



Drugs to Watch 2022



Major advances in medicine continue amid the chaos of a global pandemic

The COVID-19 crisis has disrupted the drug industry in many ways, from supply chain collapse-induced shortages of key components¹ to clinical trial delays.² Through it all, pharma and biotech companies have managed to adapt, improvising and crowdsourcing solutions³ to advance a wide array of innovative treatment candidates.

This year's Drugs to Watch™ report identifies seven late-stage experimental treatments that Clarivate analysts forecast to reach blockbuster status within five years, i.e., if approved, are expected to earn \$1 billion in annual revenue. These treatments span a remarkably diverse set of therapeutic areas, from conditions like Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM), which afflict tens of millions of patients worldwide, to very rare diseases, such as transthyretin amyloidosis (ATTR), which afflict thousands.⁴

The companies behind these promising treatments share some common traits – most notably, deep expertise in their relevant therapeutic areas and long-term strategies for pursuing therapeutic solutions.

Eli Lilly and Company has been piecing together the puzzle of treating AD for three decades.⁵ Undeterred by trials that fell short over the years,

the company has continued to place big investments in addressing this devastating condition and so was ready with its own anti-amyloid- β ($A\beta$) agent, donanemab, when the United States Food and Drug Administration (FDA) green-lighted Biogen Inc's ADUHELM™ (aducanumab) in June 2021.

Roche has invested heavily in genetics technologies, including DNA sequencing and bispecific antibody platforms.⁶ This foundational expertise enabled the company to develop faricimab, a promising vascular endothelial growth factor (VEGF)/angiopoietin-2 (Ang-2) inhibitor for treatment of degenerative eye diseases, together with partner Chugai Pharmaceutical.

Amgen and AstraZeneca were able to parlay their industry-leading expertise in biologics and respiratory treatments, respectively, into a potentially game-changing monoclonal antibody (MAB), tezepelumab, for a particularly hard-to-treat subset of severe asthma patients.

Meanwhile, manufacturers have brought dozens of vaccines and treatments for COVID-19 to market with emergency or full authorization, and hundreds more are in the pipeline, bringing hope that the SARS-CoV-2 virus might soon be rendered far less deadly. They have done so even as the pandemic continues to disrupt the

industry and delay market entry for some drugs. Of the four therapeutic candidates spotlighted in the Drugs to Watch 2021 report, three have won approval (VERQUVO®, ORGOVYX™/MYFEMBREE® and ADUHELM™), some in multiple markets and/or for multiple indications. The FDA has delayed action on a fourth, UCB's BIMZELX® for psoriasis, due to COVID-19-related travel restrictions.⁷

Companies have also continued to move forward with revolutionary medical technologies such as RNA treatments, CRISPR-Cas9, oncolytics and machine learning (ML) for drug discovery.

Advances in these technologies are laying the foundations for the development of truly personalized medicines in the decades to come.

[View the Drugs to Watch key highlights infographic here](#)

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Methodology

Since 2013, Drugs to Watch has showcased drugs expected to enter the market each year that have the potential to become blockbusters within five years. Blockbuster is defined by the common \$1 billion annual sales milestone.

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

Clarivate experts then manually evaluated each drug in its individual context, based on factors such as expected approval or launch dates, competitive landscape, regulatory status, trial results and market dynamics.

From there, we determined seven Drugs to Watch in 2022:

Drug selection criteria

01

We selected candidate drugs in phase 2 or phase 3 trials, at pre-registration or registration stage, or already launched early in 2021 for analysis, including drugs launched for a new indication that could be particularly impactful on the industry; drugs launched prior to 2021 were excluded.

- **Adagrasib**
- **Faricimab**
- **Lecanemab and donanemab**
- **Tezepelumab**
- **Tirzepatide**
- **Vutrisiran**

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 a special section on the COVID-19 vaccine and therapeutic landscape, which summarizes the vaccines and therapies that were granted emergency use authorizations/conditional approvals as of December 2021.

02

We then filtered the dataset for drugs that had total forecast sales of \$1 billion or more in 2026.

Clarivate analysts also identified key areas of therapeutic innovation and provided perspective on their potential to transform patient outcomes and drug landscape, potential development and access challenges and key companies to watch.

Please note that Clarivate analysts generated the data shown in this report on December 12, 2021.

Data sources and contributors

Since 2013, Clarivate has applied proprietary technologies, tools and techniques trusted by our 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.

Disease Landscape & Forecast provides comprehensive market intelligence and actionable insights across 180+ indications to help optimize long-term disease strategies.

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

Drug Timeline & Success Rates

is a patented analytic tool that applies statistical modeling and machine learning to reliably and accurately forecast drug development milestones, timelines and probability of success.

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

Cortellis Generics Intelligence™ provides access to reliable and integrated market performance, manufacturing and patent data in a single, easily searchable solution.

Cortellis Deals Intelligence™ combines a robust and comprehensive source of deals intelligence with enhanced visualizations of the highest quality data, to quickly find the optimal deal without compromising due diligence.

Access & 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.

Clarivate Real World Data and Analytics

provides a comprehensive view of the market and a deep, impartial view of all stakeholders and sites of service through medical claims, EHR, Rx data and more.

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

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

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Adagrasib

For patients with mutation-positive solid tumors,
this is a monumental breakthrough.

Containing
metastatic
growth

About

Producer:

Mirati Therapeutics Inc
and Zai Lab Limited

Type:

KRAS GTPase inhibitor

Usage:

Twice-daily, second-line,
oral treatment of advanced
KRAS^{G12C}-positive solid
tumors: metastatic
NSCLC and CRC

Impact:

KRAS^{G12C}-mutant disease:

- **11-13%** of metastatic NSCLC
- **3-4%** of metastatic CRC

Adagrasib is a long-awaited, targeted treatment of cancers with KRAS^{G12C} mutation and will likely be the first such treatment option in patients with colorectal cancer (CRC) with this mutation, who historically have had very few treatment options.

Despite being second to market for patients with metastatic non-small-cell lung cancer (NSCLC), the great unmet clinical need for effective therapies for this biomarker-defined population make the clinical success of adagrasib very likely.

Why is it a drug to watch?

The common variants of the KRAS oncoprotein are traditionally considered intractable drug targets, and the development of successful drugs has failed for decades, which makes the forecasted entry of a KRAS inhibitor for patients with mutation-positive solid tumors (first entry for CRC; second entry for NSCLC) so monumental.

- The KRAS^{G12C} mutation is the most common KRAS mutation in patients with NSCLC.
- Key opinion leaders (KOLs) have indicated to Clarivate experts they are cautiously optimistic that adagrasib will be more efficacious than LUMAKRAS™ (sotorasib), the first-in-class KRAS p.G12C inhibitor approved for NSCLC.
- Phase 2 (KRYSTAL-1) data show promising safety and efficacy for CRC and NSCLC.
- A phase 2 trial (KRYSTAL-7) of adagrasib and KEYTRUDA® (pembrolizumab) for first-line combination therapy and phase 3 trial (KRYSTAL-12) for second-line monotherapy of NSCLC are underway.
- For CRC, combination adagrasib plus ERBITUX® (cetuximab; epidermal growth factor receptor [EGFR] inhibitor) as second- or third-line treatment is in a phase 3 trial (KRYSTAL-10).
- Mirati Therapeutics Inc's focus on targeted therapies against KRAS has enabled the company to move quickly during development.
- Although anticipated to be available as second-line monotherapy for NSCLC initially, improved efficacy (better than standard of care) as combination first-line therapy is highly anticipated by KOLs who spoke with Clarivate analysts.

Review and approval status

NSCLC:

June 2021: For patients with KRAS^{G12C}-positive NSCLC following prior systemic therapy

- Breakthrough Therapy Designation: U.S. FDA
- Orphan Drug Designation: U.S. FDA

November 2021: An NDA submission with the U.S. FDA began in this patient group based on data from the KRYSTAL-1 study

Expected launch

United States: 2022
Europe: 2023
Japan: 2023

CRC:

Expected launch

United States: 2024
Europe: 2024
Japan: 2024

Patents estimated to expire in 2038

How will adagrasib impact the market for NSCLC and CRC?

NSCLC:

Although chemotherapy remains the backbone of the NSCLC treatment algorithm, KRAS inhibitors are part of an ever-growing arsenal of targeted therapies, including immune checkpoint, EGFR, anaplastic lymphoma kinase (ALK), BRAF/mitogen-activated protein kinase kinase (MEK), ROS1, MET and rearranged during transfection (RET) inhibitors.

Adagrasib will be in direct competition with Amgen's LUMAKRAS. Together, adagrasib and LUMAKRAS represent a new therapeutic option for metastatic NSCLC patients with KRAS^{G12C} who progress after prior treatment.

Adagrasib as monotherapy has the potential for greater efficacy and safety than LUMAKRAS based on early data, but experts view even greater potential with combination therapy.

CRC:

With its potential as the first-in-class KRAS inhibitor approved for use in combination with ERBITUX in previously treated KRAS^{G12C}-mutation-positive metastatic CRC, adagrasib is not in direct competition with other treatments, but it will be introduced as second- or third-line therapy following standard of care chemotherapy with or without bevacizumab upon initial approval.

What gaps in treatment does adagrasib fill?

Emerging therapies have struggled to target KRAS-mutant cancers, current therapies are not wholly effective, and there are few options for patients who progress after previous therapy. Not only is adagrasib expected to provide better efficacy than the current standard of care but it is also helping to set the scene for other, similar therapies to become available and provide greater choice for providers and patients.

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

For NSCLC, Amgen's LUMAKRAS has the advantage of being earlier to market for a relatively small patient population, in addition to its once-daily administration compared with twice-daily for adagrasib. Additional study results will be necessary to determine if the hinted-at superior efficacy and safety of adagrasib will be realized, which could influence its uptake. For CRC, an even smaller patient population could limit its overall sales potential.

Adagrasib
MRTX-849

Market overview

\$1.23B

expected sales in 2026

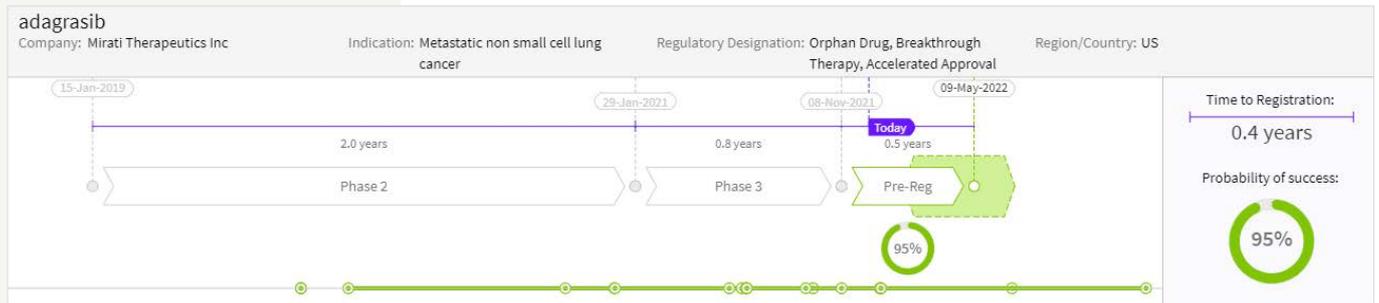
95%

probability of success

"My KRAS-positive NSCLC patients currently get chemoimmunotherapy. The two KRAS G12C inhibitors, LUMAKRAS and adagrasib, were showing a lot of promise in terms of response."

"The question is how durable are those responses? It is possible that patients with shorter response have multiple mutations, and so we may benefit from better patient segregation."

Medical oncologist, United States



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rate prediction current as of December 15, 2021

Faricimab

Expected to emerge from phase 3 trials showing superior efficacy against existing treatments.

Reversing
eye
disease

Faricimab
(RO-6867461)

About

Producer:

Roche and Chugai
Pharmaceutical

Type:

Bispecific VEGF/Ang-2 mAb

Usage:

Intravitreal (IVT)-
administered treatment of
DME and wet AMD, also
being studied to treat retinal
vein occlusion (RVO)

Impact:

- **~15%** of adults with T2DM have DME
- **3.6M** people have wet AMD in the G7 markets

For patients with diabetic macular edema (DME) or wet age-related macular degeneration (AMD) whose treatment choices include invasive, burdensome administration that limits treatment uptake, faricimab offers a potentially more convenient option as it will be administered less frequently, on average, than the standard of care.

As the first bispecific antibody to launch in ophthalmology, it also has the potential to be more efficacious than current standard of care, although data so far indicate it is non-inferior to the standard of care.

Why is it a drug to watch?

Faricimab is the first dual VEGF/Ang-2 inhibitor for the treatment of DME and wet AMD (and the first bispecific MAb in the ophthalmology therapeutic area overall). Although, due to its dual MOA, expectations were high that it would show superior efficacy to existing treatments, which are mainly VEGF inhibitors including the standard of care EYLEA® (aflibercept; Regeneron Pharmaceuticals Inc), results from phase 3 trials have shown similar visual outcomes and safety profile. However, its less-frequent dosing schedule will be attractive to both clinicians and patients.

- Faricimab has the potential to reach blockbuster status separately for DME and wet AMD.
- Faricimab has demonstrated non-inferiority to EYLEA in trial data to date.
- Pending 2-year data from phase 3 trials (DME: RHINE and YOSEMITE; wet AMD: TENAYA and LUCERNE) may demonstrate superior efficacy to existing treatments, as initially expected.
- Faricimab has a more convenient dosing schedule of 16 weeks (demonstrated to be effective for 52% of DME patients and 80% of wet AMD patients in clinical trials), compared with the 8-week (or occasionally, 12-week) schedule for EYLEA and LUCENTIS® (Genentech).

Faricimab
(RO-6867461)

Review and approval status

DME and wet AMD:

June 2021: Submitted to MHLW in Japan

July 2021: BLA submitted for priority review by the U.S. FDA and submitted to the EMA

Expected launch:

United States: 2022
Europe: 2022
Japan: 2022

Patents estimated to expire beginning in 2034

How will faricimab impact the market for DME and wet AMD?

Prevalences of both DME and wet AMD are expected to continue increasing, with aging population and rising rates of diabetes.

Mainstays of treatment are VEGF inhibitors administered via IVT injection, with EYLEA and LUCENTIS as standard of care; laser treatment is also an option.

EYLEA's dominance is expected to be challenged by the five agents currently approved or in active late-phase development:

1. Faricimab
2. KSI-301 (Kodiak Sciences)
3. RGX-314 (REGENXBIO Inc)
4. SUSVIMO™: ranibizumab port delivery system (Roche; twice yearly but ocular implantation)
5. OPT-302 (Opthea Limited)

Novel MOA of faricimab might ultimately provide greater efficacy than VEGF inhibitors, although existing results show similar efficacy and safety.

If so, faricimab is expected to reduce the overall market share of VEGF inhibitors by 67% in 2030.

Uptake of faricimab might be higher than that of other new drugs because:

- It will likely be used as early therapy.
- Switching from EYLEA or other treatments is possible given the less-frequent dosing.
- It is a potential candidate for patients with nonresponse to other treatments.
- It has the potential to increase the drug-treated population (from ~78% of wet AMD patients) due to less-frequent dosing.

What gaps in treatment does faricimab fill?

The largest unmet need for patients with DME or wet AMD has been a therapy with at least the efficacy and safety profile of existing VEGF inhibitors but with less frequent IVT dosing. The chronicity and time requirement of clinic visits take a toll on patient and caregiver quality of life and can be particularly concerning for patients or caregivers of working age. Also important is a therapy that is superior to current VEGF inhibitors for improving visual acuity.

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

The key consideration is entry into a market where the standard of care is providing the therapeutic response needed, with minimal side effects. Without clear demonstration of superior efficacy in clinical trials, adoption of faricimab might be challenged by an unwillingness to switch therapies. While the safety profile is currently consistent with existing therapies, side effects such as inflammation or vein occlusion occurring post-marketing could affect uptake.

Faricimab
(RO-6867461)

Market overview

\$1.31B

expected sales in 2026

95%

probability of success

"It seems to be a nice drug concerning its efficacy and durability, so something like brolocizumab, but maybe a little bit better in durability, and we are also waiting to see if safety is good."

"If safety is good and we can switch most of the patients or half of the patients to every 16 weeks dosing, it's very nice for sure."

Retinal specialist, France



Success Indicators		Project Overall	Number of Indicators: 10		Timeline	Success Rates	Positive Impact	Negative Impact	Neutral Impact					
Alliance Status	↓	—	Drug Developer Type	↑	—	Drug Novelty	↓	—	Drug Target Family	—	—	Geographic Area	↑	↑
Mechanism of Action	↓	↑	Regulatory Designation	↑	↑	Similar Drug Status	↓	—	Therapeutic Area	—	—	Type of Drug Compound	↑	—

Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rate prediction current as of December 15, 2021



Lecanemab and donanemab

Overcoming risks of previous therapies
to meet the critical need of patients.

Slowing cognitive decline

Lecanemab
(BAN2401)

Donanemab
(LY-3002813)

About lecanemab

Producer:

Eisai Co Ltd and Biogen Inc

Type:

Anti-A β protofibril MAb

Usage:

IV infusion every 2 weeks for the treatment of mild cognitive impairment (MCI) due to AD and mild AD

About donanemab

Producer:

Eli Lilly and Company

Type:

Anti-A β N3pG MAb

Usage:

IV infusion every 4 weeks for the treatment of MCI due to AD and mild AD

Impact:

- **~38M** people with AD globally
- **>30%** expected increase in total prevalent cases of early AD in the G7 markets by 2029 due to aging population

In this underserved market, anti-A β MAbs lecanemab and donanemab are poised to follow on the heels of the U.S. FDA's landmark accelerated approval of ADUHELM for the treatment of AD.

Lecanemab and donanemab could offer differentiated clinical profiles, which may be bolstered by phase 3 results that are expected to be reported beginning in late 2022.

Why are they drugs to watch?

Data across clinical trials suggest that sufficient exposure to optimal doses of anti-A β MAb therapy could be clinically effective in early AD. The FDA's approval of ADUHELM based on biomarker endpoints (i.e., decreased amyloid levels in the brain) has opened the flood gate for U.S. regulatory submission based on similar data from other disease-modifying therapies (DMTs). Although both lecanemab and donanemab could secure accelerated approval from the FDA in 2022, phase 3 trial readouts are expected shortly after and before a confirmatory post-marketing trial of ADUHELM is complete. These results could further validate — or refute — the efficacy of agents in the class.

Lecanemab

- Phase 3 studies (CLARITY AD and AHEAD 3-45) are ongoing in patients with early AD and preclinical AD, respectively. Data from CLARITY AD are expected in the second half of 2022.
- Phase 2 efficacy results showed a reduction in decline from baseline on the AD Composite Score (ADCOMS) and other metrics over 78 weeks and rapid, deep amyloid plaque clearance. Risk of amyloid-related imaging abnormalities (ARIA; 10%) was lower than with ADUHELM (40%) and donanemab (20%).

Donanemab

- Phase 3 studies (TRAILBLAZER-ALZ-2 and TRAILBLAZER-ALZ-3) are ongoing in patients with early AD and preclinical AD, respectively. Data from TRAILBLAZER-ALZ-2 are expected in the first half of 2023.
- Phase 2 efficacy results showed a reduction in decline from baseline on the Integrated AD Rating Scale (iADRS) and other metrics at week 76; rapid, deep reduction in amyloid plaques; and lower risk of ARIA (20%) than with ADUHELM (40%).
- A small phase 3 trial (TRAILBLAZER-ALZ-4) will compare donanemab with ADUHELM head-to-head to assess superiority of amyloid plaque reduction in early AD patients, with data expected in the second half of 2022.

Lecanemab
(BAN2401)

Donanemab
(LY-3002813)

Review and approval status

Lecanemab:

June 2021: Breakthrough Therapy Designation: U.S. FDA

September 2021: Rolling biologics license application (BLA) submitted to the U.S. FDA based on phase 2 data

Donanemab:

June 2021: Breakthrough Therapy Designation: U.S. FDA

October 2021 : Rolling BLA submitted to the U.S. FDA based on phase 2 data

Expected launch (lecanemab):

United States: 2022
Europe: 2024
Japan: 2024

Patents estimated to expire beginning in 2025

Expected launch (donanemab):

United States: 2022
Europe: 2025
Japan: 2025

Patents estimated to expire beginning in 2031

How will these drugs impact the treatment options for Alzheimer's disease?

Until the approval of ADUHELM, symptomatic therapy was the only treatment option for patients with AD. Acetylcholinesterase inhibitors and memantine, now generic, have been and will continue to be the standard of care across mild, moderate and severe disease.

Other anti-A β DMTs are in late-phase development, including gantenerumab (Roche).

Many more drugs from a range of mechanisms of action (MOAs; e.g., tau-based therapies, sigma-1 receptor inhibitors, glucagon-like peptide 1 [GLP-1] analogues, SIGLEC3 and Trem2 antibodies) are in mid- and late-phase trials, with potential for further differentiation (e.g., oral administration) and adjunctive use.

Regulatory success of anti-A β MABs could infuse more investment dollars into dementia and influence companies' decisions about which drugs to develop, potentially bypassing other MOAs to develop next-gen anti-amyloid drugs.

Until more definitive clinical data are available to differentiate their efficacy, relative uptake of ADUHELM, donanemab and lecanemab may depend on their respective safety and delivery profiles.

What gaps in treatment do donanemab and lecanemab fill?

The most critical need for patients has long been safe, effective DMTs that slow cognitive and functional decline. Initial uptake of ADUHELM has been slow for a multitude of reasons, limiting the patient benefit. Lecanemab and donanemab could offer improved risk/benefit profiles over ADUHELM, and additional therapies could eventually provide greater patient choice and potentially greater affordability.

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

While blockbuster sales should easily be within reach based on population size, market demand and pricing, questions remain about these drugs' prospects in the face of ongoing controversy regarding ADUHELM's approval, pending payer decisions and data readouts. Meanwhile, although the entry of ADUHELM could help prime health system preparedness, there remain challenges in access, reimbursement and affordability; patient/physician awareness to drive early presentation; seamless specialist referral and diagnosis pathways; infusion infrastructure; and healthcare provider perceptions about the risk/benefit of drugs in the class and their willingness to prescribe. Ultimately, uptake is likely to be slow until more data are released and reimbursement clarity is achieved. Meanwhile, regulatory decisions on ADUHELM from the European Medicines Agency (EMA) and Japan's Ministry of Health, Labour and Welfare (MHLW) are pending, which will set expectations for the approvability of others in the class in these geographies and impact global sales potential.

Lecanemab
(BAN2401)

Market overview

\$1.68B

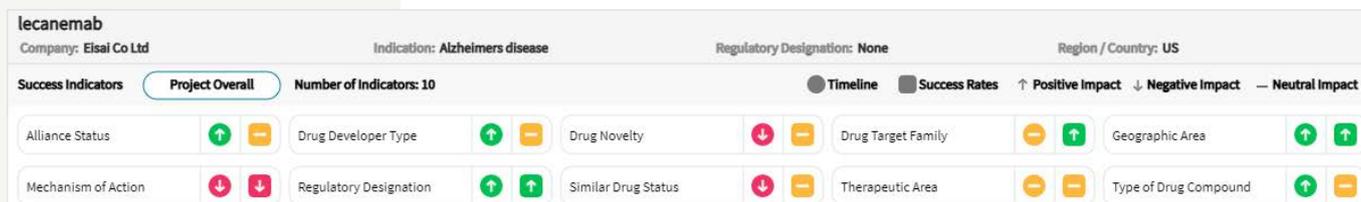
expected sales in 2026

95%

probability of success

"Based on the data from the phase 2 trial, BAN2401 could be more efficacious than aducanumab, and looking at the numbers for ARIAs, I am just speculating that they are slightly less."

Neurologist, Germany



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rate prediction current as of December 15, 2021

Donanemab
(LY-3002813)

Market overview

\$4.52B

expected sales in 2026

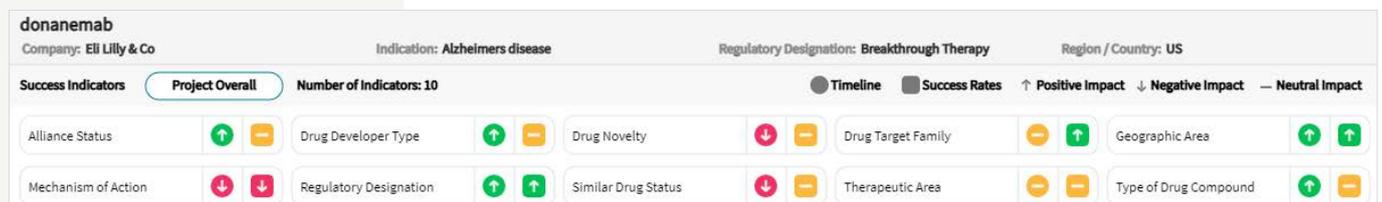
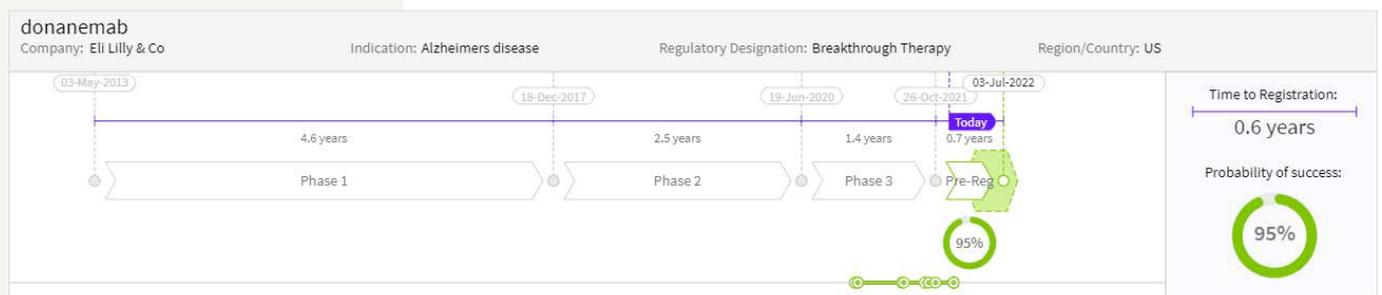
95%

probability of success

"They seem extremely interesting, but since this is still a phase 2 study, we need a large trial to understand the efficacy of this new molecule."

"We are talking about drugs that are very tricky to manage, so before being enthusiastic, I would like to have the results that give me the opportunity to offer this kind of treatment to my patients."

Neurologist, Italy



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rate prediction current as of December 15, 2021

Tezepelumab

is a potential game changer
for patients with non-TH2
or low-TH2 asthma.

Controlling
severe
asthma

Tezepelumab
(AMG-157/MEDI-9929)

About

Producer:

Amgen and AstraZeneca

Type:

MAB inhibiting thymic stromal lymphopoietin (TSLP)

Usage:

Monthly subcutaneous (SC) injection for treatment of severe asthma

Impact:

30% of patients with severe asthma have a TH2-low phenotype

Tezepelumab is a potential game changer for patients with non-TH2 or TH2-low asthma whose asthma is not well-controlled with inhaled corticosteroids, the current standard of care.

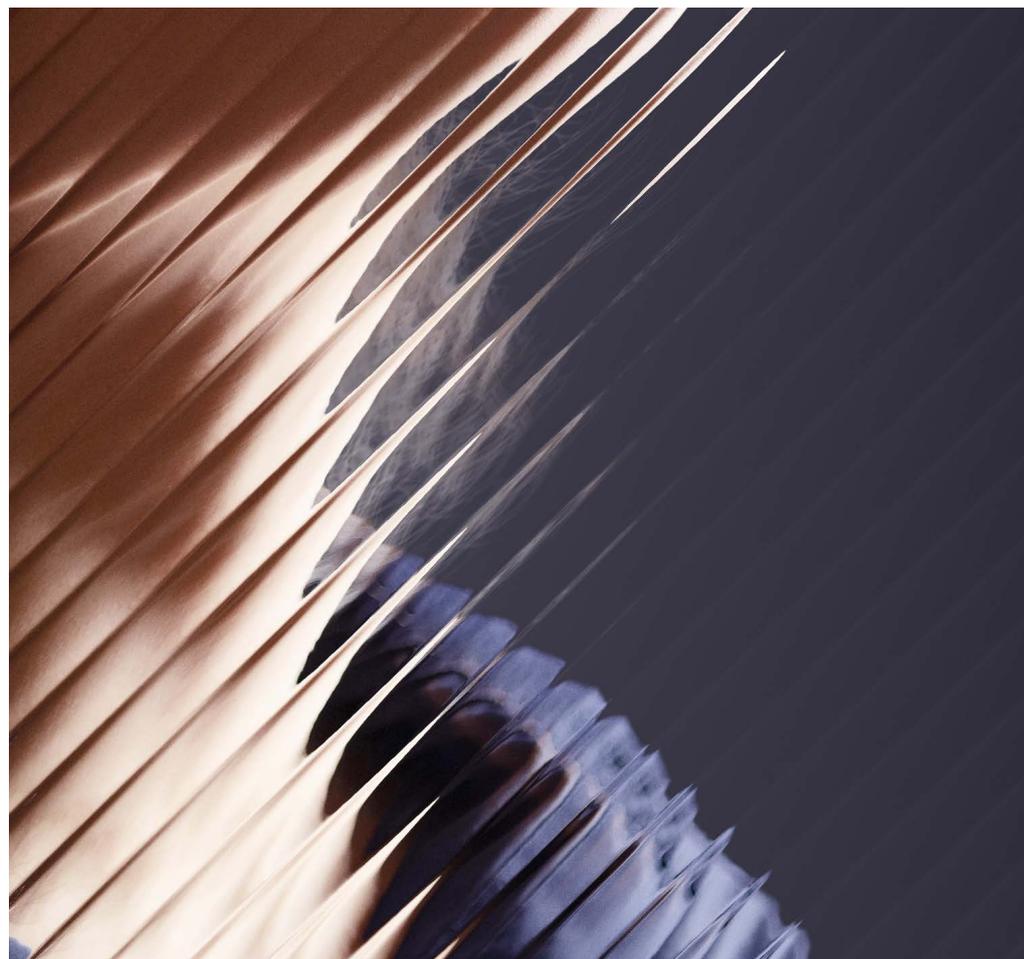
Greenlighted by FDA in December and marketed under the brand name Tezspire, it is a first-in-class biologic for this patient population.

Why is it a drug to watch?

Tezepelumab targets the inflammatory process in asthma earlier in the pathway than other asthma treatments, which expands its potential to treat both TH2-low asthma and TH2-high asthma. It is likely that tezepelumab will be a first-line biologic for severe TH2-low asthma and a treatment option for patients with TH2-high asthma for whom existing therapies have failed. Because of its MOA, high eosinophil levels do not need to be confirmed prior to administration, eliminating the need for a blood test, which could also make it attractive as a first-line option for TH2-high asthma.

In the phase 3 NAVIGATOR 3 trial, tezepelumab was well-tolerated by patients with severe asthma and resulted in reductions in the asthma exacerbation rate (AER), compared with placebo, of:

- 70% for TH2-high asthma patients,
- 41% for TH2-low asthma patients and
- 39% for non-TH2 asthma patients.



Tezepelumab
(AMG-157/MEDI-9929)

Review and approval status

September 2018: For patients with severe asthma without an eosinophilic phenotype, Breakthrough Therapy Designation: U.S. FDA

April 2021: BLA submitted to the FDA

May 2021: Filing submitted in Japan

July 2021: FDA granted priority review

August 2021: Filing submitted in the EU

December 2021: FDA authorized use as add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma

Expected launch:

United States: 2022
Europe: 2023
Japan: 2023

Patents expected to expire beginning in 2028

How will this drug impact the treatment options for asthma?

Mainstays of symptomatic treatment are oral corticosteroids.

Within this therapeutic area, the bulk of expenditure on therapies is in severe, uncontrolled asthma.

Tezepelumab is a first-in-class humanized MAb and the only member of the anti-TSLP class in late-phase clinical trials for asthma.

Novel MOA of tezepelumab is a step forward in addressing the high level of variability within the asthma patient population.

What gaps in treatment does tezepelumab fill?

Tezepelumab targets a subset of asthma patients who are underserved by available therapies and therefore have high unmet need, including patients with uncontrolled asthma with a non-TH2 /TH2-low phenotype who do not respond well to existing therapies. Dependence on oral corticosteroids for disease control is often not wholly effective and is associated with long-term side effects. As such, this is one of the most exciting emerging therapies for asthma treatment, particularly given the limitations of existing treatments, such as the long-term side effects of oral corticosteroids.

Given its potential efficacy for TH2-low asthma and the significant unmet need in this population of asthma patients, we anticipate robust uptake upon launch.

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

Tezepelumab will face significant competition in patients with TH2-high asthma, for whom it is expected to be used as a later-line therapy given physician familiarity with existing biologics. Owing to its later-to-market entry compared with other biologics for this patient population, payer restrictions could constrain uptake, similar to other high-priced biologics. For patients with TH2-low asthma, there is no competition. However, for both phenotypes, the niche population of patients with uncontrolled severe asthma could limit its overall patient share.

Tezepelumab
(AMG-157/MEDI-9929)

Market overview

\$1.17B

expected sales in 2026

95%

probability of success

"I think the thing that's most exciting is that it's obviously for the type-2-low patient. Because there are limited options for that group of patients, I'm very excited about it."

Pulmonologist, United States



tezepelumab
Company: Amgen Inc

Indication: Asthma

Regulatory Designation: Breakthrough Therapy, Priority Review / Region / Country: US

Success Indicators: Project Overall (Number of Indicators: 10)

Legend: Timeline (●), Success Rates (■), ↑ Positive Impact, ↓ Negative Impact, — Neutral Impact

Alliance Status	↑	Drug Developer Type	↑	Drug Novelty	↓	Drug Target Family	—	Geographic Area	↑
Mechanism of Action	↓	Regulatory Designation	↑	Similar Drug Status	↓	Therapeutic Area	—	Type of Drug Compound	↑

Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rate prediction current as of December 15, 2021

Tirzepatide

Class-leading reductions in weight loss
and glycemic control.

Reducing
diabetic related
obesity

Tirzepatide
(LY3298176)

About

Producer:

Eli Lilly and Company

Type:

GLP-1/gastric inhibitory polypeptide (GIP) receptor agonist

Usage:

Weekly SC administration to treat T2DM

Also being studied to treat obesity and non-alcoholic steatohepatitis (NASH)

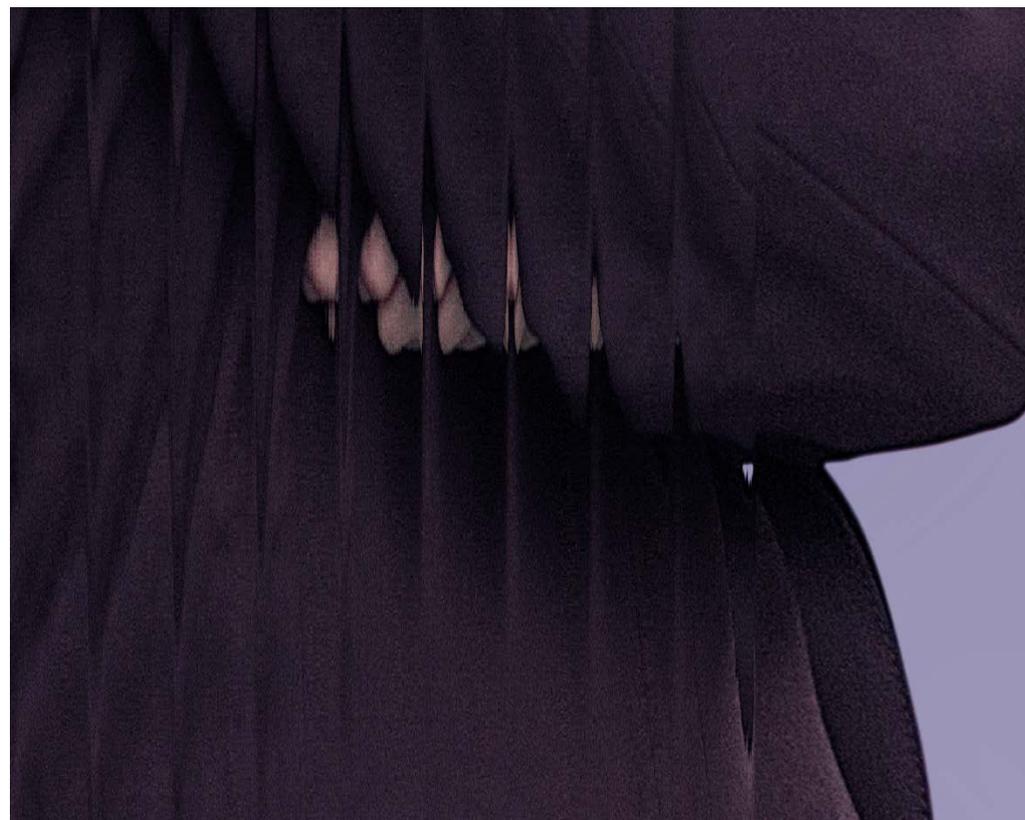
Impact:

- **462 million** people globally have T2DM
- **1.4% annual increase** in drug-treated populations in G7 due to increasing rates of obesity and the aging population

Tirzepatide offers indication-leading reductions in weight loss and improvements in glycemic control in a growing patient population, which has the potential to reduce the incidence of T2DM-related complications.

Why is it a drug to watch?

- Given the increasing rates of obesity and aging population worldwide, the prevalence of T2DM and associated complications continues to rise. Therefore, a new treatment that can more effectively address both weight loss and glycemic control than existing treatments is of great interest to the industry. Tirzepatide will likely be prescribed for patients with T2DM who are currently only being acceptably managed with another drug or to new patients who would benefit from weight loss.
- Large-scale SURPASS trials (>20,000 patients) have shown greater efficacy for weight reduction and glycemic control (HbA1c) than any other approved non-insulin T2DM therapy.
- Phase 3 SURPASS trials are ongoing, including a large cardiovascular outcomes trial (CVOT; n=12,500) comparing the efficacy of tirzepatide with:
 - placebo background therapy,
 - insulin,
 - TRULICITY® (dulaglutide) or
 - OZEMPIC® (semaglutide).
- Sufficient data, including regarding CV risk, are now available for regulatory submissions.
- Eli Lilly and Company has a long history of bringing T2DM therapies to market.



Tirzepatide
(LY3298176)

Review and approval status

October 2021: New drug application (NDA) submitted to the FDA and Marketing authorization application (MAA) submitted to the EMA

Expected launch:

United States: 2022
Europe: 2023
Japan: 2023

Patents estimated to expire beginning in 2031

How will this drug impact the treatment options for type 2 diabetes mellitus?

Tirzepatide has demonstrated superiority over semaglutide (GLP-1 receptor agonist), which is the most efficacious noninsulin T2DM therapy currently available, which could result in a significant market advantage over other therapies.

The impressive weight loss and glycemic control data associated with tirzepatide are anticipated to result in strong uptake of this agent.

What gaps in treatment does tirzepatide fill?

Reducing body weight has become a focal point in the management of patients with T2DM. Several classes of antidiabetic agents are associated with no changes in weight or even weight gain, and only a handful offer weight loss. Moreover, the net reduction provided by these current agents is limited. With the promising results for both weight loss (clinically significant 15% weight loss) and glycemic control demonstrated to date, tirzepatide could help delay disease progression and therefore delay the transition to insulin-based treatment.

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

One concern that arose in phase 2 trials was the large number of patients discontinuing tirzepatide because of gastrointestinal side effects; however, these subsided after time. Barriers to uptake, especially for patients who require less weight loss or glycemic control, could include the need to titrate tirzepatide, the availability of sodium-glucose co-transporter-2 (SGLT-2) inhibitors in generic formulations, competition from nearly as efficacious GLP-1 receptor inhibitors such as OZEMPIC® and RYBELSUS® and the high cost of tirzepatide.

Tirzepatide
(LY3298176)

Market overview

\$4.55B

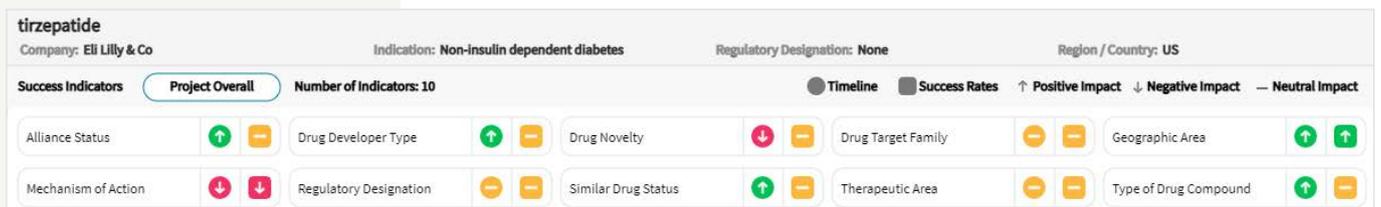
expected sales in 2026

95%

probability of success

"It has amazing data regarding bigger HbA1c reductions and bigger reductions in weight, so it's potentially a game-changer. It will need cardiovascular data since all the other drugs will have cardiovascular data, but it's really promising."

Endocrinologist, United States



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rate prediction current as of December 15, 2021

Vutrisiran

Improves deteriorating muscle function, with less frequent dosage than other ATTR-specific drugs on the market.

Improving
quality
of life



Vutrisiran
(ALN-TTRSC02)

About

Producer:

Alnylam® Pharmaceuticals

Type:

siRNA transthyretin (TTR) gene inhibitor delivered using a GalNAc-conjugate delivery platform

Usage:

Every-three-month SC administration for treatment of ATTR polyneuropathy

Impact:

Two subtypes of ATTR:

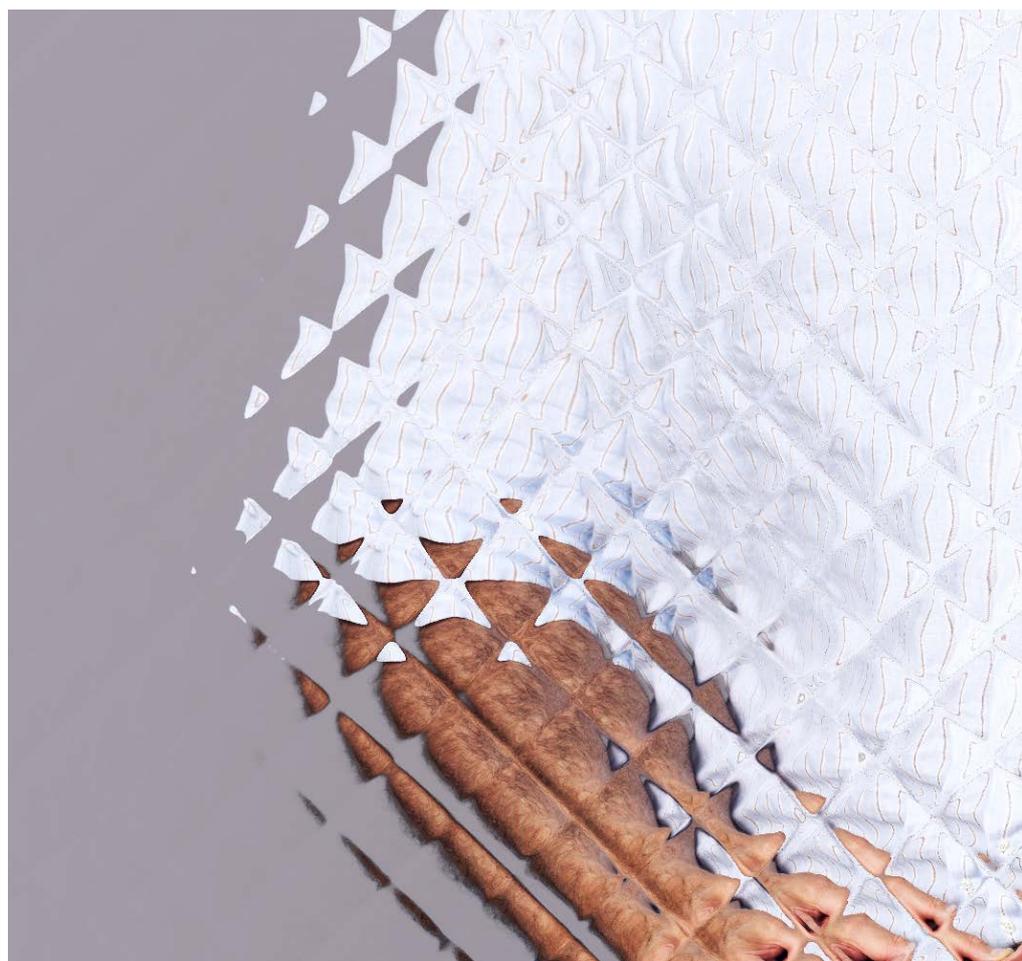
- Hereditary ATTR (hATTR): 1,233 people in the United States in 2021
- Wild-type ATTR: 1,300 people in the United States in 2021

For a progressive disease that has a lot of unmet need, this drug brings efficacy, a generally favorable safety profile and improvements in delivery that will provide benefits for patient quality of life.

Why is it a drug to watch?

This patient population has few treatment options, especially for those with wild-type ATTR. If vutrisiran is reimbursable for patients with wild-type ATTR polyneuropathy, this would be a huge win for these patients. Not only does this drug enter a relatively underserved market overall, it also has more convenient dosing than other ATTR-specific drugs on the market.

- Phase 3 HELIOS trials are underway. Results to date have shown improvements in polyneuropathy, quality of life and cardiac biomarkers.
- Vutrisiran demonstrated statistically significant efficacy on the same key endpoints for hATTR polyneuropathy as ONPATTRO® (patisiran) but with a more convenient administration method (SC vs one-hour IV infusion) and less frequent dosing (every three months vs weekly or every three weeks).
- It has demonstrated good tolerability and an encouraging safety profile.



Vutrisiran
(ALN-TTRSC02)

Review and approval status

May 2018: Orphan Drug designation by FDA and EMA for the treatment of ATTR

May 2020: Fast Track designation by the FDA for the treatment of the hATTR-related polyneuropathy in adults

September 2021: Submitted to the EMA

April 14, 2022: PDUFA date

Expected launch:

United States: 2022
Europe: 2022

Patents estimated to expire beginning in 2037

How will this drug impact the treatment options for ATTR-related polyneuropathy?

The market is currently composed of therapies approved for other indications (e.g., multiple myeloma) that are used off-label to treat the effects of amyloid build-up in nerves and major organs (e.g., the heart and liver).

For hereditary ATTR polyneuropathy, there are two approved drugs: ONPATTRO, administered intravenously every three weeks, and TEGSEDI® (inotersen), administered via SC injection once a week.

Treatment also includes chemotherapy and, as a last resort, organ transplant.

What gaps in treatment does vutrisiran fill?

ATTR is a rare, undiagnosed, rapidly progressive, debilitating and fatal disease with very few effective treatment options. Vutrisiran represents another drug in the therapeutic arsenal with a less-frequent dosing schedule and relatively convenient administration method (SC vs IV infusion). With its MOA, vutrisiran should help slow, if not stop, the accumulation of amyloid throughout the body. It has generally mild side effects, compared with TEGSEDI and standard chemotherapy.

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

Vutrisiran might face some competition from ONPATTRO and TEGSEDI for patients with hATTR polyneuropathy, especially with the limited patient population and if it enters the market at a high price.

Vutrisiran
(ALN-TTRSC02)

Market overview

\$1.42B

expected sales in 2026

95%

probability of success

"If I am giving vutrisiran every three months, that would be perfect. I'm sure it would beat all the other therapies."

Amyloidosis specialist, Germany



Source: Cortellis Competitive Intelligence, Drug Timeline & Success Rate prediction current as of December 15, 2021

COVID-19 vaccines and therapies

Development activity over the past 18 to 24 months has been dominated by vaccines and therapies targeted at ending the COVID-19 pandemic, resulting in more than 240 vaccines in development and more than 750 therapies in development.

Not all have succeeded to market, but the learnings accumulated over this time have been folded into other programs, both for COVID-19 and other therapeutic areas such as oncology and other infectious diseases such as the flu and HIV.⁸



Approved COVID-19 vaccines

Company(s)	Vaccine name	Countries/regions
Single-dose recombinant viral vector vaccine		
CanSino Biologics Inc; the Beijing Institute of Biotechnology of the Academy of Military Medical Sciences	Ad5-nCoV (Convidecia™)	Chile, Mainland China, Hungary, Mexico, Pakistan
Johnson & Johnson; Biomedical Advanced Research and Development Authority (BARDA); Emergent Biosolutions®; Catalent; Grand River Aseptic Manufacturing	JNJ-78436735 (Ad26.COVS-2)	Austria, Bahrain, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, United Kingdom, United States, WHO
Two-dose recombinant viral vector vaccine		
AstraZeneca, University of Oxford	AZD-1222 (Vaxzevria; COVISHIELD™; ChAdOx1 nCoV-19)	Afghanistan, Angola, Antigua and Barbuda, Argentina, Australia, Austria, Bahamas, Barbados, Belgium, Belize, Botswana, Brazil, Bulgaria, Cabo Verde, Cambodia, Canada, Chile, Colombia, Croatia, Cyprus, Czech Republic, Congo, Denmark, Dominican Republic, Egypt, El Salvador, Estonia, Finland, France, Gambia, Germany, Ghana, Greece, Grenada, Guatemala, Guyana, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Italy, Ivory Coast, Jamaica, Japan, Jordan, Kenya, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malawi, Malaysia, Maldives, Mali, Malta, Mauritius, Mexico, Moldova, Mongolia, Morocco, Nepal, Netherlands, Nigeria, Norway, Oman, Pakistan, Papua New Guinea, Philippines, Poland, Portugal, Romania, Rwanda, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Saudi Arabia, Senegal, Serbia, Seychelles, Slovakia, Slovenia, South Africa, South Korea, Spain, Sri Lanka, Sudan, Suriname, Sweden, Taiwan, Thailand, Trinidad and Tobago, Uganda, Ukraine, United Kingdom, Vietnam
Gamaleya Research Institute of Epidemiology and Microbiology	Gam-COVID-Vac (Sputnik V)	Algeria, Angola, Argentina, Armenia, Azerbaijan, Bahrain, Belarus, Bolivia, Bosnia and Herzegovina, Cameroon, Congo, Djibouti, Ecuador, Egypt, Gabon, Ghana, Guatemala, Guinea, Guyana, Honduras, Hungary, India, Iran, Iraq, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Laos, Lebanon, Macedonia, Mali, Mauritius, Mexico, Moldova, Mongolia, Montenegro, Morocco, Myanmar, Namibia, Nicaragua, North Macedonia, Pakistan, Palestine, Paraguay, Philippines, Russia, Saint Vincent and the Grenadines, San Marino, Serbia, Seychelles, Slovakia, Sri Lanka, Syria, Tunisia, Turkmenistan, United Arab Emirates, Uzbekistan, Venezuela, Vietnam, West Bank, Zimbabwe
Two-dose inactivated vaccine		
Sinopharm; Beijing Institute of Biological Products Co Ltd; Henan Provincial Center for Disease Control and Prevention	BBIBP-CoV	Argentina, Bahrain, Belarus, Bolivia, Cambodia, Mainland China, Egypt, Guinea, Guyana, Hungary, Iran, Iraq, Jordan, Laos, Maldives, Montenegro, Morocco, Mozambique, Nepal, Pakistan, Peru, Senegal, Serbia, Seychelles, United Arab Emirates, Venezuela, Zimbabwe
Sinovac Biotech Ltd; Dynavax Technologies; Instituto Butantan; Bio Farma	CoronaVac	Azerbaijan, Brazil, Cambodia, Chile, Mainland China, Colombia, Dominican Republic, Ecuador, Hong Kong, Indonesia, Laos, Malaysia, Philippines, Thailand, Turkey, Ukraine, Uruguay, Zimbabwe, WHO
Bharat Biotech International; Ocugen Inc	COVAXIN®	India, Iran, Nepal, Mauritius, Zimbabwe
Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products of Russian Academy of Science	CoviVac	Russia

Company(s)	Vaccine name	Country(s) in which approved for use
Two-dose, lipid nanoparticle RNA vaccine		
Moderna; Ginkgo Bioworks; Takeda Pharmaceutical Company Limited; Catalent; Recipharm	mRNA-1273 (TAK-919; elasomeran; SPIKEVAC™)	Austria, Australia, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Faroe Islands, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Mongolia, Netherlands, Norway, Poland, Portugal, Qatar, Romania, Rwanda, Seychelles, Singapore, Slovakia, Slovenia, South Korea, Spain, Sweden, Switzerland, United Kingdom, United States
BioNTech SE, Pfizer Inc, Fosun Pharma	Tozinameran (BNT-162b2, COMIRNATY®)	Albania, Argentina, Australia, Austria, Bahrain, Belgium, Botswana, Brazil, Bulgaria, Canada Chile, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Estonia, Faroe Islands, Finland, France, Germany, Greece, Greenland, Hong Kong, Hungary, Iceland, Iraq, Ireland, Israel, Italy, Japan, Jordan, Kuwait, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Macedonia, Malaysia, Maldives, Malta, Mexico, Moldova, Monaco, Mongolia, Netherlands, New Zealand, Norway, Oman, Panama, Peru, Philippines, Poland, Portugal, Qatar, Romania, Rwanda, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Tunisia, Ukraine, United Arab Emirates, United Kingdom, United States, Uruguay, Vatican, West Bank, WHO
Two-dose synthetic peptide		
State Research Center of Virology and Biotechnology VECTOR	EpiVacCorona	Russia
Three-dose DNA		
Zydus Cadila Healthcare Ltd.	ZyCov-D	India
Three-dose protein subunit		
Anhui Zhifei Longcom Biopharmaceutical Co Ltd (subsidiary of Chongqing Zhifei Biological Products Co Ltd); Institute of Microbiology, Chinese Academy of Sciences	ZF2001 (RBD-dimer, Zifivax)	Mainland China, Indonesia, Uzbekistan

COVID-19 therapies with full or emergency use approval

Company(s)	Therapy name	Country(s) in which approved for use
Corticosteroid		
Oxford University; Bausch Health	Dexamethasone phosphate (DEXAVAN)	Poland
Broad-spectrum antiviral; Viral RNA-dependent, RNA polymerase inhibitor		
Fujifilm Holdings; Fujifilm Toyama Chemical Co Ltd; Medivector Inc; Zhejiang Hisun Pharmaceutical Co Ltd; Sihuan Pharmaceutical Holdings Group; Genentech; Appili Therapeutics; Glenmark Pharmaceuticals Ltd; Dr. Reddy's Laboratories Ltd	Favipiravir (Reequonus™, Avigan®)	Mainland China, Egypt, India, Russia
Gilead Sciences Inc; Cipla Limited; Hetero; Dr. Reddy's Laboratories Ltd	Remdesivir (VEKLURY®)	European Union, India, Japan, United States
Janus kinase inhibitor		
Eli Lilly and Company, Incyte	Baricitinib (OLUMIANT®)	India, Japan, United States
MAB		
Abcellera Biologics Inc; Eli Lilly and Company	Bamlanivimab (LY-3819253, LY-CoV555)	Canada, Germany, Hungary, Israel, Kuwait, Morocco, Panama, Rwanda, Saudi Arabia, United Arab Emirates, United States
Regeneron Pharmaceuticals Inc; Roche	Casirivimab and imdevimab (REGEN-COV™; Ronapreve™; REGN-10933 plus REGN-10987; REGN-COV2)	Canada, European Union, India, Japan, Switzerland, United Kingdom, United States
Shanghai Junshi Biosciences Co Ltd; Abcellera Biologics Inc; Eli Lilly and Company	Etesevimab (LY-CoV016)	Italy, United States
Celltrion	Regdanvimab (Regkirona; CT-P59)	Brazil, Indonesia, South Korea
Vir Biotechnology; Wuxi Biologics; National Institute of Allergy and Infectious Diseases (NIAID); Biogen Inc; Xencor Inc; GlaxoSmithKline plc; Samsung Biologics	Sotrovimab (GSK4182136, VIR-7831, VIR-7832)	Australia, United States
Genentech; Chugai Pharmaceutical	Tocilizumab (Actemra; Roactemra)	United States
AstraZeneca	Tixagevimab and cilgavimab (AZD-7442; combination of AZD-8895 and AZD-1061; Evusheld)	United States
Main protease (Mpro) inhibitor		
Pfizer Inc.	Nirmatrelvir and ritonavir (PF-07321332; PAXLOVID™)	United States, European Union

Source: BioWorld

Key therapeutic development areas to watch

The drug innovation landscape is evolving, and many companies are developing platforms to address challenges in delivery and targeting across therapeutic areas.

These are likely to have significant impacts on society and the treatment landscape. Patients with rare, genetic diseases are likely to be the first to benefit but as these platforms expand from hyper-targeted applications to broader systemic conditions, they will benefit a broader range of patients.



Cell and gene therapies

Market access and impact for patients and society

In addition to addressing typically underserved patient populations, these therapies have the potential to have a long-term clinical benefit after a single administration, reducing the treatment burden and long-term treatment costs. However, payers are reportedly concerned about the substantial financial burden on the healthcare system due to the high expense of gene and CAR-T cell therapies.

The introduction of lower-cost allogeneic options that use donor cells instead of a patient's own CAR T-cells could significantly increase patient access through a more standardized manufacturing process.²⁵ Currently, insurance companies are paying providers to administer CAR-T cell therapies on a case-by-case basis, and there is a desire to standardize the process. Payers are also discussing new payment models with pharma companies to ensure patients have access to treatments: pay-for-performance, long-term payment plans and stop-loss insurance.

Cell and gene therapies are transforming treatment for rare diseases and certain oncology indications, providing new hope for many patients that previously had very few options. Gene therapies are also expanding into larger patient populations such as AD and retinal diseases, while cell therapies are aiming to tackle solid tumors. However, patient access barriers include the high cost of treatments, and collaborative efforts will be important to ensure patients can benefit from the treatment while minimizing the burden on the overall healthcare system.

Cell and gene therapies are highly personalized treatments that alter a patient's own cells to potentially offer longer-lasting effects than other therapies.

Five chimeric antigen receptor (CAR)-T cell therapies have been approved by the U.S. FDA^{9,13} since the first in 2017 (four of which are approved in the EMA,¹⁴⁻¹⁷ two in Japan^{18,19} and one in Mainland China²⁰), to treat B-cell precursor acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and multiple myeloma, resulting in substantially higher remission rates than chemotherapy and other targeted therapies. Other cell therapies in clinical development include T cell receptor (TCR-T), natural killer (NK) and tumor-infiltrating lymphocyte (TIL) cell therapies.²¹ The TIL cell therapy, lifileucel, from lovance Therapeutics could be the next non-CAR-T cell therapy approved for a solid tumor indication (malignant melanoma), which be a significant breakthrough in the treatment of solid tumors.²²

Other advancements include:

- the development of allogeneic cell therapies for hematologic cancers,²³ which could contribute to efficacious “off-the-shelf” therapies at a faster development time and lower cost;
- label expansions of CAR-T cell therapies to earlier lines of treatment in hematological malignancy; and
- dual-targeting CAR-T cell therapies.²⁴

An ongoing challenge for cell therapies is to reduce the manufacturing time, which currently takes a median two to three weeks after the patient's cells are extracted and can be treatment-prohibitive in patients with aggressive cancers.²⁵ Shorter times could be a key differentiator for companies in this space. Regarding competition, cell therapies will face another market threat from other drug therapies; bispecific antibodies for hematologic diseases have demonstrated very promising clinical results, particularly in aggressive non-Hodgkin's lymphoma.²⁶

Approved gene therapies include those to treat rare genetic disorders such as spinal muscular atrophy²⁷ and inherited retinal dystrophies such as retinitis pigmentosa and Leber's congenital amaurosis,²⁸ and there are promising treatments in clinical development for diseases such as Duchenne muscular dystrophy.²⁹

Because of the small patient populations and narrow window in which treatment would be of most benefit, these therapies can be particularly expensive to develop and are typically priced high to recoup some of the development costs. Other development challenges include the need to collect long-term data to assess safety and durability.

Research activity

62%

Increase in academic articles from 2011 to 2020

4.5K

Active clinical trials* with 399,965 anticipated patients

"In recognition of significant clinical and societal benefits of cell and gene therapies for cancers and a host of other diseases, U.S. payers, providers and pharmaceutical companies are testing novel payment schemes to make these therapies economically feasible."

"As more of these expensive therapies become available to broader patient populations, payers will increasingly control access to therapy through prior authorization and other utilization management strategies."

**Chris Lewis, Primary Research Manager,
U.S. Access & Reimbursement, Clarivate**

Key companies

- Abeona Therapeutics Inc
- Achilles Therapeutics
- Allogene Therapeutics
- Aruvant Sciences
- Atara Biotherapeutics Inc
- Athersys Inc
- Austrianova
- Autolus Therapeutics
- Biogen Inc
- bluebird bio Inc
- BridgeBio Pharma
- Bristol-Myers Squibb
- Cellectis S.A.
- Celularity Inc
- CRISPR Therapeutics
- Fosun Kite Biotechnology
- Gamida Cell
- Gilead Sciences Inc
- Iovance Biotherapeutics
- Janssen Pharmaceutical Companies of Johnson & Johnson
- JW Therapeutics
- Krystal Biotech
- Legend Biotech
- MediGene AG
- Novartis
- Oxford Biomedica
- Passage Bio
- ReNeuron
- Sangamo Therapeutics
- Spark Therapeutics
- Transgene
- uniQure

*As reported for phase 2 and 3 clinical trials categorized as "Cell therapies" or "Gene therapies"

Market access and impact for patients and society

Within the next five years, clinical trial data from current early-phase trials are expected to start becoming available. That will inform how quickly CRISPR will be translated into clinical therapeutics. Patients with life-debilitating diseases and few treatment options, such as Duchenne muscular dystrophy, ATTR and beta-thalassemia, are likely to be the first to benefit from CRISPR development.

Potential hurdles to adoption include ethical concerns from the public, regulatory review of a novel technique and the need for widespread education. Patient advocacy groups may have a role to play in ensuring access to CRISPR-related therapies.

CRISPR

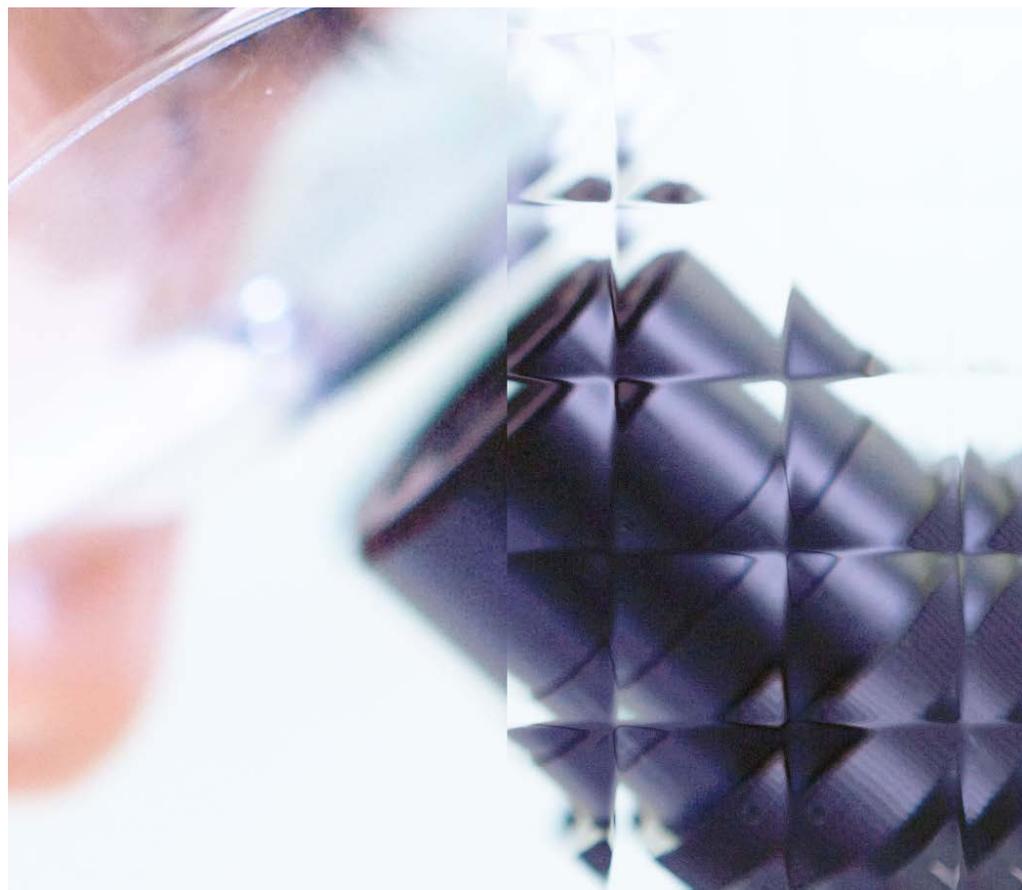
CRISPR techniques have the potential to transform therapeutic approaches for diseases with very few treatment options, but there could be ethical hurdles to overcome. It remains unknown how long it will take for CRISPR to have a commercial and clinical impact.

CRISPR has emerged as a hot platform in the past decade, with a number of biotech companies developing therapeutic approaches using the technology. Delivery approaches include ex vivo and in vivo approaches,³⁰ both of which are being refined to address some of the technical challenges that have been experienced to date, such as off-target effects and immunotoxicities.³¹

Orphan diseases have been a focus for several companies, with promising results demonstrated for ATTR in the phase 1 evaluation of Intellia Therapeutics Inc's NTLA-2001 program³² and for sickle cell and beta thalassemia in the phase 1 evaluation of CRISPR Therapeutics and Vertex Pharmaceuticals' CTX001 program.³³

Development is also underway for immune-oncology, with techniques to edit autologous T cells for hard-to-treat cancers such as multiple myeloma and melanoma.³⁴

COVID-19 has also propelled some CRISPR development, including a CRISPR-Cas13-based strategy, PAC-MAN (prophylactic antiviral CRISPR in human cells), that can effectively degrade RNA from SARS-CoV-2 sequences in human lung epithelial cells.³⁵ This could become an important pan-coronavirus inhibition strategy.



Research activity

6946%

Increase in academic articles from 2011 to 2020

62

Active clinical trials* with 3,675 anticipated patients

"With the current growth rate and evolution of CRISPR, one could envisage CRISPR-mediated medicines emerging from beyond cell and gene therapies and underpinning genuine cures for more common diseases such as those within cardiovascular, cancer and neurodegenerative indications."

"To achieve that, however, it will be important to collaborate across the whole of the research ecosystem and involve pharma, biotech, academia and non-profit industry partnerships."

Mike Ward, Global Head of Thought Leadership, Life Sciences and Healthcare, Clarivate

Key companies

- CRISPR Therapeutics
- Editas Medicine
- Intellia Therapeutics Inc
- Modalis Therapeutics
- Repare Therapeutics

*As reported for phase 1/2, 2 or 3 clinical trials that include CRISPR in the protocol

Drug discovery driven by artificial intelligence and machine learning

Market access and impact for patients and society

The broad applications of AI as a toolkit to access and analyze large datasets will contribute to streamlining drug development, from preclinical discovery through synthetic control arms, which can be particularly useful for rare disease populations. It has the potential to not only speed time to market but also address unmet needs for many different patient populations.

Artificial intelligence (AI) and ML have the potential to significantly reduce time for drug discovery and development, and there has been considerable investment and partnering activity in this space. A key challenge will be overcoming the perception of AI as a mysterious component (“black box”) and instilling confidence in algorithmic outcomes.

Increasing volumes of data from approved drugs, clinical trials, chemistry, previously failed molecules and more data sources have begun to overwhelm drug development. AI and ML can reduce the friction and loss from drug development steps, frontload experimental designs and create iterative feedback loops by using new models to leverage all the data.

This is true for serendipitous drug development, through use of real-world patient data; phenotypic drug design, by identifying particular protein targets; and rational drug design, drawing on prior knowledge of the structure, function and mechanism of the target and avoiding random testing of thousands of molecules.

With each exciting discovery in this space, companies are beginning to think about how to apply AI to legacy data and to generate new data specifically suited to AI methods.

Numerous organizations, both new and established, are using AI methods to inform toxicology, to understand metabolics, for lead generation, to predict efficacy, and more.³⁶ Partnerships between companies with drug development expertise and companies with AI expertise are enabling transformative progress without the need for large, risky, internal investments in knowledge and resources.

Quick wins are those that can be plugged into existing data sources, workflows and programs, such as drug mechanistic screening, radiological inputs in oncology or synthetic control arms in rare disease trials. In the meantime, investments in integrating multiple data sources and making data usable for AI are establishing a foundation for future developments. Some collaborations are establishing a full end-to-end development program, such as the agreement between Exscientia and GlaxoSmithKline plc to develop clinical drug candidates for chronic obstructive pulmonary disease (COPD).³⁷

Research activity

500%

Increase in
academic articles
from 2011 to 2020

4.5K

Active clinical
trials* with ~400,000
anticipated patients

"One of the major challenges is ensuring the quality of the data, which is key for developing any AI model. For a predictive model to be effective and accurate, it is important that the dataset has not had bias introduced, such as during data input or in the tagging of data."

Garima Kaul, Senior Director, Clarivate

Key companies

- Abcellera Biologics Inc
- Atomwise
- BenevolentAI
- BioSymetrics
- Cellarity
- Exscientia
- Genesis Therapeutics
- Insilico Medicine
- insitro
- Recursion
- Relay Therapeutics®
- Roivant Sciences
- XtalPi

*As reported for phase 2 or 3 clinical trials that indicate they are enabled by "artificial intelligence" and / or "machine learning" as per their protocol

Market access and impact for patients and society

Other targeted therapies, such as cell and gene therapies, might be entering the market at the same time, offering competition in certain therapeutic areas. However, some RNA therapies might be less expensive and therefore have an advantage.

Development of vaccines using RNA technology have the potential to address long-standing public health challenges and reduce the infectious disease burden in many countries worldwide. Patients with few treatment options are likely to benefit from availability of drugs targeting rare and orphan diseases.

RNA

Development of RNA therapies offers another avenue of targeted treatments for diseases that have been lacking therapeutic options. The COVID-19 pandemic has propelled development of RNA-based vaccines and therapies, helping to pave the way for others to enter the market.

The idea of using RNA to fight disease is not new. It was first investigated three decades ago, but researchers long struggled to overcome the innate challenges of instability and high innate immunogenicity.³⁸ RNA interference (RNAi) can induce targeted gene suppression of particular genes of interest to cause a temporary loss of function, and RNAi drugs such as vutrisiran from Alnylam Pharmaceuticals Inc could help fill the treatment gap for patients with hard-to-treat diseases.

Following the proof-of-concept use of messenger RNA (mRNA) by Moderna and BioNTech SE for COVID-19 vaccines, other hurdles such as manufacturing infrastructure and regulatory acceptance have been overcome.⁸ Their vaccine success has enabled Moderna and BioNTech SE to reinvest in other programs and restore their momentum.

In addition, other established and start-up companies are joining the fray, investing money into determining where the advantages of mRNA will have the greatest benefit (vaccines, therapeutic vaccines and therapies for active disease):³⁸

- Safety (minimized risk of infection or insertional mutagenesis)
- Degradation by normal cellular processes
- Ability to regulate the half-life in vivo
- Ability to modify it for greater stability and translatability
- More consistent, precise results

Self-amplifying RNA (saRNA) has the potential to allow delivery of lower concentrations,³⁸ at lower cost, minimizing the risk of adverse effects and facilitating multivalent administration.

Research activity

36%

Increase in academic articles from 2011 to 2020

46

Active clinical trials* with 2,575 anticipated patients

"RNA as a platform to develop treatments and vaccines was enhanced by its role in the development of vaccines against COVID-19 but it is its potential to treat cancers that will drive future development."

"While there are still stability issues that need to be resolved, a number of research groups and biotech start-ups are now looking to develop next-generation RNA therapeutics."

Mike Ward, Global Head of Thought Leadership, Life Sciences and Healthcare, Clarivate

Key companies

- Abogen Biosciences
- Alnylam Pharmaceuticals
- Arbutus Biopharma Corporation
- Arrowhead Pharmaceuticals
- Ascleptis Pharma Inc
- AstraZeneca
- Benitec Biopharma Inc
- BioNTech SE
- CureVac
- Dicerna Pharmaceuticals Inc
- eTheRNA immunotherapies NV
- InteRNA Technologies
- Ionis
- Moderna
- Phio Pharmaceuticals Corp
- Regulus Therapeutics Inc
- Silence Therapeutics
- StemiRNA Therapeutics
- Sylentis
- VaxEquity
- Viridian Therapeutics Inc

*As reported for phase 2 or 3 clinical trials that indicate drug pipeline technology is RNA-based

Targeted cancer therapies

Market access and impact for patients and society

For patients who have drug-resistant mutations that have failed prior therapies — both non-targeted and targeted — the entry of new therapies is beneficial for disease outcomes and quality of life. These new therapies are advancing the reality of personalized medicine, where treatment options can be tailored to the patient depending on their genetic or molecular makeup.

Market pricing and reimbursement decisions will have an impact on how soon and how many patients are able to take advantage of exciting, targeted drugs in the pipeline such as KRAS inhibitors, EGFR inhibitors, FLT3 inhibitors, non-covalent BTK inhibitors and more.

Targeted cancer therapies are advancing personalized medicine for patients with oncological indications that have a specific genetic component or mutation. Although oncology is a crowded market, these therapies are filling the gaps in efficacious and long-term treatment outcomes. However, a lack of diagnostic infrastructure and high treatment costs could be barriers to patient access.

Drugs entering the market for a selection of indications are becoming more granular regarding biomarkers and targets. For patients with diseases that have long been considered undruggable, including cancers with KRAS^{G12C} mutation, drugs in development such as adagrasib and others are offering hope of an efficacious treatment.

With each successful launch, the industry gains more momentum to continue developing agents targeting other specific mutations. Companies are finding ways to differentiate themselves against competitors that might have labels for broader applications within a specific therapeutic area by identifying niche patient populations who have unmet treatment needs. The oncology market, for example, is becoming increasingly fragmented as companies find ways to navigate the crowded market and achieve a solid commercial return.

Challenges for both researchers and manufacturers include the availability of a suitable, accurate companion diagnostic to identify patients eligible for the drug. For some indications such as metastatic NSCLC, comprehensive genetic test panels are available,³⁹ and physicians are accustomed to routinely screening for a range of mutations to determine the best course of treatment. For other indications that have fewer targeted therapies available, tests are not available, and patients are not routinely tested.

Companion diagnostics will not only influence patient benefit but also market uptake — physicians provided feedback that offering treatment with tazemetostat, a first-in-class, oral EZH2 inhibitor for follicular lymphoma, was challenged by a lack of a biomarker test in clinical practice. Therefore, planning for both the drug and companion diagnostic in the early phases is likely to be beneficial to successfully launch the drug.



Research activity

193%

Increase in academic articles from 2011 to 2020

276

Active clinical trials* with 37,533 anticipated patients

"In the era of precision medicine, biomarker-driven therapies are transforming care across oncology. Integrating biomarker testing in routine clinical practice and educating all stakeholders are critical in this rapidly changing field."

Khurram Nawaz, Senior Director, Oncology, Clarivate

Key companies

- AbbVie
- Amgen
- AstraZeneca
- BeiGene
- CStone Pharmaceuticals
- Eisai Co Ltd
- Eli Lilly and Company
- GlaxoSmithKline plc
- Jiangsu Hengrui Medicine
- Innovent
- Janssen Pharmaceutical Companies of Johnson & Johnson
- Merck
- Mirati Therapeutics Inc
- Novartis
- Roche
- Sanofi
- Shanghai Junshi Biosciences Co Ltd

*As reported for phase 2 or 3 oncology clinical trials that indicate drug pipeline targeted-based action is EGFR



\$32.6B of U.S. sales at risk due to generic competition

Generics comprise most prescriptions in the world's top markets. Their share is only likely to grow, with biosimilars also beginning to make a serious impact.

Generics broaden access to medicines, offer potentially substantial cost savings to patients and payers alike and sustain innovation. However, for originators, the decline in sales can be steep.

Over the next five years

95+

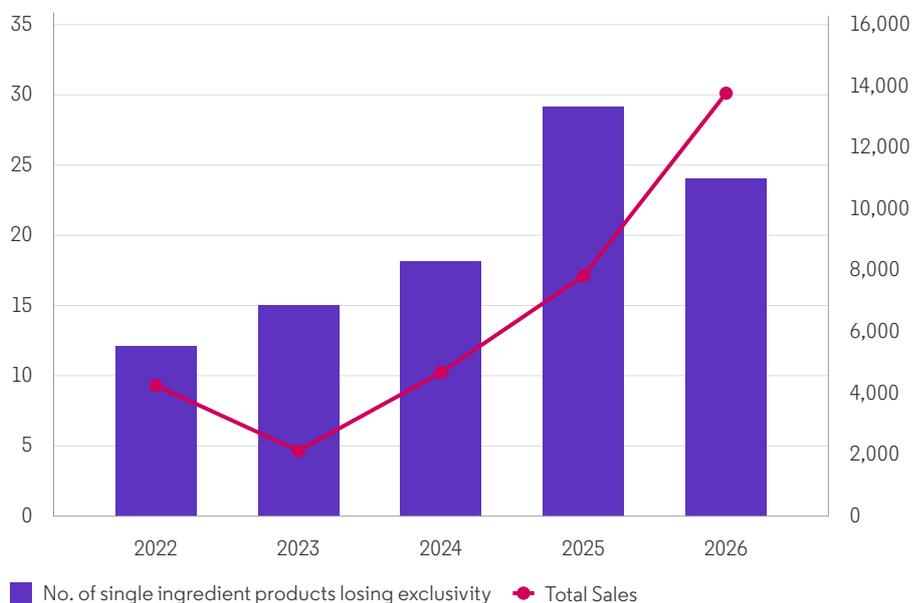
Molecules with total sales valued at

\$32.6B

are predicted to lose exclusivity in the U.S. market.

Biosimilars face a tougher path to market because they are much more difficult, risky and expensive to develop, and it is nearly impossible to precisely duplicate them. Accordingly, the approvals process is far more rigorous. Given that these therapeutics are not identical to the molecules they are designed to imitate, physicians can be reluctant to switch patients to a biosimilar.

U.S. loss of exclusivity landscape: 2022-2026



Source: Cortellis Generics Intelligence

U.S. loss of exclusivity sales value: 2022-2026

Year	Number of single ingredient products losing exclusivity	Total sales (\$M)
2022	12	4,238.1
2023	15	2,142.1
2024	18	4,689.0
2025	29	7,861.8
2026	24	13,701.2

Source: Cortellis Generics Intelligence

As identified in *The future of the generics landscape 2021* report,⁴⁰ key branded drugs losing exclusivity in 2021 and beyond include BROVANA® (arformoterol tartrate), CALQUENCE® (acalabrutinib), HUMIRA® (adalimumab), JANUVIA® (sitagliptin), VEMLIDY® (tenofovir alafenamide), VIMPAT® (lacosamide) and XARELTO® (rivaroxaban). As the drugs with the potentially greatest competition in 2022, this report highlights JANUVIA, VIMPAT and HUMIRA.

With the entry of less expensive options, patients could benefit from additional treatment options, with some patients potentially being able to access therapy for the first time. Conversations with KOLs suggest that this has already been observed with HUMIRA in Europe, where newly diagnosed patients are being prescribed biosimilars, but physicians are less likely to switch patients from HUMIRA to a biosimilar.

Company	Indication	2020 sales and proportion of total 2020 company revenue	Patent expiries
JANUVIA (sitagliptin)			
Merck	T2DM	\$3.31, 6.9%	United States: 30-month stay expiries in 2022-2023 European Union: supplementary protection certificate (SPC) expiries in 2022 Japan: patent expiries in 2026
VIMPAT® (lacosamide)			
UCB	Partial-onset seizures and diabetic neuropathic pain	€1.45, 28.7%	United States: Final FDA approval of ANDAs for lacosamide tablets and oral solution will not be effective until patent expires on March 17, 2022. European Union: SPC expiries in 2022 Japan: Re-examination period in Japan expires on April 7, 2024, while patents expire in 2030
HUMIRA® (adalimumab)			
AbbVie	Autoimmune conditions (e.g., rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, juvenile idiopathic arthritis, ulcerative colitis)	\$19.83, 43.3%	The majority have expired in the United States; the product is generic in the European Union.

Sources: Cortellis Generics Intelligence; 2020 Annual Reports from Merck, UCB and AbbVie



Regulatory impacts on the 2021 Drugs to Watch

Reflecting on the status of the drugs Clarivate analysts identified as potential blockbusters in the Drugs to Watch 2021 report, we found that ADUHELM has encountered considerable challenges following regulatory approval, both from the public and payers, while bimekizumab has been affected by COVID-19-related delays for FDA inspections, ultimately delaying its approval in the United States.

Relugolix might face some competition based on a recently discovered genetic component of endometriosis⁴¹ that could lead to non-hormonal therapies, but it will be many years before it feels the impact. For patients with chronic heart failure with reduced ejection fraction (HFrEF), a new digital patient management tool⁴² could help identify patients that would benefit from vericiguat, potentially increasing its uptake due to a greater awareness of patient-treatment suitability.



Review and approval status:

United States

June 2021: Approval for treatment of AD

July 2021: Indication revised to MCI due to AD or mild AD

Europe

October 2020: MAA submitted

December 2021: EMA rejected the MAA

Japan

December 2020: NDA submitted

February 2021: NDA submitted

Aducanumab (ADUHELM)

Indication(s):

Alzheimer's disease

Description:

Recombinant chimeric human IgG1 mAb targeting A β Novel MOA simultaneously targeting both IL-17A and IL-17F

Company(s):

Biogen Inc and Eisai Co Ltd

Impact:

Initially priced at \$56,000 per year, a price that Biogen promised to freeze for four years

Q3 sales of \$300,000

Prescribed to 43 patients in the United States in 2021**

Slower than expected launch

Awaiting confirmation of clinical benefits from a confirmatory phase 3 trial

PET scan or cerebrospinal fluid (CSF) test is required to determine eligibility

Side effect of ARIA is concerning and requires MRI to monitor

CMS coverage still pending

In the meantime, some commercial insurance companies do not cover it

Renewed industry attention in drugs for AD and dementia signal opportunity for new deals and partnerships to further other drugs

Launched an entire economy on finding new, less invasive and more effective methods of detecting eligible (i.e., amyloid-positive) patients early

Review and approval status:

United States

October 15, 2021: FDA PDUFA date*

Europe

August 2021: Recommended by the U.K. National Institute for Health and Care Excellence (NICE) as an option to treat adults with severe plaque psoriasis

European Commission (EC) granted marketing authorization for moderate to severe plaque psoriasis in adults

Japan

February 2021: NDA submitted

Bimekizumab (BIMZELX)

Indication(s):

Psoriasis

Description:

Humanized monoclonal IgG1 antibody

Novel MOA simultaneously targeting both IL-17A and IL-17F

Company(s):

UCB

*delayed until potentially Q1 2022 due to FDA's inability to conduct onsite facility inspections due to COVID-19 travel restrictions

Review and approval status:

United States

December 2020: Approved to treat prostate cancer

May 2021: Approved by FDA as once-daily treatment for management of heavy menstrual bleeding associated with uterine fibroids

September 2021: FDA accepted for review the supplemental NDA for treatment of endometriosis-related pain

May 6, 2022: PDUFA date

Europe

July 2021: EC approved MAA for the treatment of moderate to severe symptoms associated with uterine fibroids

Japan

February 2019: Approved to treat uterine fibroids

Relugolix (ORGOVYX/ MYFEMBREE)

Indication(s):

Prostate cancer, endometriosis, uterine fibroids

Description:

GnRH receptor antagonist

Company(s):

Takeda Pharmaceutical Co Ltd and licensees Myovant Sciences Ltd, Pfizer Inc, ASKA Pharmaceutical Co Ltd and Gedeon Richter

Impact:

ORGOVYX prescribed to 1078 patients in the United States in 2021**

Review and approval status:

United States

January 2021: Approved for treatment of adults with chronic HFrEF following hospitalization for HF or receiving outpatient intravenous diuretics

Europe

July 2021: EC approved MAA for treatment of adults with chronic HFrEF

Japan

June 2021: Approved for treatment of adults with chronic HFrEF

Vericiguat (VERQUVO)

Indication(s):

HFrEF

Description:

Soluble guanylate cycle stimulator

Company(s):

Bayer and Merck

Impact:

Prescribed to 236 patients in the United States in 2021**

**as of October 26, 2021

Sources: Cortellis Competitive Intelligence, Derwent Innovation, Disease Landscape & Forecast



Key takeaways for industry executives

It's impossible to know with certainty how things will turn out in the unpredictable business of drug approvals, but these seven experimental treatments show great promise to realize improved patient outcomes, as well as financing the next generation of innovative medicines.

Here are the key takeaways from our deep dive into company pipelines:



Drug makers are making great strides towards unlocking technologies that will facilitate truly personalized medicines.

We see this in the emerging field of cell and gene therapies, CRISPR, RNA treatments, digital therapeutics and the use of AI and ML in drug discovery. With patent expiries and a growing number of biosimilars set to take a bite out of company revenues in the coming decade, pharma companies are placing big bets on these technologies in order to realize the next big wave of medical innovation.



These treatments often come with an enormous price tag, so proving their value will be an ever more critical task for pharma companies seeking to win market approval and make them accessible to patients.

This will be particularly so with major markets still absorbing the economic impacts of the pandemic. Payers are increasingly taking a holistic and systemic view of costs, evaluating treatments based on a complex mix of factors and measures rather than a per-unit basis. Innovators can ease approvals and reimbursements by appealing to this big picture on costs.



Regulators are showing an openness to new technologies and methodologies and an appetite for bold action against diseases for which there are few or no treatments,

as we saw with FDA's approval of ADUHELM. While controversial, the agency's move opened up a class of potential treatments — the first advance against the disease in decades — and signaled a willingness to balance temperamental conservatism with calculated risk to address severe patient unmet need.



Pharma's battle against COVID-19 continues,

with hundreds of vaccines and treatments in development even as some markets look to transition from pandemic to endemic disease mitigation.

After a difficult few years for patients, healthcare professionals and all of humanity, we are hopeful that 2022 will be a good year for human health.

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