AscellaHealth®

Specialty and Rare Pipeline Digest™

Q1 • 2025

WELCOME TO ASCELLAHEALTH'S SPECIALTY AND RARE PIPELINE DIGEST™

As the pipeline of new specialty pharmaceuticals continues to evolve, it becomes even more crucial to stay abreast of recent and emerging therapeutic options on the horizon. Our quarterly publication provides all industry stakeholders with important insights into specialty, rare disease and cell and gene therapy pipelines, recent approvals, and upcoming FDA reviews.

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WHO WE ARE

AscellaHealth is a global partner that delivers proven end-to-end solutions to both life sciences and healthcare companies to enhance quality of life for patients with complex, chronic conditions. Every day our team gets critical healthcare products from manufacturers to patients while ensuring an efficient flow of funds between payers and pharma.

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WHAT WE DO

AscellaHealth's global end-to-end solutions for life sciences manufacturers, payers and other stakeholders span the entire product lifecycle and are instrumental in the launch of specialty and rare disease medications, and include:

- Pre-Commercialization & Market Access
- International Specialty Pharmacy Fulfillment
- Exclusive Distribution Partnerships & Supply Chain Logistics
- Patient Support & HUB Services
- Unique Financial Pharmaceutical Services for High-Cost Therapies
- Integrated Copay Assistance Programs
- Specialty Pharmacy & Medical Benefit Management
- Customized Clinical Programs

Recent Branded Specialty Drug Approvals

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Romvimza (vimseltinib)	Ono Pharmaceutical; Deciphera	Oral	Kinase inhibitor	Tenosynovial giant cell tumor (TGCT)	Approved (02/14/2025)	$347,000 annually	Low

On February 14, 2025, the FDA approved Romvimza (vimseltinib) for adult patients with symptomatic tenosynovial giant cell tumor (TGCT) when surgical resection would result in worsening functional limitations or severe morbidity.

Tenosynovial giant cell tumors are noncancerous growths that form in the soft tissue around your joints. They usually do not spread to other parts of the body, but they can develop and grow quickly. They can cause damage to the surrounding tissue and structures of the affected limb. Symptoms can include pain, swelling, tenderness, warmth at the location and limitation of movement of the joint.

The approval was based on data from a trial which evaluated vimseltinib, a kinase inhibitor that inhibits colony-stimulating factor 1 receptor in patients with a confirmed diagnosis of TGCT. Participants received either vimseltinib 30mg or placebo orally twice weekly for 24 weeks. The primary endpoint was overall response rate at week 25. Findings showed an overall response rate (ORR) of 44% among patients treated with vimseltinib compared with an ORR of 0% among placebo treated patients.

Prior to Romvimza, Turalio (pexidartinib) was the only FDA-approved systemic therapy for TGCT, with an ORR of 38% in its trial. Romvimza's comparable ORR (40%) and favorable safety profile position it as a promising alternative for patients with TGCT not amenable to surgery. Unlike Turalio, Romvimza does not carry a black box warning for hepatotoxicity, which may influence treatment preference. Romvimza's cost is approximately 15% higher than the cost for Turalio.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Gomekli (mirdametinib)	Pfizer; SpringWorks Therapeutics	Oral	MEK inhibitor	Neurofibromatosis type 1	Approved (02/11/2025)	$22,000 for pediatric patients and $30,000 for adults per month	Low

On February 11, 2025, the FDA approved Gomekli (mirdametinib) for adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF-1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection.

NF1 is a genetic disorder that currently affects approximately 100,000 children and adults in the US. The NF1 gene codes for neurofibromin, a protein that acts as a tumor suppressor. Patients with the genetic disorder have a 30%-50% lifetime risk of developing PN, which are tumors that grow along the peripheral nerve sheath and are difficult to surgically remove. They can cause skin disfigurement, pain and functional impairment.

Gomekli is a kinase inhibitor that targets mitogen-activated protein kinase kinases 1 and 2. These enzymes are responsible for cell growth and are overactive in patients with NF1.

Approval was based on results from a trial of patients 2 years of age and older with symptomatic inoperable NF1-associated PN causing significant morbidity. The primary endpoint was confirmed overall response rate (ORR), defined as the proportion of patients with at least a 20% reduction in target tumor volume on consecutive scans during the 24-cycle treatment phase. Findings showed treatment with mirdametinib resulted in statistically significant ORRs (41% in adults and 52% in pediatric patients). Median time to onset of response was 7.8 months for the adult cohort and 7.9 months for the pediatric cohort. Additionally, significant improvements in pain and health-related quality of life were observed.

Gomekli will directly compete with Koselugo. Gomekli treats a broader population (inclusive of adults and pediatric patients) where Koselugo has a narrow indication inclusive of pediatric patients.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Journavx (suzetrigine)	Vertex	Oral	Sodium channel blocker	Acute pain	Approved (01/30/2025)	$460 for a 14-day supply	Moderate

On January 30, 2025, the FDA approved Vertex Pharmaceuticals' Journavx® (suzetrigine), a sodium channel blocker, for the treatment of moderate to severe acute pain in adults. Journavx is a first-in-class, oral non-opioid analgesic that selectively blocks the NaV1.8 voltage-gated sodium channel expressed in peripheral sensory neurons, thereby inhibiting the transmission of pain signals to the brain. This is the first approval of a new class of pain medicine in more than 20 years.

The efficacy of Journavx was evaluated in two trials in adult patients with acute pain following abdominoplasty and bunionectomy. In both trials, Journavx demonstrated a statistically significant superior reduction in pain compared to placebo, without any evidence of addictive potential.

Although Journavx did not demonstrate superiority over hydrocodone bitartrate/acetaminophen, it is possible that many patients would accept a less effective medication with a more favorable safety profile. Despite a significantly higher price as compared to generic alternatives ($460 per two-week course of therapy vs. $<10), Journavx may be a consideration to support efforts in curbing the opioid epidemic by reducing unnecessary or inappropriate short-term opioid use. Additionally, the use of Journavx longer than 14 days or as repeated for acute pain episodes has not been studied. These factors will likely limit the use of Journavx until more definitive head-to-head and longer-term studies are conducted.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Ozempic (semaglutide)	Novo Nordisk	Subcutaneous	Glucagon-like peptide-1 (GLP-1) agonist	Chronic kidney disease*	Approved (01/28/2025)	$17,000 per year for 1mg once weekly	Moderate

On January 28, 2025, Novo Nordisk announced that the FDA approved Ozempic® to reduce the risk of kidney disease worsening, kidney failure (end-stage kidney disease), and death due to cardiovascular disease in adults with type 2 diabetes and chronic kidney disease (CKD).

CKD is defined as the presence of kidney damage or decreased kidney function for ≥3 months, regardless of the cause. It involves the gradual loss of the ability to filter waste products from the blood. High blood pressure and diabetes are the main causes of CKD; 50% of CKD patients also have diabetes or CVD.

The approval was based on data from a trial which evaluated the effects of semaglutide as an adjunct to standard of care for the prevention of progression of renal impairment and risk of renal and cardiovascular mortality. The study enrolled 3,533 participants with T2D and CKD. Study participants were randomly assigned to receive semaglutide 1mg once weekly (n=1767) or placebo (n=1766) and were followed for a median of 41 months.

Findings showed treatment with semaglutide reduced the incidence of kidney disease worsening, kidney failure and death from cardiovascular disease by 24% compared with placebo. Additionally, it cut the risk of major cardiovascular events by 18% and reduced the risk of all-cause mortality by 20%.

Ozempic was originally approved in 2017 to treat type 2 diabetes, and in 2020, it was approved to reduce the risk of major cardiovascular events in adults also with known heart disease. Semaglutide, the generic formulation of Ozempic is also approved for weight loss and weight maintenance in patients 12 years and older with obesity.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Leqembi IV (lecanemab)	Eisai; Biogen; BioArctic Neuroscience	Intravenous	Amyloid beta protein inhibitor	Alzheimer's disease*	Approved (01/26/2025)	$13,000 per year for an 80kg patient and monthly dosing	Moderate

Leqembi® was originally granted accelerated approved for the treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of the disease. It received traditional approval on July 6, 2023. Leqembi is the first amyloid-targeting monoclonal antibody to receive full FDA approval.

Alzheimer's disease (AD) is the most common cause of dementia, accounting for an estimated 60% to 80% of cases. It is a progressive, irreversible neurodegenerative disease associated with cognitive, functional, and behavioral impairments. It is thought to be caused by the progressive accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs) formed by aggregated tau protein.

The original approval of Leqembi was based on data from a study which showed that Leqembi reduced the accumulation of plaque in the brain in study participants over 18 months. This approval allows for the maintenance dose of Leqembi to go from once every two weeks to once every four weeks after completing biweekly treatment for 18 months.

The long-term safety and tolerability of lecanemab is currently being evaluated as well. This study is being done to determine whether treatment with lecanemab is superior to placebo at 216 weeks of treatment in reducing brain amyloid accumulation. The estimated study completion is January 2031.

Leqembi can cause amyloid related imaging abnormalities, characterized as ARIA with edema and ARIA with hemosiderin deposition. ARIA is usually asymptomatic, although serious and life-threatening events can occur. ARIA can be fatal and serious intracerebral hemorrhages greater than 1 cm have occurred in patients treated with this class of medications.

Leqembi is the second anti-amyloid monoclonal antibody to be approved by the FDA for the treatment of AD, after Biogen's Aduhelm (aducanumab) in 2021, which has been discontinued by the manufacturer in January 2024. Another agent, Kisunla, was approved in July 2024 as a once-monthly injection for IV infusion for adults with early symptomatic Alzheimer's disease, which includes patients with mild cognitive impairment as well as people with mild dementia stage of AD, with confirmed amyloid pathology. Kisunla is the first and only amyloid plaque-targeting therapy with evidence to support stopping therapy when amyloid plaques are removed, which can result in lower treatment costs and fewer infusions.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Datroway (datopotamab deruxtecan)	AstraZeneca; Daiichi Sankyo	Intravenous	Cytotoxic agent; Topoisomerase I inhibitor; Anti-Trop2 antibody; Antibody-drug conjugate	Hormone receptor positive breast cancer	Approved (01/17/2025)	$415,700 for 70kg patient assuming 17 cycles per year	Low

On January 17, 2025, the FDA approved AstraZeneca (AZ)/Daiichi Sankyo's Datroway (datopotamab deruxtecan-dlnk), a trophoblast cell-surface antigen 2 (TROP2)-directed antibody and topoisomerase inhibitor conjugate, for adult patients with unresectable or metastatic, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (immunohistochemistry [IHC] 0, IHC1+, or IHC2+/in situ hybridization [ISH]−) breast cancer (BC) who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease.

BC is the second leading cause of cancer-related deaths among women. Hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) BC, the most common subtype, affects about 70% of patients with BC, totaling an estimated 221,865 cases per year in the United States.

Approval was based on data from the Phase 3 TROPION-Breast01 trial, in which patients treated with Datroway experienced a median progression-free survival (PFS) of 6.9 months versus 4.9 months for patients who received chemotherapy. The overall response rate (ORR) was 36% for Datroway versus 23% for chemotherapy, and the median duration of response (DOR) was 6.7 months for Datroway and 5.7 months for chemotherapy. However, the difference in median overall survival (OS) between the Datroway and chemotherapy groups, 18.6 months versus 18.3 months, respectively, was not statistically significant.

Datroway will compete primarily with Gilead's Trodelvy (sacituzumab govitecan-hziy), another TROP2-directed antibody-drug conjugate (ADC) approved for a similar patient population with BC. While Trodelvy's label includes a Boxed Warning for neutropenia and diarrhea, Datroway's label carries a Boxed Warning for interstitial lung disease (ILD), pneumonitis, and ocular toxicities, including keratitis and stomatitis.

Datroway is also being evaluated for the treatment of patients with locally advanced or metastatic epidermal growth factor receptor (EGFR)–mutated non–small cell lung cancer (NSCLC) who have received prior systemic treatment. The FDA granted Priority Review designation for Datroway for the NSCLC indication, and a decision is expected in 3Q 2025.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Imcivree (setmelanotide acetate)	Ipsen; Rhythm Pharmaceuticals	Subcutaneous	Peptide melanocortin receptor agonist	Obesity*	Approved (12/20/2024)	$65,000 per month at a dose of 0.5mg per day	Low

On December 20, 2024 Rhythm Pharmaceuticals announced that the FDA has approved an expanded indication for Imcivree (setmelanotide) to include children as young as 2 years old. Imcivree is now indicated to reduce excess body weight and maintain weight reduction long-term in patients 2 years of age and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS) or genetically confirmed pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin type 1 (PCSK1), deficiency or leptin receptor (LEPR) deficiency. Imcivree first received approval in November 2020 for patients 6 years old and older with POMC, PCSK1 or LEPR deficiencies and approval in June 2022 for use in patients with BBS.

BBS and POMC, PCSK1 and LEPR deficiencies are rare melanocortin-4 receptor (MC4R) pathway diseases with hallmark characteristics that include hyperphagia, or pathological, insatiable hunger and impaired satiety accompanied by persistent and abnormal food-seeking behaviors, and early-onset obesity. Imcivree is the first and only precision medicine to target impairment of the hypothalamic MC4R pathway, a root cause of hyperphagia and obesity due to BBS and POMC, PCSK1 and LEPR deficiencies in adults and children as young as 2 years old.

The approval for younger patients was based on data from a study which included 12 patients aged 2 to less than 6 years of age with obesity due to biallelic POMC/PCSK1 or LEPR deficiency or a clinical diagnosis of BBS. The results demonstrated 83.3% of patients achieved a clinically meaningful decrease in BMI and the majority of caregivers reported a reduction in patient hunger at 52 weeks compared with before the trial.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Trikafta (tablets) (elexacaftor; ivacaftor; tezacaftor)	Vertex	Oral	CFTR corrector; CFTR potentiator	Cystic fibrosis patients with CFTR gene mutations*	Approved (12/20/2024)	$346,000 per year	Moderate
Alyftrek (deutivacaftor; tezacaftor; vanzacaftor)	Vertex	Oral	CFTR corrector; CFTR potentiator	Cystic fibrosis patients with CFTR gene mutations	Approved (12/20/2024)	$370,000 per year	Moderate

Trikafta (elexacaftor/tezacaftor/ivacaftor) was FDA approved to treat cystic fibrosis (CF) in October 2019 and has received approval for multiple label expansions since that time. Trikafta is currently approved for the treatment of CF in patients 2 years of age and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive.

Cystic fibrosis is an inherited autosomal recessive disease caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Normally, a healthy CFTR gene makes a protein known as CFTR that is found in the cells that line various organs, like the lungs and the pancreas. The protein controls the movement of chloride ions into and out of cells, which also determines the movement of water across cells. Mutations in the CFTR protein gene lead to the creation of a dysfunctional protein or a shortage or absence of CFTR protein at the cell surface, causing cells to produce mucus that is abnormally thick and sticky.

Cystic fibrosis is a progressive, multi-organ, life-threatening disease, with the greatest impact on the lungs. Abnormal mucus in the lungs can lead to airway obstruction, inflammation, and infection. Over time, significant lung damage occurs leading to tissue remodeling, progressive deterioration in lung function, and ultimately respiratory failure.

On December 20, 2024, the FDA approved 94 additional non-F508del CFTR mutations to be added to the Trikafta label. This means approximately 300 additional patients with CF in the United States are eligible for treatment with Trikafta. Additionally, the FDA also updated safety information regarding liver injury and liver failure from warnings and precautions to a boxed warning.

On December 20, 2024, the FDA approved Vertex Pharmaceuticals' Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor) oral tablets for the treatment of cystic fibrosis (CF) in patients 6 years of age and older who have at least one F508del mutation or another responsive in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Approval of Alyftrek was supported by results from several trials, which compared once-daily Alyftrek with twice-daily Trikafta (elexacaftor, tezacaftor, and ivacaftor) in patients >12 years of age. The results showed that Alyftrek was noninferior in the change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) compared with Trikafta, and a superior reduction in sweat chloride (SwCl) levels through week 24. Alyftrek was also evaluated in a trial for children 6 to 11 years of age. This trial demonstrated a safety profile consistent with the adult trials. Additionally, it showed further reduced levels of SwCl compared with baseline treatment with Trikafta.

Alyftrek competes mainly with Vertex's own Trikafta and the company's other CFTR modulator products. Given its enhanced efficacy in reducing SwCl levels and once-daily dosing, Alyftrek may gain market share as compared to Trikafta.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Alhemo (concizumab)	Novo Nordisk	Subcutaneous	Tissue factor pathway inhibitor (TFPI) antagonist	Hemophilia A or B	Approved (12/20/2024)	$750,000 per year for a 60kg patient and a dose of 0.2mg/kg once daily.	High

On December 20, 2024, the FDA approved Novo Nordisk's Alhemo (concizumab-mtci), a tissue factor pathway inhibitor (TFPI) antagonist, to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ≥12 years of age with hemophilia A (congenital factor VIII [FVIII] deficiency) with FVIII inhibitors or hemophilia B (congenital factor IX [FIX] deficiency) with FIX inhibitors.

Hemophilia is an X-linked genetic disease that interferes with the normal coagulation process, which causes bleeding into soft tissues, joints, and internal organs. Hemophilia can also cause severe bleeding and death in traumatic incidents.

Alhemo works by reducing the amount, and therefore, the activity of naturally occurring tissue factor pathway inhibitor (TFPI). This increases the amount of thrombin that is generated, which is expected to prevent or reduce the frequency of bleeding episodes. Traditional hemophilia treatments work by replacing clotting factors.

The approval of Alhemo was based on a study in which patients were given either on-demand treatment with bypassing agents or prophylaxis with Alhemo. Patients receiving Alhemo had an 86% reduction in the annualized bleeding rate (ABR) compared to those who received no prophylaxis. The estimated mean ABR was 1.7 for patients receiving Alhemo prophylaxis and 11.8 for patients not on prophylaxis.

Alhemo is the second TFPI antagonist approved for the treatment of hemophilia A and B. The first was Pfizer's Hympavzi (marstacimab-hncq), a weekly subcutaneous TFPI antagonist, approved in October 2024 for the treatment of hemophilia A and B without inhibitors. It is currently being studied in patients with inhibitors and results are expected in 3Q 2025. Additionally, a decision is expected for Sanofi/Alnylam's fitusiran, a once-month subcutaneous small interfering ribonucleic acid agent. Alhemo is also being investigated in patients with hemophilia A and B without inhibitors and a decision is expected in July 2025.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Zepbound (tirzepatide)	Eli Lilly	Subcutaneous	Glucagon-like peptide-1 (GLP-1) agonist; Glucose-dependent insulinotropic polypeptide (GIP) receptor agonist	Sleep apnea*	Approved (12/20/2024)	$14,000 per year	Low

On December 20, 2024, the FDA approved Eli Lilly's Zepbound for adults with moderate-to-severe obstructive sleep apnea (OSA) and obesity. Zepbound is the first prescription drug to be approved for this indication. Positive airway pressure (PAP) therapy is recommended to most patients with OSA but involves wearing a mask overnight which deters many people from using it.

Approval of Zepbound for OSA was based on results from a trial which evaluated Zepbound for the treatment of moderate-to-severe OSA in adults with obesity, with and without PAP therapy compared with placebo for 12 months. Patients in the Zepbound without PAP group experienced 25 fewer breathing disruption per hour compared with 5 fewer in patients who received placebo. In patients who received AP therapy, Zepbound demonstrated 29 fewer breathing disruption per hour compared with 67 in patients who received placebo. After one year, 42% of patients who received Zepbound only and 50% of patients who received Zepbound with PAP therapy experienced remission or mild, non-symptomatic OSA, compared with 16% and 14% of patients who received placebo, respectively.

Zepbound is the first prescription drug and the first anti-obesity medication (AOM) to be approved for OSA and the second AOM to receive an expanded indication outside of chronic weight management, after Novo Nordisk's Wegovy (semaglutide) received approval to reduce the risk of major adverse cardiovascular events (MACEs) in patients with obesity or overweight in March 2024. Additionally, Wegovy is currently being investigated in the treatment of metabolic dysfunction-associated steatohepatitis (MASH) as well as for the treatment of heart failure in patients with obesity. Zepbound is also being studied in the treatment of heart failure in patients with obesity.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Tryngolza (olezarsen Sodium)	Ionis Pharmaceuticals; Akcea	Injectable	Antisense oligonucleotide	Familial chylomicronemia syndrome (FCS)	Approved (12/19/2024)	$595,000 per year	Low

On December 19, 2024, the FDA approved Ionis Pharmaceuticals' Tryngolza (olezarsen), an antisense oligonucleotide-GalNAc3 conjugate that reduces serum apolipoprotein C-III (apoC-III), as an adjunct to diet to reduce triglycerides (TGs) in adults with familial chylomicronemia syndrome (FCS).

Tryngolza is the first FDA-approved treatment for FCS, a rare, genetic form of severe hypertriglyceridemia (sHTG) that can lead to acute pancreatitis (AP). Patients with FCS typically have fasting TG levels ≥880 mg/dL (normal: <150 mg/dL) and a history of pancreatitis.

The approval was based on data from the double-blind, placebo-controlled study, which included adult patients with genetically identified FCS and fasting TG levels greater than or equal to 880mg/dL. The trial included a run-in period where patients followed a low-fat diet (≤20g fat per day) for at least 4 weeks, after which they were randomly assigned to receive olezarsen 80mg or placebo as a subcutaneous injection once every 4 weeks. The primary endpoint was the percent change from baseline in fasting triglyceride levels at 6 months.

Results showed a statistically significant reduction of 42.5% in fasting triglyceride levels with olezarsen 80mg compared with placebo at 6 months. Consistent lowering of triglyceride values was observed over the 12-month treatment period; the mean reduction at month 12 was 57%.

Another drug for the treatment of FCS, Arrowhead Pharmaceuticals' plozasiran, is currently being reviewed by the FDA with a decision expected by November 2025.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Cost	Impact
Crenessity (crinecerfont)	Neurocrine Biosciences	Oral	Corticotropin-releasing factor type 1 (CRF1) receptor antagonist	Congenital adrenal hyperplasia	Approved (12/13/2024)	$466,000 per year for capsules	Low

On December 13, 2024, the FDA approved Crenessity (crinecerfont) capsules and oral solution as an adjunct to glucocorticoid (GC) replacement therapy for the control of androgens in adults and pediatric patients 4 years of age and older with classic congenital adrenal hyperplasia (CAH).

Classic CAH is a genetic disorder that impairs the production of cortisol and aldosterone and requires lifelong treatment with GCs. Crenessity is a corticotropin-releasing factor type 1 (CRF1) receptor antagonist designed to control excess adrenal androgens through a non-glucocorticoid mechanism, allowing for a reduction in the glucocorticoid dose needed to maintain disease stability.

Crenessity was tested in two separate trials: one for children and adolescents and one for adults. Results from both studies showed that after 28 weeks, crinecerfont hit its primary endpoint of producing a statistically significant reduction in daily glucocorticoid dose compared to placebo, while also maintaining androgen control.

Reducing daily GC doses can significantly improve a patient's quality of life and reduce the risk of the many adverse effects associated with long-term GC use. No long-term studies with Cressenity have demonstrated these effects or shown a decrease in healthcare-related expenditures. At the expected cost of approximately $466,000 annually, this will need to be shown to minimize the long-term effects of GC use.

Pending FDA Approvals

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Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
Amvuttra (vutrisiran sodium)	Alnylam Pharmaceuticals; Arbutus Biopharma	Subcutaneous	Small interfering RNA (siRNA)	Transthyretin amyloid cardiomyopathy (ATTR-CM)	Pending (03/23/2025)	sNDA

Amvuttra is an RNA-interference (RNAi) therapy being investigated for the treatment of ATTR amyloidosis with cardiomyopathy (ATTR-CM). ATTR-CM is a potentially fatal condition affecting mostly older adults. It occurs when the TTR protein misfolds and amyloid deposits build up in the extracellular space of the heart's muscle tissues. This causes the heart walls to become stiff, affecting the regular pumping of blood. Amvuttra rapidly knocks down mutant and wildtype TTR in order to address the underlying cause of ATTR-CM. Amvuttra is currently approved to treat polyneuropathy of hereditary transthyretin-mediated hATTR (hATTR-PN).

Amvuttra was studied in a Phase III HELIOS-B trial, in which Amvuttra met the primary endpoint, demonstrating a statistically significant reduction in the composite of all-cause mortality and recurrent cardiovascular events during the double-blind period in both the overall population of 654 patients, including those who were on Pfizer's tafamadis, and in the monotherapy population (patients not receiving tafamadis at baseline).

Results demonstrated that Amvuttra reduced the risk of death or recurrent cardiovascular events by 28% versus placebo. Of those in the monotherapy group—which comprised 60% of the patients in the trial—Amvuttra reduced the risk of death or recurrent cardiovascular events by 33% compared to placebo. Additionally, in the overall patient population there was a 36% reduction in the risk of death up to month 42, while in the Amvuttra monotherapy group, there was a 35% reduction in the risk of death over the same period.

As an RNA interference drug, Amvuttra may have a mechanism of action edge on tafamidis and the recently approved Attruby as a TTR silencer. While it reduces the circulating levels of the transthyretin (TTR) protein and hence the amyloid clumps in the heart, tafamidis works by stabilizing the TTR.

If approved, Amvuttra will introduce a novel mechanism of action in the treatment of ATTR-CM, which may appeal to patients who experience inadequate response to tafamidis. The cost is projected to be similar to the cost for hATTR-PN, about $477,000 per year, which is nearly twice as much as tafamidis and Attruby.

Amvuttra would be the first drug in the broader amyloidosis category to have an indication to treat both hATTR-PN and ATTR-CM, which may make it the preferred agent amongst patients with a mixed phenotype, exhibiting symptoms of both PN and CM.

Wainua (eplontersen) was approved in 2023 for the treatment of hATTR-PN and is currently being investigated for ATTR-CM. The estimated primary completion date of the study is April 2026, with approval potentially later in 2026.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
DCCR (diazoxide choline)	Soleno Therapeutics	Oral	Potassium channel opener	Prader-Willi syndrome	Pending (03/27/2025)	505b2 NDA

DCCR is an extended release, crystalline salt formulation of diazoxide and is administered as an oral tablet formulation once daily for Prader-Willi Syndrome (PWS) in patients 4 years of age and older. The parent molecule, diazoxide, has been used for decades in rare diseases in neonates, infants, children and adults, but is not approved for use in PWS.

PWS is a rare and complex genetic multisystem disorder resulting from the loss of function of specific genes on chromosome 15 leading to disintegration in the regular function of the hypothalamus. It is characterized by severe hypotonia and poor feeding during early infancy, followed by a tremendous appetite that develops between 2 and 6 years of age, which results in the gradual development of morbid obesity in early childhood. The mechanism in which DCCR exerts its therapeutic benefit is through reducing the synthesis and secretion of the appetite stimulatory neuropeptides NPY and AgRP, thereby reducing hyperphagia.

Individuals often exhibit developmental delays, behavioral issues, and some degree of cognitive impairment. Hypogonadism is present in both males and females and manifests as genital hypoplasia, incomplete pubertal development, and, in most, infertility. Common physical features include short stature, distinct facial characteristics, strabismus, and scoliosis. Obesity associated with Prader-Willi syndrome leads to many predictable complications, including cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), dyslipidemia, diabetes, sleep apnea, and respiratory failure.

DCCR was evaluated in a trial of 127 patients, 4 years of age and older. The results showed that patients in the DCCR group experienced improvement in body composition, as evidenced by statistically significant changes in lean body mass and the ration of lean body mass to fat mass, based on DXA scanning. Additionally, patients in the DCCR group had reduced levels of leptin, fasting insulin, and an improvement in insulin sensitivity, as well as a statistically significant increase of adiponectin, a cardioprotective marker, compared to placebo.

There are currently no approved therapies to treat hyperphagia and related behaviors of PWS. There are multiple drugs in the pipeline, including one late phase competitor, Acadia's ACP-101, with possible approval in 2027. Growth hormone products are typically given to address the growth failure associated with PWS.

The estimated cost is between $200,000 and 400,000 per year.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
Fitusiran (fitusiran)	Sanofi; Genzyme; Alnylam Pharmaceuticals	Subcutaneous	Small interfering RNA (siRNA)	Hemophilia A or B	Pending (03/28/2025)	NDA
Alhemo (concizumab)	Novo Nordisk; Dicerna Pharmaceuticals	Subcutaneous	Tissue factor pathway inhibitor (TFPI) antagonist	Hemophilia A or B*	Pending (07/2025)	BLA

Fitusiran, is a small interfering RNA subcutaneous therapy being developed to prevent bleeding episodes in adults and adolescents with hemophilia A or B, with or without inhibitors.

Hemophilia is a disease that interferes with the normal coagulation process. This causes bleeding into soft tissue, joints, and internal organs. It can also cause severe bleeding and death in traumatic incidences. The two most common types of hemophilia are hemophilia A, which is the lack of factor VIII (FVIII) and hemophilia B, which is the lack of factor IX (FIX). Both genes are located on the X chromosome, therefore, almost all people who have hemophilia are male.

Patients with hemophilia A typically receive prophylaxis with factor VIII products or Hemlibra and patients with hemophilia B typically receive prophylaxis with factor IX products. Treatment with factors is incredibly burdensome for patients and costly. Hemgenix and Beqvez are approved gene therapies for the treatment of hemophilia B (approved on November 22, 2022, and April 25, 2024, respectively) and Roctavian is an approved gene therapy for the treatment of Hemophilia A (approved June 29, 2023).

Fitusiran is a RNA-based therapy designed to limit the production of antithrombin, a natural anticoagulant protein that inhibits multiple clotting factors. The antithrombin protein is coded in the genome by the SERPINC1 gene. When that gene is read, an intermediary molecule called SERPINC1 messenger RNA (mRNA) is made to be used by the cell's protein-making machinery as template for antithrombin's production.

As a small interfering RNA (siRNA), fitusiran works by binding to and promoting the degradation of SERPINC1 mRNA molecules, thereby interfering with the synthesis of antithrombin and reducing its levels. A particular feature of fitusiran is that it contains a molecule called N-acetylgalactosamine attached to the siRNA molecule. This is designed to deliver the therapy directly to liver cells, which are the main producers of clotting factors. By limiting the production of antithrombin in the liver, fitusiran is expected to improve the body's ability to form blood clots. This may help to control excessive bleeding or bruising in hemophilia patients, regardless of the presence of neutralizing antibodies (inhibitors) against FVIII or FIX.

Fitusiran was evaluated in a multi-part trial (ALTAS-A/B, ATLAS-INH and ATLAS-PPX) with each study demonstrating a significant reduction in annualized bleeding rates as compared to traditional factor therapies.

Potential advantages of fitusiran include less frequent dosing, it can be used in patient with or without inhibitors and has the potential to eliminate risk of inhibitor formation. The estimated annual cost is projected to be between $750,000 and $1,000,000.

On December 20, 2024, the FDA approved Novo Nordisk's Alhemo (concizumab-mtci), a tissue factor pathway inhibitor (TFPI) antagonist, to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ≥12 years of age with hemophilia A (congenital factor VIII [FVIII] deficiency) with FVIII inhibitors or hemophilia B (congenital factor IX [FIX] deficiency) with FIX inhibitors.

It is now being investigated to expand its current indication to include the prevention or reduction of the frequency of bleeding episodes in adult and pediatric patients ≥12 years of age with hemophilia A (congenital factor VIII [FVIII] deficiency) without FVIII inhibitors or hemophilia B (congenital factor IX [FIX] deficiency) without FIX inhibitors in addition to those with inhibitors for hemophilia A and B.

Alhemo is the second TFPI antagonist approved for the treatment of hemophilia A and B. Unlike traditional hemophilia treatments that replace clotting factors, Alhemo reduces the amount, and therefore, the activity of, naturally occurring TFPI. This increases the amount of thrombin that is generated, which is expected to prevent or reduce the frequency of bleeding episodes.

The study evaluating the safety and efficacy of Alhemo in patients with hemophilia A and B without inhibitors included male patients 12 years of age or older who had severe hemophilia A, moderate or severe hemophilia B and did not have inhibitors. Additionally, these participants were on replacement treatment within 24 weeks before screening. After a pause due to non-fatal blood clots that arose in three patients, the study resumed. Patients were treated with either concizumab or on-demand clotting factor. The primary endpoint was the number of spontaneous and traumatic bleeding episodes for patient with hemophilia A and hemophilia B separately. Patients treated with concizumab, delivered daily under the skin for at least 32 weeks using an injector pen reduced mean annualized bleeding rates by 86% in patients with hemophilia A and by 79% in patients with hemophilia B.

The cost for a 70kg patient is approximately between $960,000 to 1.1 million annually.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
Translarna (ataluren)	PTC Therapeutics	Oral	Inhibitor of premature protein translation termination	Duchenne muscular dystrophy	Pending (1Q 2025)	NDA

Translarna is a protein restoration therapy designed to enable the formation of a functioning protein in patients with genetic disorders caused by a nonsense mutation. A nonsense mutation is an alteration in the genetic code that prematurely halts the synthesis of an essential protein. The resulting disorder is determined by which protein cannot be expressed in its entirety and is no longer functional, such as dystrophin in Duchenne muscular dystrophy (DMD). Around 13% DMD cases are caused by this type of mutation.

Duchenne muscular dystrophy is a progressive, X-linked, degenerative neuromuscular disease that results in disabling muscle weakness and eventually leads to early death. DMD is caused by mutations in the dystrophin gene resulting in reduced or near absence of dystrophin, a protein that helps keep muscle cells intact. The estimated incidence of DMD is 1 in 3,500–5,000 male births (i.e., 400 to 600 boys per year) with prevalence estimates ranging between 10,000 and 15,000 males.

The study evaluated Translarna versus placebo and the results showed that after 72 weeks of Translarna treatment, there was a significant benefit demonstrated in the six-minute walk distance (6MWD), NorthStar Ambulatory Assessment, 10-meter walk/run, 4-stair climb, and time to 10% worsening of 6MWD. Additionally, the results showed significant long-term treatment benefit, with treatment resulting in a 3.5-year delay in loss of ambulation and a 1.8-year delay in reaching a predicted forced vital capacity of less than 60%, a critical threshold of lung function compared to standard of care. If approved, Ataluren would be the first protein translation termination inhibitor indicated for the treatment of nonsense mutation DMD and would be an add on treatment to standard of care corticosteroids.

The annual cost is projected to be between $750,000 and $1,000,000.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
Dupixent (dupilumab)	Sanofi; Genzyme; Regeneron	Subcutaneous	Interleukin 4 receptor (IL-4R) antagonist	Chronic idiopathic urticaria (CIU)*	Pending (04/18/2025)	sBLA

Dupixent is a monoclonal antibody that blocks the interleukin (IL)-4 receptor alpha, leading to the inhibition of IL-4 and IL-13 cytokine signaling. Dupixent is currently approved for atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, prurigo nodularis and chronic obstructive pulmonary disease.

Chronic spontaneous/idiopathic urticaria (CIU) occurs when cases of hives (i.e., urticaria) lasts more than six weeks and can last months or up to 5 years. It can affect 1.4% of the general population and is seen in women twice as commonly as men. CIU is commonly treated with second generation antihistamine products.

The LIBERTY-CSU CUPID program includes three randomized, double-blind, placebo-controlled Phase 3 trials called Studies A, B and C. The primary outcome of all studies is change from baseline in weekly itch severity score (ISS7) at Week 24. The ISS7 is derived by adding up the average daily itch scores from the 7 preceding days. The ISS7 ranges from 0 to 21. Each day the patient scores their itch on a scale of 0 (no itch) to 3 (severe itch).

In Study A, Dupixent was evaluated as add-on therapy to standard-of-care H1 antihistamines compared to antihistamines alone in patients with CSU 6 years of age and older who remained symptomatic despite antihistamine use and were not previously treated with omalizumab. The results showed a 63% reduction in ISS7 with Dupixent versus 35% with placebo.

In Study B, Dupixent was evaluated as add-on therapy to standard-of-care H1 antihistamines compared to antihistamines alone in patients with CSU 12 years of age and older who remained symptomatic despite antihistamine use and were intolerant or incomplete responders to Xolair. In this trial, positive numerical trends in reducing itch and hives were observed, but the results from the interim analysis did not demonstrate statistical significance.

Study C enrolled 151 children six years of age and older and adults with uncontrolled, biologic-naïve CSU receiving background therapy with antihistamines. Participants were randomized to receive Dupixent or placebo added to H1 antihistamines. The primary endpoint was the change from baseline in itch at 24 weeks (measured by the weekly itch severity score [ISS7], 0-21 scale). At 24 weeks, efficacy results were as follows: an 8.64-point reduction in itch severity from baseline with Dupixent versus a 6.10-point reduction with placebo. A 15.86-point reduction in urticaria activity (itch and hive) severity from baseline with Dupixent versus an 11.21-point reduction with placebo. In addition, 30% of Dupixent-treated patients reported no urticaria (complete response) compared to 18% of those on placebo.

The LIBERTY-CSU CUPIDKids trial is evaluating the pharmacokinetics and safety of Dupixent in patients ≥2 years to <12 years of age with uncontrolled CSU despite the use of H1-antihistamine treatment. The trial is estimated to be completed in 3Q 2025.

Dupixent will compete with Xolair, currently the only biologic currently approved for CSU, to treat patients 12 years of age and older with moderate to severe CSU who are refractory to H1 antihistamines. The lack of demonstrated efficacy of the LIBERTY-CSU CUPID Study B will likely limit Dupixent's use to patients who are Xolair treatment-naïve.

The estimated cost is $52,000 per year. The cost of Xolair is $73,600 per year.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
Tremfya (guselkumab)	Johnson & Johnson (Janssen); MorphoSys	Intravenous; Subcutaneous	Interleukin 23 (IL-23) antagonist	Crohn's disease	Pending (04/2025)	sBLA

Tremfya is a monoclonal antibody that targets IL-23 and is being investigated for the treatment of Crohn's Disease in adults. Tremfya is currently approved for plaque psoriasis, psoriatic arthritis and moderate to severe ulcerative colitis.

Crohn's Disease (CD) is an inflammatory bowel disease that causes chronic inflammation of the gastrointestinal tract. The peak incidence of CD occurs among patients aged 15 to 25 years, but all ages are affected. Hallmark/cardinal symptoms of CD include abdominal pain, diarrhea, and fatigue; weight loss, fever, growth failure, anemia, recurrent fistulas, or extraintestinal manifestations can also be presenting features.

One trial evaluating the safety and efficacy of Tremfya versus Stelara showed that after 48 weeks of treatment, 37.2% and 33.2% of patients who received subcutaneous Tremfya at 200mg every four weeks and 100mg every eight weeks, respectively, achieved endoscopic remission. The rate was 24.7% for those who received Stelara.

The results of another study showed 56.1% of patients treated with subcutaneous Tremfya achieved clinical remission at 12 weeks, versus 21.4% in the placebo group. At 48 weeks, the clinical remission rate jumped to 60% for patients taking the 100mg maintenance dose of Tremfya, given every eight weeks. Maintenance at 200mg every four weeks resulted in a 66.1% clinical remission rate and the rate for the placebo group was 17.1%. Additionally, clinical remission was achieved by 70.3% of patients on Tremfya 200mg SC every 4 weeks and 100mg SC every 8 weeks respectively compared to 62.9% of patients on Stelara.

If approved, Tremfya will be the only IL-23 inhibitor to offer both subcutaneous and intravenous induction options for Crohn's disease. The cost is projected to be between $100,000 and $200,000 annually.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
Nucala (mepolizumab)	GSK	Subcutaneous	Interleukin 5 (IL-5) antagonist	COPD with eosinophilic bronchitis	Pending (05/07/2025)	sBLA

Nucala is an anti-interleukin 5 (IL-5) monoclonal antibody initially approved by the FDA in 2015 for severe eosinophilic asthma. It is also indicated for the treatment of chronic rhinosinusitis with nasal polyps, eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome. It is now being investigated as an add-on therapy to maintenance treatment for chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype.

COPD is a common, chronic lung disease. It results from gene-environment interactions occurring over an individual's lifetime that can damage the lungs and/or alter their normal development/aging process. Tobacco smoking and indoor/outdoor air pollution are the most common causes of COPD. People with COPD are at higher risk of other health problems such as lung infections, lung cancer, cardiovascular diseases, osteoporosis, depression, and anxiety.

Eosinophilic COPD is a type of COPD that is characterized by high levels of eosinophils in the blood. Eosinophils are a type of white blood cell that play a role in inflammation.

The study investigating Nucala in the treatment of COPD with an eosinophilic phenotype is supported by data from several studies. In the trials, Nucala was studied as add-on to triple inhaler therapy in COPD patients with a history of exacerbations.

Current or former smokers (≥10 pack-years) and nonsmokers were included. In the METREX trial, patients were included regardless of blood eosinophil levels. In the METREO trial, only patients with an eosinophilic phenotype were eligible. The primary endpoint of both trials was the annual rate of moderate and severe exacerbations. The primary outcome was statistically significant in the METREX trial but not the METREO trial.

A third Phase 3, randomized, double-blind, placebo-controlled trial called MATINEE (NCT04133909) is being conducted in patients with COPD on triple inhaler therapy who are current or former smokers (history of cigarette smoking of ≥10 pack-years) with an eosinophil count of ≥300 cells/μL at study entry and a history of ≥150 cells/μL within the past year. Participants had to experience one or more severe exacerbations requiring hospitalization or two or more moderate exacerbations in the past 12 months. In MATINEE, Nucala is administered as a SC injection (100 mg/ml) once every 4 weeks, which is the same dosing regimen used to treat adults with asthma. In September 2024, GSK announced that MATINEE met the primary endpoint with a statistically significant reduction in the annualized rate of moderate/severe exacerbations versus placebo with patients treated for up to 104 weeks. Numerical data were not disclosed. The preliminary safety results appear to be consistent with the known safety profile of Nucala.

Nucala will compete with Dupixent for the same patient population: as an add-on to triple inhaler therapy in patients with moderate to severe eosinophilic COPD and a history of exacerbations. The estimated annual cost is approximately the same cost as the treatment cost for asthma, $49,400.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
KVD900 (sebetralstat)	KalVista Pharmaceuticals	Oral	Plasma kallikrein inhibitor	Hereditary angioedema	Pending (06/17/2025)	NDA
IONIS-PKK-LRx (donidalorsen sodium)	Ionis Pharmaceuticals	Subcutaneous	Antisense oligonucleotide	Hereditary angioedema	Pending (08/21/2025)	NDA

Sebetralstat is an oral plasma kallikrein inhibitor under investigation for on-demand treatment of HAE attacks in adults and in patients aged 12 years and older.

Hereditary angioedema (HAE) is a rare genetic disorder that results in unpredictable, recurrent attacks of localized subcutaneous or mucosal swelling in various parts of the body including the face, hands, feet, airways, and intestinal tract. Attacks can happen at any age after birth. HAE affects ~1:50,000 (or ~7,000) individuals in the United States.

Treatment of HAE uses 2 broad strategies for medical management.

- On-demand therapy to minimize the impact of HAE attacks. FDA-approved products for on-demand treatment include: Firazyr, Berinert, Kalbitor, and Ruconest.
- Prophylactic therapy in appropriate patients, to reduce the frequency and severity of attacks. Cinryze, Haegarda, Takhzyro and Orladeyo are approved for prophylaxis.

One study evaluated the safety and efficacy of sebetralstat 300mg and 600mg versus placebo for the on-demand treatment of HAE in adult and pediatric patients 12 years of age and older. A total of 136 patients participated in the study. The results showed that participants in the 300mg dose had a median time to symptom relief of 1.61 hours and the 600mg dose yielded symptom relief at a median time of 1.79 hours, while placebo required a median of 6.72 hours to yield symptom relief. The secondary endpoints for both the 300mg dose and 600mg dose showed that participants receiving sebetralstat achieved a significantly faster time to reduction in attack severity and faster time to complete attack resolution compared to placebo.

If approved, sebetralstat would be a more convenient oral option compared to current therapies, such as intravenously administered Ruconest and Berinert, subcutaneous Firazyr or Kalbitor.

The estimated annual cost is approximately $200,000-$300,000 per year.

Donidalorsen is an antisense oligonucleotide designed to target and block the production of prekallikrein (PKK), a precursor of plasma kallikrein. It is intended to lower levels of plasma kallikrein and subsequently lower the risk of swelling attacks in adult and pediatric patients 12 years of age and older. Donidalorsen is under development as a once monthly/every 2 months subcutaneous (SC) injection for the prevention of HAE attacks.

The new drug application was based on results from the phase 3 OASIS-HAE and OASISplus studies and the ongoing phase 2 open-label extension (OLE) study. In the ongoing phase 2 OLE and phase 3 studies, donidalorsen was found to reduce HAE attacks with an overall sustained mean reduction rate of 96% from baseline. This result was maintained for up to 3 years.

If approved, donidalorsen would be the first once monthly/every 2 months SC prekallikrein antisense oligonucleotide for the prevention of HAE attacks. It would compete with the following prophylactic products:

- CSL's Haegarda administered SC twice weekly (every 3 or 4 days).
- Takeda's Takhzyro, which is dosed SC every 2 weeks. Takhzyro's dosing interval can be extended to every 4 weeks in patients that are well controlled for 6 months.
- BioCryst's Orladeyo administered orally once daily.
- Takeda's Cinryze administered intravenously twice a week (every 3 or 4 days).

Donidalorsen's comparable efficacy and once monthly/every 2-month dosing interval may provide an administration frequency advantage over other plasma kallikrein inhibitors (e.g. Takhzyro and Orladeyo).

The estimated annual cost is between $500,000 and $750,000.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
M281 (nipocalimab)	Momenta; Johnson & Johnson (Janssen)	Intravenous; Subcutaneous	FcRn antagonist	Myasthenia gravis	Pending (2Q 2025)	BLA

Nipocalimab is an investigational monoclonal antibody that binds with high affinity and specificity to block neonatal fragment crystallizable receptor (FcRn) and reduce levels of circulating immunoglobulin G (IgG) autoantibodies potentially without impact on other immune functions.

Myasthenia gravis (MG) is an autoimmune disorder characterized by muscle weakness and fatigue. The degree of muscle weakness can fluctuate and vary in severity from person to person; however, it will generally improve with rest and worsen with physical activity. Other precipitating factors include pregnancy, infection, surgery, emotional stress, etc. The cause of MG is unknown, but it is usually diagnosed in young women (20 to 30 years of age) or men ≥50 years of age. There are two classifications of MG: ocular, where weakness is limited to eyelids and extraocular muscles, and generalized, where weakness involves ocular muscles as well as bulbar, limb, and respiratory muscles.

The study evaluating the safety, tolerability, and efficacy of nipocalimab demonstrated that 52% of patients who received nipocalimab saw at least a 2-point reduction in Myasthenia Gravis-Activities of Daily Living scores from baseline for at least 4 consecutive weeks across all dosing arms vs. 15% in the placebo group.

An additional study evaluating efficacy and safety compared to placebo demonstrated that participants with generalized MG (gMG) received an IV infusion every two weeks of either nipocalimab or placebo on top of the standard for care. At weeks 22 to 24, 68.8% of trial participants were responders compared to 52.6% of those who received placebo. 11% of patients in the nipocalimab arm experienced peripheral edema or swelling.

If approved, nipocalimab would be the first FcRn antagonist approved for gMG patients with anti-LRP4 antibodies. The estimated annual cost is between $300,000-$500,000.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
NP001 (sodium chlorite)	Neuvivo	Intravenous	Neuroprotective agent	Lou Gehrig's disease (amyotrophic lateral sclerosis (ALS)	Pending (2Q 2025)	NDA

NP001 is an immunotherapy designed to restore balance within a dysfunctional innate immune system where pro- and anti-inflammatory processes are no longer in equilibrium. By regaining balance, NP001 may help slow the progression of ALS and preserve skeletal muscle function, including the diaphragm.

Amyotrophic lateral sclerosis (ALS) [also known as Lou Gehrig's disease] is a fatal, progressive, neurodegenerative disorder that affects upper and lower motor neurons. A loss of motor neurons in the brain and spinal cord initially leads to focal weakness, with muscle weakness spreading over time. Most patients will die of respiratory failure within 2-5 years of onset. The average survival rate for ALS from the time of diagnosis is 3-5 years, with an incidence in the United States of 2 newly diagnosed cases within a population of 100,000 people.

Only 3 therapies have been approved for ALS, riluzole, Radicava (IV and oral suspension), and Qalsody. None of the current therapies stop the progression of ALS, and they only modestly slow the progression of disease. Qalsody is approved for a rare genetic form of ALS, SOD1 ALS. Riluzole has shown to slightly increase overall survival (2-3 months) although it has not been shown to have an effect on physical functioning.

Radicava has not been shown to have an effect on overall survival at this time; however, it has been shown to have an effect on physical functioning. Although the FDA approved Radicava with a broad label for ALS, the early-onset ALS patients (those patients newly diagnosed with definite or probable ALS) had a greater magnitude of effect.

Three studies were completed to evaluate the safety and efficacy of NP001. The first study evaluated multiple doses of NP001 and the possible efficacy in patients with ALS. Results demonstrated that no significant benefit was seen with NP001 in ALS progression over a 6-month period. There was a slow Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) scores decline in the NP001 treatment groups in patients with high systemic inflammation at baseline. In this subset of patients, there was a 41% reduction in progression with high-dose (2mg/kg) NP001 vs placebo, compared with 13% decrease for the group as a whole. In a subset of patients, symptom progression halted in a dose-dependent fashion: 25% vs 19% vs 11% in the 2 mg/kg, 1 mg/kg, and placebo groups, respectively.

In another trial, NP001 failed to meet the primary endpoint, showing no significant differences between placebo and active treatment with respect to change in ALSFRS-R scores or vital capacity (secondary endpoint).

An analysis of participants with systemic inflammation who participated in the trials above also demonstrated that NP001-treated participants had a 36% slower decline in their ALSFRS-R scores over the six-month period compared with the placebo group

If approved, NP001 would be the first disease-modifying treatment with a novel mechanism of action for patient with ALS having uncontrolled inflammation. The estimated annual cost is $100,000 - $200,000 per year.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
Zepbound (tirzepatide)	Eli Lilly	Subcutaneous	Glucagon-like peptide-1 (GLP-1) agonist; Glucose-dependent insulinotropic polypeptide (GIP) receptor agonist	Heart failure in patients with obesity*	Pending (3Q 2025)	sNDA
Wegovy (semaglutide)	Novo Nordisk	Subcutaneous	Glucagon-like peptide-1 (GLP-1) agonist	Heart failure in patients with obesity*	Pending (2H 2025)	sNDA

Tirzepatide is a long-acting agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, approved by the U.S. Food and Drug Administration for treatment of Type 2 diabetes for weight management in people with overweight or obesity. On December 20, 2024, the FDA approved tirzepatide under the brand name Zepbound for moderate to severe obstructive sleep apnea and obesity, and on November 8, 2023 for the treatment of adults with obesity or those who are overweight who also have a weigh-related comorbid condition. On May 13, 2022, the FDA approved tirzepatide under the brand name Mounjaro to improve blood sugar control in adults with type 2 diabetes (T2D), as an addition to diet and exercise. It is currently being investigated in patients with heart failure with preserved ejection fraction (HFpEF) and obesity.

The study evaluating HFpEF and obesity enrolled a total of 731 adults, ages 40 years and older who had been diagnosed with HFpEF and obesity. All participants had measurements of ejection fraction >50% and they all had body mass index (BMI) measurements of >30kg/m2. Participants received a weekly injection of tirzepatide or placebo, and the weekly dose was gradually increased from 2.5 mg to a possible maximum dose of 15 mg per week. All participants continued taking their regular medications including those for heart failure while enrolled in the study.

The study found participants in the tirzepatide group had a reduced combined risk of cardiovascular death and worsening heart failure events compared to the participants in the placebo group. The results showed that cardiovascular death or worsening heart failure events occurred in 36 patients (9.9%) in the tirzepatide group and 56 patients (15.3%) in the placebo group, representing a 38% reduction in risk among those taking tirzepatide. Worsening heart failure events occurred in 29 patients (8.0%) in the tirzepatide group compared to 52 (14.2%) in the placebo group, representing a 46% reduction in risk for those taking tirzepatide. There were 15 cardiovascular deaths total among both groups, and 11 were not preceded by worsening heart failure, and 2 in the tirzepatide group occurred after patients had not taken the medication for more than 15 months. Among all participants, there were 34 deaths for any reason.

The estimated cost is approximately $14,000 per year.

Wegovy is a GLP-1 RA that was initially approved in June 2021 for chronic weight management in adults with obesity or overweight with at least one weight-related comorbid condition. Since then, Wegovy has received two additional indications:

- December 2022: Approved in pediatric patients 12 years of age and older with obesity.
- March 2024: Approved to reduce the risk of major adverse cardiovascular events (MACEs), including CV death, nonfatal MI, and nonfatal stroke, in adults with established CVD and either obesity or overweight.

Wegovy is currently being investigated for the treatment of heart failure in patients with obesity and it is also being investigated in non-alcoholic steatohepatitis (MASH/NASH).

The study evaluated 529 patients who had heart failure with preserved ejection fraction and a body mass index of 30 or higher to receive once weekly semaglutide (2.4mg) or placebo for 52 weeks. Results of the study found a mean change from baseline in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) of 16.6 points in patients treated with Wegovy compared to 8.7 points with placebo. The mean change from baseline in the 6-minute walk distance was 21.5 meters with semaglutide versus 1.2 meters with placebo. The mean percentage change in bodyweight was -13.3% with semaglutide and -2.6% with placebo.

The annual cost is estimated to be around $17,500, similar to the cost for other indications.

Additionally, Wegovy is currently being studied in metabolic dysfunction-associated steatohepatitis (MASH). The study compared semaglutide to placebo for 72 weeks. It included patients with biopsy-confirmed MASH and liver fibrosis of stage F1, F2 or F3. MASH resolution was achieved with no worsening of fibrosis in 40% in the 0.1mg group, 36% in the 0.2mg group, 59% in the 0.4mg group and 17% in the placebo group. An improvement in fibrosis stage occurred in 43% of the patients in the 0.4-mg group and in 33% of the patients in the placebo group.

Given its favorable glycemic and weight loss profile, semaglutide will likely be an attractive treatment option if approved. The company anticipates filing for FDA accelerated approval in 1H 2025, setting up potential approval at the end of 2025 at the earliest and would compete with Rezdiffra. If approved the anticipated cost of therapy for MASH would be significantly less than Rezdiffra.

Brand (Generic)	Manufacturer	Route	Mechanism of Action	Indication	Stage	Submission Type
CORT125134 (relacorilant)	Corcept Therapeutics	Oral	Glucocorticoid antagonist	Cushing's disease*	Pending (4Q 2025)	NDA

Relacorilant is a selective cortisol modulator that binds to the glucocorticoid receptor but not to the body's other hormone receptors. It is unique compared to Corcept's Korlym, in that it has no affinity for the progesterone receptor; therefore, it does not cause antiprogesterone side effects including endometrial hypertrophy, irregular vaginal bleeding, and risk of pregnancy termination. It is currently being investigated in the treatment of patients with endogenous hypercortisolism (Cushing's syndrome).

Cushing's syndrome (CS) refers to a constellation of symptoms that occur from chronic exposure to excess amounts of glucocorticoids (exogenous or endogenous). CS can result from many etiologies, which are categorized based on adrenocorticotropic hormone (ACTH) dependency. CS can also be iatrogenic, caused by long-term use of exogenous glucocorticoids.

The study, which was designed as a 2-part study, with the first part being an open-label phase where 152 patients with Cushing's syndrome and either diabetes or high blood pressure or both, received relacorilant 100mg once daily with titration up to 400mg based on tolerability or placebo for 22 weeks. Results of the study demonstrated mean improvement of systolic blood pressure and diastolic blood pressure of 7.9mmg Hg and 5.4 mmHg, respectively and 63% of patients with hypertension met the study's response criteria.

In adults with hyperglycemia, the results showed a mean improvement of HbA1c of 0.3% and fasting glucose of 12.4 mg/dL. 50% of patients with hyperglycemia met the study's response criteria.

Among all adults participating in the open-label phase, improvements were seen in body weight (mean change, 3.3 kg) waist circumference (mean change, 2.8 cm) tissue fat mass as measured by DXA scan (mean change, 1.8%) tissue lean mass (mean change, 1.8%) and sit-to-stand test (mean change, 1.5 seconds).

The second part of the trial was to assess blood pressure control and patients either continued with relacorilant or switched to placebo for 12 weeks. The results indicated loss of blood pressure control was 83% less likely to occur among patients in the relacorilant group compared to placebo. Additionally, patients that switched to placebo experienced significant increases in HbA1c, which was not observed among the relacorilant group.

If approved, relacorilant will be an alternative therapy for Korlym, and may be preferred, especially in females, due to the fact that it does not cause antiprogesterone side effects. The estimated annual cost is between $400,000-$500,000.

GENE THERAPY

Gene therapies work by replacing or modifying the disease-causing gene to treat or cure a disease. While only a small number of diseases are currently treatable with gene therapies, there are more than 500 gene therapies undergoing research to make sure they are safe and effective.

Gene Pipeline

The following gene therapies could be approved within the next 12 months.

Fitusiran/Sanofi Pharmaceuticals

Route	Mechanism of Action	Proposed Indication	Approval (PDUFA) Date	Projected Estimated Cost
Subcutaneous	Gene Therapy	Hemophilia A and B	3/28/2025	$750,000 - $1M Annually

Hemophilia is an X-linked recessive genetic disorder that primarily affects males, although in rare cases, females can have the disorder. It is caused by mutations in the genes that encode coagulation factors. This causes bleeding into soft tissue, joints, and internal organs. There are two types of hemophilia: hemophilia A is caused by a deficiency in coagulation factor VIII (FVIII), and hemophilia B is caused by a deficiency in coagulation factor IX (FIX).

Depending on severity and bleed frequency, patients with hemophilia A may receive prophylaxis with IV infused FVIII products or Hemlibra, a subcutaneous administered bispecific antibody designed to mimic the function of FVIII. About 30% of patients with severe hemophilia A and 3%–13% of patients with mild or moderate hemophilia A develop antibodies to FVIII, known as inhibitors. Patients with inhibitors are treated with Hemlibra or with high-dose FVIII in combination with blood products that bypass the inhibited clotting factors. Hemophilia treatment options include factor replacement therapies and extended life factor replacement therapies (e.g., Altuviiio), Hemlibra and the recently approved tissue factor pathway inhibitors (i.e., Alhemo, Hympavzi) gene therapies (i.e., Roctavian, Hemgenix) that address the underlying genetic cause.

Fitusiran is an investigational gene therapy that contains small interference RNA (siRNA) therapy, as a treatment option for hemophilia A and B patients, regardless of their inhibitor status. Positive results from the ATLAS clinical development program were published in April 2023. The ATLAS-INH study is a randomized, open-label Phase III study designed to evaluate the safety and efficacy of fitusiran in males ≥12 years with severe hemophilia A or B with inhibitors to factor VIII or IX. Patients receiving on-demand treatment with bypassing agents (BPA) were randomized to receive fitusiran prophylaxis or continue with on-demand BPA. The primary endpoint was annualized bleeding rate. Results have shown that 66% of fitusiran-treated patients experienced zero monthly bleeding episodes, compared to 5% of control patients who were treated with an on-demand bypassing agent.

ATLAS-A/B is a Phase III randomized, open-label study investigating the efficacy and safety of fitusiran in males ≥12 years with severe hemophilia A or B without inhibitors who had previously been treated with on-demand clotting factor concentrates. Patients were randomized to receive fitusiran or on-demand clotting factor concentrates. The primary endpoint was annualized bleeding rate. Fifty-one percent of those receiving fitusiran showed zero monthly bleeding episodes, compared to 5% of those treated with on-demand clotting factors.

Fitusiran is likely to compete with other hemophilia agents. Fitusiran differs from other gene therapies, as it is administered monthly via a SC injection, while many gene therapies such as Roctavian offer one-time infusions for long-term clotting factor production. When comparing to non-gene therapy options, many of these agents require frequent infusions often on multiple doses per week, weekly or biweekly basis. Fitusiran's monthly dosing could provide a less frequent dosing option for patients.

The PDUFA date for fitusiran is set for March 28, 2025. If approved, fitusiran would provide another long-acting prophylactic therapy treatment option for individuals with hemophilia A or B.

prademagene zamikeracel (pz-cel)/Abeona Therapeutics

Route	Mechanism of Action	Proposed Indication	Approval (PDUFA) Date	Projected Estimated Cost
Intravenous	Gene Therapy	Recessive dystrophic epidermolysis bullosa	4/29/2025	$1M - $2M Annually

Prademagene zamikeracel is an investigational autologous epidermal cell sheet therapy for patients 6 years of age and older with recessive dystrophic epidermolysis bullosa (RDEB). Dystrophic epidermolysis bullosa is a genetic disorder caused by mutations in the COL7A1 gene, leading to fragile skin that blisters and scars easily, with severe forms also affecting internal linings like the esophagus.

The condition can be inherited dominantly or recessively, with RDEB being more severe and associated with complications like chronic wounds, scarring, and a heightened risk of aggressive skin cancer. Current management of DEB consists of wound care, pain management, and infection prevention. Available pharmacologic agents include Vyjuvek™ and Filsuvez™.

Prademagene zamikeracel is manufactured for each patient from autologously derived keratinocytes that are corrected with functional COL7A1 genes using an AAV vector. The corrected cells are grown as cultures, then surgically transplanted once as cell "sheets" onto the patient's wounds to enable normal Type VII expression and skin function.

In a Phase I/II trial, treatment resulted in significant and durable wound healing, with up to 6 years of follow-up, with continuous Type VII collagen expression being observed for more than 2 years after treatment. The co-primary endpoints at Week 24 were the proportion of RDEB wound sites with ≥50% healing compared to baseline in treated and untreated wounds, and pain reduction associated with wound dressing changes between treated and untreated wounds. Of the wounds treated with prademagene zamikeracel, 81.4% shrunk by at least 50% in six months, compared to 16.4% treated with placebo (P<0.0001). The average pain reduction, per the Wong-Baker FACES Scale, was 3.07 in prademagene zamikeracel treated wounds and 0.90 in the control group (P=0.0002).

On April 22, 2024, Abeona announced that it received a complete response letter (CRL) from the FDA regarding the BLA for prademagene zamikeracel for the treatment of RDEB. The FDA requested additional information regarding certain manufacturing testing methods to satisfy Chemistry Manufacturing and Controls (CMC) requirements before the BLA can be approved. On August 8, 2024, Abeona shared data and reports addressing almost all deficiencies noted in the CRL. In October 2024, Abeona resubmitted its BLA to the FDA, addressing the CMC requirements outlined in the FDA's complete response letter. This BLA was accepted by the FDA in November 2024 and a new Prescription Drug User Fee Act (PDUFA) date for prademagene zamikeracel was set for April 2025.

Prademagene zamikeracel will likely compete with Vyjuvek and Filsuvez. The estimated annual cost for Filsuvez is approximately $585,000, while the Vyjuvek is approximately $630,000. These competing agents may provide a lower cost option for patients with DEB when compared to prademagene zamikeracel. However, cost will vary significantly among patients based on the frequency of wound dressing changes, the total body surface area of open wounds, and disease severity.

RP-L102 (mozafancogene autotemcel)/Rocket

Route	Mechanism of Action	Proposed Indication	Approval (PDUFA) Date	Projected Estimated Cost
Intravenous	Gene Therapy	Fanconi Anemia	1H 2025	$2M - $3M

Fanconi anemia (FA) is a rare and serious inherited blood disorder that leads to bone marrow failure. It prevents bone marrow from making enough new blood cells for the body to work properly or can also cause bone marrow to make faulty blood cells. This can lead to serious health problems such as leukemia. In the United States, about 31 babies are born with the disease each year, with about one in every 181 people in the United States is a carrier of Fanconi anemia.

Mozafancogene is an investigational gene therapy product that contains patient derived stem cells that have been genetically modified and infused back into the patient with the goal of preventing bone marrow failure. The current standard of care treatment for FA is stem cell transplantation, which is associated with significant toxicities and complications. About 80% of patients with FA will require a transplant within the first decade of their life. Results from a global clinical trial demonstrated that mozafancogene conferred sustained genetic correction in 8 of 12 evaluable patients with more than 12 months of follow up. The safety profile remains favorable with no known significant preliminary safety signals.

Mozafancogene has fast track, rare pediatric, and orphan drug designations. Rocket has initiated a rolling Biologics License Application (BLA) for RP-L102. If accepted by the FDA with priority review, mozafancogene may be approved in the first half of 2025.

Kresladi (marnetegragene autotemcel)/Rocket

Route	Mechanism of Action	Proposed Indication	Approval (PDUFA) Date	Projected Estimated Cost
Intravenous	Gene Therapy	Primary immunodeficiency; severe leukocyte adhesion deficiency	TBD	$3M - $3.5M

Severe Leukocyte Adhesion Deficiency-I (LAD-I) is a rare pediatric disease caused by mutations in the ITGB2 gene. This gene is responsible for producing a component of CD18, a key protein that facilitates the immune response against infections. As a result, white blood cells, or leukocytes, do not function normally. Children with this disease experience life-threatening bacterial and fungal infections that respond poorly to antibiotics and antifungal medications. Children who survive infancy experience recurrent severe infections including pneumonia, mouth ulcers, necrotic skin ulcers, and blood infections. LAD-I is estimated to impact between 800 to 1,000 children in the United States and Europe. Currently the only potential curative treatment is a stem cell transplant and itself is associated with substantial morbidity and mortality. However, without a successful bone marrow transplant, survival beyond childhood is rare.

Marnetegragene is an investigational one-time gene therapy that contains patient-derived stem cells that have been genetically modified to deliver a functional copy of the ITGB2 gene. Positive data from a global Phase I/II study of marnetegragene demonstrated 100% overall survival at 12 months post-infusion and for the entire 12-to-24-month duration of follow-up for all nine LAD-I patients. Data also showed large decreases compared with pre-treatment history in the incidences of significant infections, combined with evidence of resolution of LAD-I-related skin lesions and restoration of wound repair capabilities. It was well tolerated in all patients with no serious treatment related adverse events.

The PDUFA date for Kresladi was originally set for March 31, 2024, but the FDA extended the review period by three months to June 30, 2024, to allow additional time to review clarifying Chemistry, Manufacturing, and Controls (CMC) information submitted by Rocket in response to FDA information requests. Rocket has already met with FDA leaders from the Center for Biologics Evaluation and Research (CBER) to resolve and provide additional CMC information needed to support the drug's approval. It is unclear when the new anticipated approval date will be.

If approved, Kresladi would be the first therapy available for patients with severe LAD-I without the need for a matched donor, as well as the first FDA-approved therapy for this indication.

CELL THERAPY

Cell therapy works to treat diseases by restoring or altering certain sets of cells or by using cells to carry a therapy through the body. With cell therapy, cells are cultivated or modified outside the body before being injected into the patient. The cells may originate from the patient or a donor.

Recent FDA Approvals

Ryoncil (remestemcel-L)/Mesoblast, Inc.

Route	Mechanism of Action	Proposed Indication	Approval (PDUFA) Date	Estimated Cost
Intravenous	Cell Therapy	Steroid-refractory acute graft-vs-host-disease	12/18/2024	$300,000-$500,000

On December 18, 2024, the FDA approved Ryoncil (remestemcel-L) for the treatment of steroid-refractory acute graft versus host disease (SR-aGvHD) in pediatric patients 2 months of age and older. Acute GHVD occurs in approximately 50% of patients who receive an allogenic bone marrow transplant (BMT). Over 30,000 patients worldwide undergo an allogenic BMT annually, primarily during treatment for blood cancers, including about 20% in pediatric patients. SR-aGVHD is associated with mortality as high as 90%. Remestemcel-L is a cell therapy composed of mesenchymal stromal cells derived from bone marrow that inhibits activation and proliferation of effector T cells and cytokines.

Remestemcel-L was evaluated in a phase III study that enrolled 54 pediatric patients with aGVHD who did not respond to steroids. Results showed that remestemcel-L produced an overall response rate (ORR) of 70.4% at day 28 vs the prespecified ORR of 45% (P = .0003), meeting the study's primary end point. The 100-day overall survival (OS) rate was 87% for patients who achieved a response on day 28 vs 47% for those who did not have a response on day 28 (P = .0001).

In April 2020, the FDA granted priority review to the initial application for remestemcel-L. Then in August 2020, the FDA's Oncologic Drugs Advisory Committee voted 8 to 2 in favor of approving remestemcel-L, however, in October 2020, the FDA sent a complete response letter (CRL) to Mesoblast requesting further data from at least one randomized, controlled trial involving both adult and/or pediatric patients with SR-aGVHD. The FDA issued another CRL in August 2023, requesting more data to support its approval.

The BLA was resubmitted on July 8, 2024, and addressed chemistry, manufacturing, and control issues. The FDA considered the resubmission to be a complete response. With the acceptance of the BLA, a PDUFA date was originally set to January 7, 2025. However, on December 18, 2024 Ryoncil was approved.

Ryoncil will be given as a series of infusions dosed twice weekly for 4 weeks. Ryoncil is the first allogeneic "off-the-shelf" cellular therapy available in the United States for commercial use and the first treatment option for children under 12 with SR-aGVHD.

Encelto (revakinagene taroretcel-lwey)/Neurotech Pharmaceuticals, Inc.

Route	Mechanism of Action	Proposed Indication	Approval (PDUFA) Date	Estimated Cost
Intravitreal Implantation	Cell Therapy	Macular Telangiectasia	3/6/2025	TBD

Macular Telangiectasia (MacTel) is a rare, progressive retinal disease that affects the macula, the central part of the retina responsible for detailed vision. The condition leads to the formation of abnormal blood vessels and deposits in the retina, causing damage to the central vision over time. It typically affects individuals between the ages of 50 and 70 and can progress slowly, leading to vision loss that primarily impacts central vision, making daily tasks difficult.

Encelto is a novel ophthalmic neuroprotectant therapy that secretes ciliary neurotropic factor (CNTF). Therapy consists of a small hollow cylindrical membrane designed to be implanted into the vitreous cavity of the eye. It encapsulates human epithelial cells genetically engineered to continuously produce CNTF. Currently there are no FDA-approved pharmacological treatments for MacTel. Treatment relies on symptom management through the use of vitreous surgery, laser therapy, anti-VEGF inhibitors, and corticosteroids.

In November 2022, Neurotech announced positive topline results from two pivotal Phase III clinical trials, Protocol A and Protocol B. These multicenter, randomized, placebo-controlled studies assessed the safety and efficacy of Encelto in MacTel patients. Both trials met their primary endpoint, demonstrating a statistically significant reduction in the rate of ellipsoid zone (EZ) area loss, which is a marker of photoreceptor degeneration. Protocol A observed a 56% reduction ($p<0.0001$), while Protocol B showed a 29% reduction ($p=0.021$). At the American Academy of Ophthalmology 2024 meeting, further analyses were presented, supporting Encelto's safety profile across Phase I, Phase II, and Phase III studies, with follow-up data extending up to 9 years.

Following these results, Neurotech received priority review designation from the FDA for the BLA of Encelto. The PDUFA date for Encelto was originally scheduled for March 18, 2025, however, the FDA approved Encelto on March 6, 2025. Encelto is the first pharmacological treatment option approved for MacTel and is expected to be available in June 2025.

Cell Pipeline

The following gene therapies could be approved within the next 12 months.

Zevorcabtagene autoleucel (zevor-cel)/CARsgen Therapeutics

Route	Mechanism of Action	Proposed Indication	Approval (PDUFA) Date	Estimated Cost
Intravenous	Cell Therapy	Relapsed/Refractory Multiple Myeloma	TBD	TBD

Zevorcabtagene autoleucel is a fully human, autologous BCMA (B-cell maturation antigen) CAR T-cell product for the treatment of adult patients with relapsed/refractory multiple myeloma. Multiple myeloma is a type of cancer that begins in plasma cells, a type of white blood cell found in the bone marrow. These abnormal plasma cells grow uncontrollably and produce abnormal proteins, which can cause damage to the bones, kidneys, and other organs. Symptoms include bone pain, fatigue, frequent infections, and high calcium levels. Treatment options include chemotherapy, immunotherapy, stem cell transplants, and targeted therapies, aiming to manage the disease and improve the patient's quality of life. Multiple myeloma accounts for approximately 10% of all hematological cancers.

The drug was approved in China in February 2024 and has been granted breakthrough therapy designation by the FDA and is currently under investigation in phase II studies.

A Phase Ib/II LUMMICAR study evaluated the safety and efficacy of zevorcabtagene autoleucel in relapsed/refractory multiple myeloma. In December 2023, the FDA put a clinical hold on this study due to chemistry, manufacturing, and control issues. However, in November 2024, the FDA lifted these holds.

Most recent findings for zevor-cel looked at 102 patients with relapsed/refractory multiple myeloma who had received at least 3 prior lines of therapy including an immunomodulatory drug and a proteasome inhibitor. The objective response rate (ORR) was 92.2%, the stringent complete response (sCR) or complete response (CR) was 71.6%. With a median follow-up of 20.3 (range: 0.4 to 27) months, the median duration of response (DOR), progression-free survival (PFS), and overall survival (OS) data were not mature and therefore, 18-month (18m) and estimated 30-month (30m) event free rates were used as efficacy outcomes for subgroup analyses. The DOR, PFS and OS were not impacted by age or ISS. These subgroup analyses indicate that baseline characteristics have minimal impact on the clinical efficacy of zevorcabtagene autoleucel, demonstrating that even relapsed/ refractory multiple myeloma patients with poor prognostic factors may potentially benefit from zevorcabtagene autoleucel.

Tabelecleucel (Ebvallo)/Atara Biotherapeutics, Inc.

Route	Mechanism of Action	Proposed Indication	Approval (PDUFA) Date	Estimated Cost
Intravenous	Cell Therapy	Relapsed/refractory Epstein-Barr Virus-Positive Posttransplant Lymphoproliferative Disease	TBD	TBD

Epstein-Barr Virus (EBV) positive post-transplant lymphoproliferative disease (EBV+ PTLD) is a complication that can occur following solid organ transplantation, resulting from the reactivation of EBV in immunosuppressed patients. EBV is a common virus that typically remains dormant in the body after an initial infection, but in transplant recipients, the immunosuppressive medications used to prevent organ rejection can impair the body's ability to control the virus. This leads to abnormal proliferation of B lymphocytes, which may progress to lymphoma or other forms of cancer. The condition most commonly affects individuals who are EBV seronegative prior to transplantation and receive an EBV-positive organ, increasing their susceptibility to the disease.

Management involves reducing the levels of immunosuppressive therapy to allow for immune recovery. Additional treatments may include antiviral therapies and targeted immunotherapies, such as rituximab.

Tabelecleucel (Ebvallo) is an allogeneic EBV-specific T-cell immunotherapy aimed at treating relapsed/refractory EBV+ PTLD by utilizing donor-derived T-cells that are specifically engineered to target and attack cells infected with EBV.

In May 2024, Atara Biotherapeutics submitted a BLA to the FDA for tabelecleucel. In December 2024, updated results from the phase III ALLELE clinical trial were presented at the 66th American Society of Hematology Annual Meeting. The study included 75 patients with the primary endpoint being the overall response rate (ORR), along with secondary endpoints of duration of response (DOR), overall survival (OS), and time to response (TTR). The study found that tabelecleucel achieved a 51% ORR and a 28% complete response rate with a median DOR of 23 months and median OS of 18.4 months. Safety results were consistent with prior studies, with no reports of cytokine release syndrome, tumor flare reactions, or graft vs. host disease.

However, on January 16, 2025, the FDA issued a complete response letter (CRL) regarding the BLA. The CRL was related to observations as part of a standard pre-license inspection of a third-party manufacturing facility for Ebvallo. The CRL did not identify any deficiencies related to the manufacturing process, the clinical efficacy, or clinical safety data in the BLA, and the FDA did not request any new clinical trials to support the approval of Ebvallo.

The Institute for Clinical and Economic Review (ICER) evaluated tabelecleucel and concluded that current evidence indicates tabelecleucel has a net health benefit compared to standard of care, extending survival in patients with relapsed or refractory EBV+ PTLD. The therapy was deemed cost-effective if priced between $143,900 and $273,700 per treatment cycle, however pricing has not yet been disclosed.

Ebvallo has already been approved in Europe for treating relapsed/refractory EBV+ PTLD in patients aged 2 years and older.

Biosimilars Pipeline

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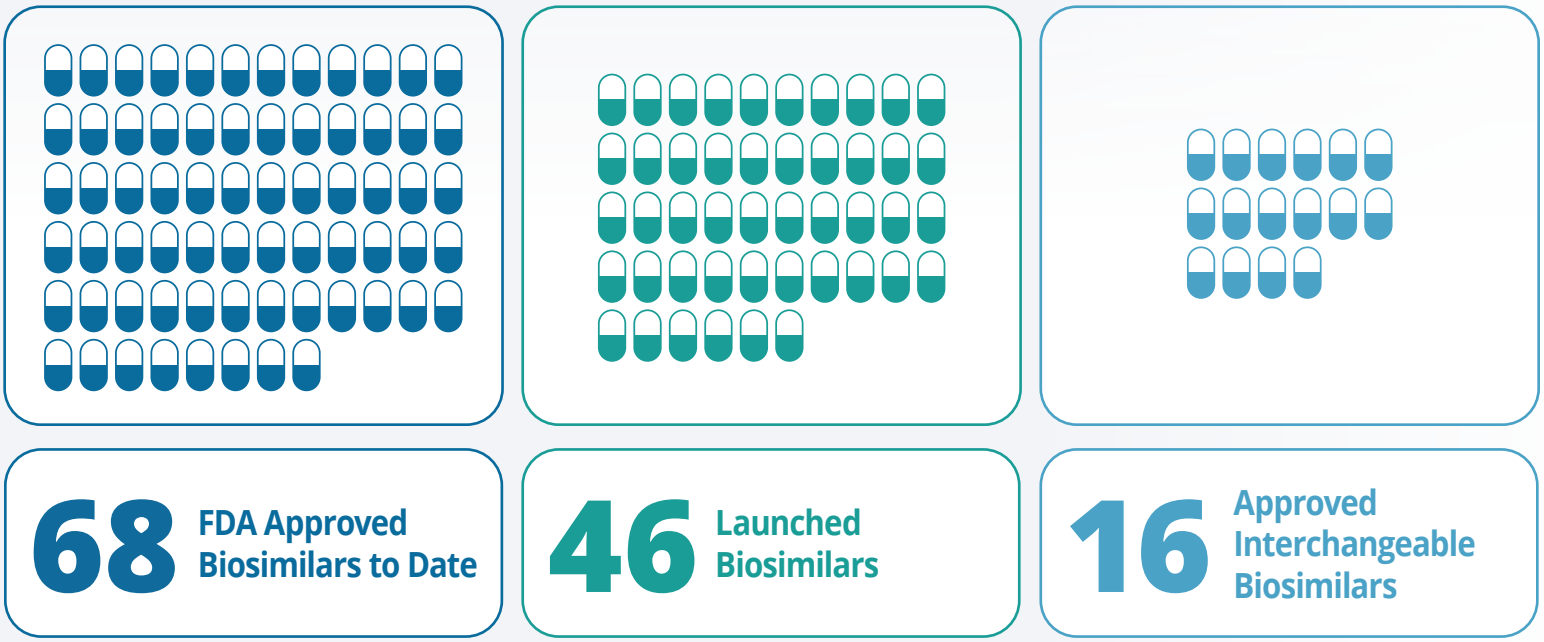
QUICK FACTS



68 FDA Approved Biosimilars to Date

46 Launched Biosimilars

16 Approved Interchangeable Biosimilars

The U.S. Food and Drug Administration has proposed that biosimilar drugs seeking agency's interchangeable designation will no longer need studies showing the impact of switching between them and the branded drug. There have been no changes or updates to this proposal and the draft guidance remains the current status quo while awaiting finalization.

Recent FDA Approvals

FDA Approves Third Biosimilar to Actemra® (tocilizumab)

On January 30, 2025, the FDA approved Avtozma® (tocilizumab-anoh), a biosimilar to Actemra, (tocilizumab), for the treatment of multiple diseases including rheumatoid arthritis (RA), giant cell arteritis (GCA), polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (sJIA), and COVID-19. Avtozma is the third biosimilar to reference Actemra following approvals of Tofidence (tocilizumab-bavi) and Tyenne (tocilizumab-aazg).

Approval was based on data from a 52-week, phase III, randomized clinical trial that assessed the efficacy, pharmacokinetics, safety, and immunogenicity of Avtozma compared to tocilizumab. The study included 471 patients with moderate to severe RA who had an inadequate response to at least one disease-modifying anti-rheumatic drug (DMARD). Patients were randomized to receive either Avtozma or tocilizumab intravenously every four weeks up to week 20. After week 24,444 patients were re-randomized to either continue their original treatment or switch from reference tocilizumab to Avtozma, continuing treatment

until week 48, followed by a four-week follow-up period. Results showed that the mean change in disease activity scores remained consistent across all treatment groups after switching, with clinical improvements up to week 52. Response rates and remission rates were comparable between groups as well as the efficacy, safety, and immunogenicity.

Avtozma will be available in IV formulations of 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), and 400 mg/20 mL (20 mg/mL), as well as a subcutaneous (SC) version with a 162 mg/0.9 mL dose in a single-dose prefilled syringe or autoinjector. The IV formulation is expected to be available in the U.S. by August 2025.

FDA Approves First Novolog® Biosimilar

On February 14, 2025, the FDA approved Sanofi's Merilog® (insulin-aspart-szjj) as the first biosimilar to Novolog (insulin aspart) for the treatment of adult and pediatric patients with diabetes mellitus. Merilog is a rapid-acting human insulin analog used to manage mealtime glucose control. Merilog is the third overall insulin biosimilar to receive FDA approval, following insulin glargine biosimilars Semglee (insulin glargine-yfgn) and Rezvoglar (insulin glargine-aglr).

The approval of Merilog was based on data from the GEMELLI 1 study, a 6 month, randomized, open-label, phase III study that compared the efficacy, safety, and immunogenicity of Merilog to insulin aspart in 597 patients with type 1 or type 2 diabetes. The study showed that Merilog had similar reductions in HbA1c levels and comparable safety outcomes. Additionally, fasting glucose, postprandial glucose, and insulin dosages were comparable between groups as well.

Merilog will be available in both a 3 mL single use prefilled pen and a 10 mL multiple dose vial. Merilog will be priced at $35 for a 30-day supply according to Sanofi. The prices for NovoLog range from $70-$140 for a 30-day supply.

FDA Approves Denosumab Biosimilars

On February 14, 2025, the FDA approved the Biologics License Applications (BLA) for Ospomyv (denosumab-dssb) and Xbryk (denosumab-dssb), biosimilars to Prolia (denosumab) and Xgeva (denosumab), respectively. Both biosimilars were developed by Samsung Bioepis. Ospomyv is approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture, to increase bone mass in men with osteoporosis, and for other indications related to bone loss. Xbryk is indicated to prevent skeletal-related events in patients with multiple myeloma and bone metastases, and for the treatment of hypercalcemia of malignancy, among other uses. The FDA also granted interchangeability for Ospomyv and Xbryk, allowing them to be substituted for their respective reference products, Prolia and Xgeva, at the pharmacy level without requiring provider approval.

Approval for Ospomyv was based on comprehensive clinical data, including a phase I trial and a phase III trial comparing denosumab-dssb to Prolia. The phase III study demonstrated that denosumab-dssb was comparable to Prolia in efficacy, safety, immunogenicity, and pharmacokinetics. The primary endpoint of percent change in lumbar spine bone mineral density at week 12 was met in both analysis sets. Additionally, switching from Prolia to denosumab-dssb showed comparable results over 18 months.

Approval for Xbryk was based on a phase II open-label, single-arm study that assessed the safety and efficacy of denosumab in 33 patients who had hypercalcemia of malignancy refractory to bisphosphonate therapy. Patients received Xbryk subcutaneously every 4 weeks, with additional doses on Days 8 and 15 of the first month. Xbryk effectively reduced serum calcium levels in patients with hypercalcemia of malignancy, with a median time to response of 9 days and a median duration of response of 104 days.

The FDA continued to approve additional biosimilars in this therapeutic area. On March 4, 2025, the FDA approved Stoboclo (denosumab-bmwo) and Osenvelt (denosumab-bmwo), biosimilars referencing Prolia and Xgeva, respectively, for all indications. These biosimilars were developed by Celltrion.

Approval of Stoboclo and Osenvelt was based on a phase III clinical trial involving 477 postmenopausal women with osteoporosis. The results showed no difference in treatment outcomes between patients receiving Stoboclo and those receiving Prolia, based on lumbar spine density after 52 weeks. Stoboclo was well tolerated, with a safety profile comparable to denosumab. No safety concerns were identified following the transition from Prolia to Stoboclo, with results remaining consistent through Week 78.

In accordance with a settlement agreement with Amgen, Stoboclo and Osenvelt are expected to be available in the U.S. in June 2025. Information regarding Ospomyv and Xbryk availability have not been announced.

Upcoming Biosimilars

CT-P39 – Biosimilar to Xolair®

CT-P39 is an antibody that binds to IgE in the body causing reduced levels of circulating free IgE, which reduces IgE mediated immune responses throughout the body. In March 2024, Celltrion filed a BLA with the FDA for a biosimilar to Xolair (omalizumab) for the treatment of allergic asthma, chronic spontaneous urticaria (CSU), and chronic rhinosinusitis with nasal polyps.

The BLA is based on data from a phase III clinical trial of CT-P39 compared to Xolair. The primary endpoint was the change in the Weekly Itch Severity Score (ISS7) at week 12 compared to baseline. CT-P39 met the predefined criteria for equivalence and showed similar results to the original medication in secondary endpoints such as safety and immunogenicity evaluations. Results were recently published in January 2025.

In May 2024, Celltrion announced that the European Commission had approved CT-P39 (Omlyclo). Omlyclo is the first European Commission approved anti-IgE antibody biosimilar referencing Xolair. In December 2024, Omlyclo was then approved in Canada.

Xolair's substance patent has already expired, and the formulation patent is set to expire November 2025 in the U.S. If approved, the goal is for CT-P39 to be given an interchangeable designation. The PDUFA date for CT-P39 is not yet known but is anticipated to be in the first half of 2025.

AVT05- Biosimilar to Simponi®

In January 2025, the FDA accepted a BLA for review seeking approval of AVT05 (golimumab) from Teva Pharmaceuticals as a biosimilar to Simponi to treat multiple inflammatory conditions. Golimumab is used to treat conditions of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis by targeting and blocking TNF alpha to reduce inflammation.

The BLA is based on data from a phase III study that was a randomized, double-blind, 2-arm, multicenter trial. The primary endpoint was the change from baseline to week 16 in the Disease Activity Score-28 in patients with moderate to severe rheumatoid arthritis. Results showed that AVT05 was therapeutically comparable to golimumab in individuals with moderate to severe rheumatoid arthritis. The primary endpoint was met, demonstrating therapeutic equivalence, with safety and immunogenicity evaluations also showing similar results through week 24.

Additionally, positive results were shared from a pharmacokinetic study conducted in November 2023, which compared the pharmacokinetics, safety, and tolerability of AVT05 to golimumab in 336 healthy participants. This study demonstrated that AVT05 showed similar pharmacokinetics, safety, and tolerability to golimumab in healthy participants.

If approved, AVT05 would be the first biosimilar to Simponi. The FDA review is anticipated to be completed by the fourth quarter of 2025.

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