumbled, its share of the overall U.S. market is reported to have been barely impacted. Muted physician and patient appetite for biosimilars accounts for some the robust defence of Humira's market share, but biosimilar manufacturers, their trade organizations and U.S. politicians believe that structural issues in the U.S. healthcare system, including misaligned incentives within the market, are to blame for biosimilars adoption trailing expectations.

According to the Association for Accessible Medicines, patients are not yet benefiting from these products as pharmacy benefits managers (PBMs) and health plans take advantage of high rebates instead of preferring the lower-cost biosimilars. Biosimilar advocates are expected to step up their efforts to persuade PBMs to reduce out-of-pocket spending and increase access to FDA-approved biosimilars.

Clarivate analysts believe that adalimumab biosimilars will not be able to topple Humira's dominant market position in the near term. Indeed, 62% of payers surveyed in the United States expected to cover Humira as a preferred brand on the formulary. AbbVie, they say, is trying to maintain Humira's market by offering higher rebates and exclusivity agreements with payers to retain its preferred brand status on formularies. However, as many of the adalimumab biosimilars are also citrate-free formulations, the analysts forecast that the biosimilars will generate a 64% market share by 2031.

→ FDA-approved adalimumab biosimilars

Biosimilar	Manufacturer	aBLA approval	U.S. launch
AMJEVITA™ (adalimumab-atto)	Amgen	Sep 23, 2016	Jan 31, 2023
CYLTEZO® (adalimumab-adbm)	Boehringer Ingelheim	Aug 25, 2017	Jan 31, 2023
HYRIMOZ® (adalimumab-adaz)	Sandoz	Oct 30, 2018	Jul 1, 2023
HADLIMA™ (adalimumab-bwwd)	Samsung Bioepis	Jul 23, 2019	Jul 1, 2023
YUSIMRY™ (adalimumab-aqvh)	Coherus BioSciences	Dec 20, 2021	Jul 1, 2023
YUFLYMA® (adalimumab-aaty)	Celltrion	May 24, 2023	Jul 2, 2023
HULIO® (adalimumab-fkjp)	Mylan	Jul 6, 2020	Jul 3, 2023
IDACIO® (adalimumab-aacf)	Fresenius Kabi	Dec 14, 2022	Jul 3, 2023
ABRILADA™ (adalimumab-afzb)	Pfizer Inc	Nov 15, 2019	To be determined

Source: FDA, company data

Real world data

RWD offers promise for speeding up innovation cycles and flagging safety issues

Real world data (RWD) are no substitute for a well-run randomized clinical trial, but they can help developers, regulators and clinicians better understand patients and how a drug candidate stands to impact patient care.

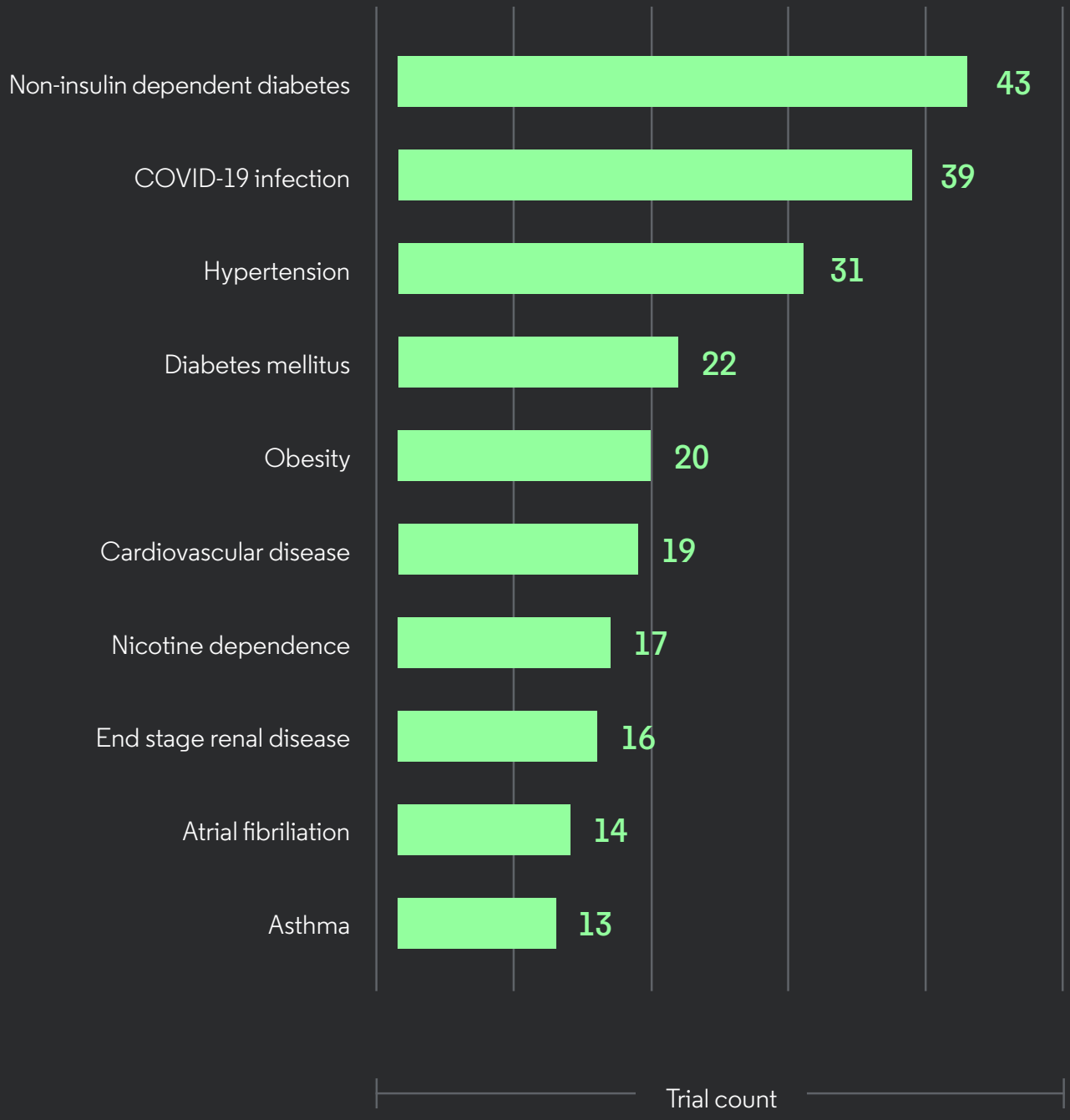
RWD sources such as claims, EHR/EMR and registry data are helping companies to shape, supplement, enhance and accelerate their clinical trials, including:

- identifying underserved populations and understanding which patient groups stand to benefit most from new treatments,
- enabling targeted site and investigator selection to ensure successful and expeditious trial completion,
- making clinical trials more representative of real world patient populations, and
- anticipating patient unmet needs and barriers to treatment.

"There are a lot of different ways that we can use RWD in research," said Sam Chesney, Lead Consultant, Services at Clarivate. "That ranges from understanding which patients the drug is going to benefit most in the early stages to choosing which sites and investigators we want to use in the later stages of trial planning. RWD gives you a good idea of what your market size is going to be before pushing your asset forward. It also gives you an idea of what your struggle is going to be like, because you understand how many patients are walking through the doors with this disease. Epidemiological data is useful, but real world data gets to a more granular level than that."

Although no novel drug has been approved based solely on RWD, between 1998 and 2019, there were 17 cases in which RWD were used as supplementary information in a new drug application (NDA) and 10 cases in which it was used for line extensions, based on Clarivate Analytics data. The NDAs of all 17 products were approved. Postmarket safety offers another critical use case for RWD. According to Clarivate, Cortellis Competitive Intelligence, there were 42 drugs withdrawn from the market post-approval in the past 10 years based on postmarketing studies and/or RWD.

→ Top 10 conditions for which EHR/EMR data was included in clinical trials



Source: Cortellis Clinical Trials Intelligence™

Drugs to Watch 2024

Key takeaways for industry executives

01. **Pharmas demand potential partners do their homework**

After a couple years of florid financing at the height of the COVID-19 pandemic, the party has wound down, and life sciences dealmaking has hit an austere stretch. It's not that pharmas aren't still doing partnerships, mergers and acquisitions — in fact, as we found in our recent report, *Where pharmas are investing for the future of medicine*, the value of biopharma partnering deals in 2022 was the second highest ever recorded, even as the volume of deals was the lowest since 2018. Rather, pharmas are being choosier about what bets they place, and as a result, biotechs intending to sell or license out assets are being asked to show prospective partners how their molecules would perform in the marketplace. That means understanding the addressable market, the epidemiological picture, how the regulatory landscape is likely to evolve, and key priorities for those stakeholders engaged in pricing and reimbursement.

02. **The IRA dials up the pressure to get more efficient**

The Inflation Reduction Act will take a sizable bite out of many pharmas' revenues in the coming years, just as companies are navigating treacherous patent expirations. To soften the blow, pharmas will be forced to redouble their efforts at improving the economics of research and development, getting viable drugs to market faster and cheaper and cutting bait on iffy molecules earlier in the innovation cycle. AI and ML have a role to play here in aiding drug design, optimizing clinical trials and identifying repurposing opportunities, among other use cases.

03. **AI and ML get real**

This year, we'll begin to see more tangible real world examples of how AI/ML are going to transform the discovery, development and delivery of innovative new medicines. To realize the potential of these technologies, companies will need to train these tools with the most robust, highest quality data available and acquire the expertise to manage them.

04. **Pharmas realize the value of RWD**

Companies are now using real world data across the innovation lifecycle, from identifying addressable markets and understanding clinical trial optimization to fine-tuning their physician outreach strategies. We will see increasing use of these data in determining valid clinical endpoints and supporting value-based propositions for pricing and reimbursement. As with AI/ML, companies will need to develop strategies for the collection, curation and management of these data sets.

The life science industries face tricky challenges in 2024, from patent cliffs to regulatory and financial uncertainty. At the same time, the strides being made against disease and the benefits being delivered to patients are extraordinary. With new tools and pathways for drug development opening up, 2024 looks to be a promising year for the advancement of human health.

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Navigating the global healthcare landscape is increasingly complex and discovering, developing and commercializing successful treatments that change patient lives is a monumental task. **Learn how Clarivate can help** with experts and connected data and solutions across the product lifecycle.

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