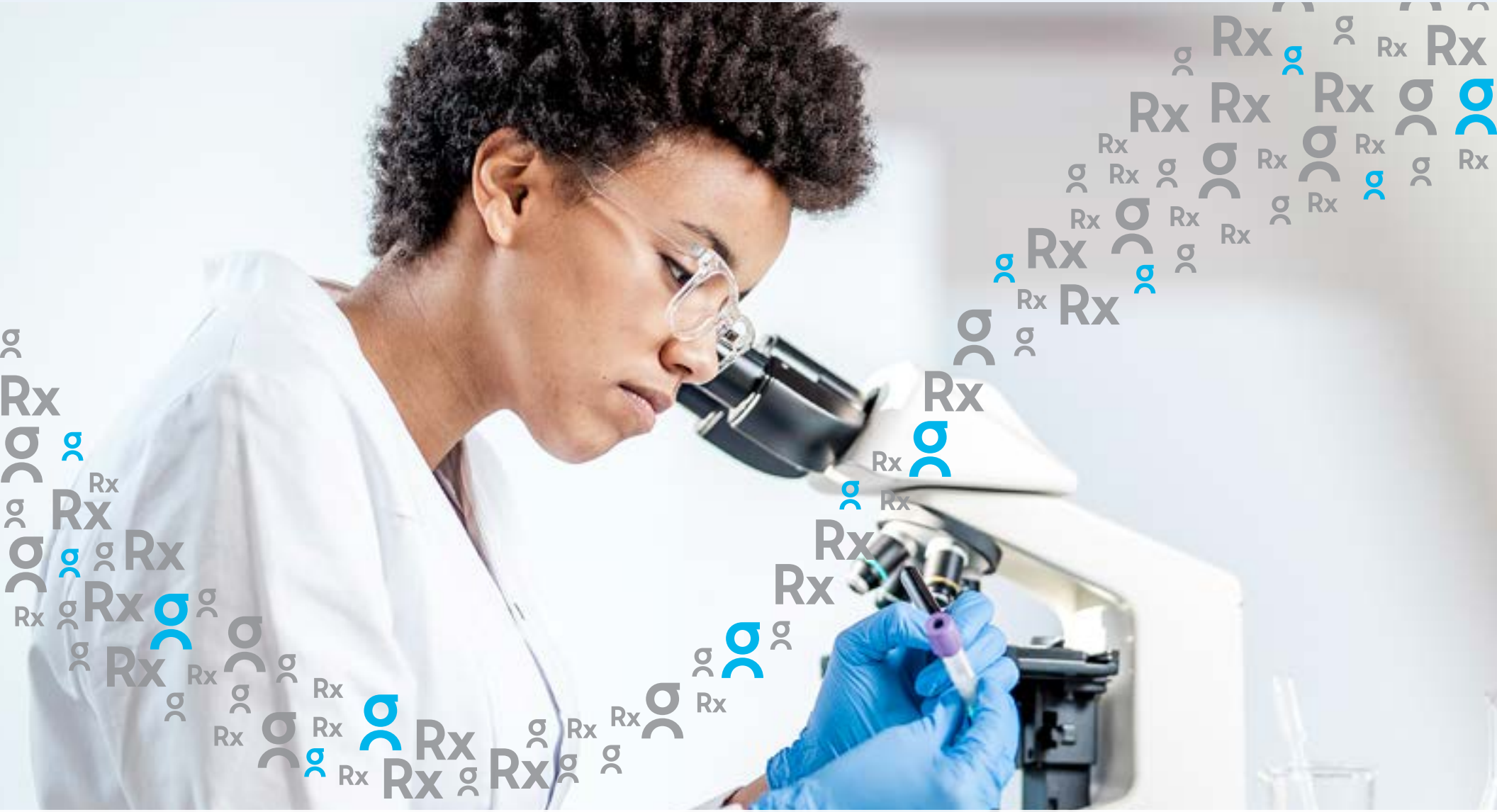
Today, we are CarelonRx, but when we created this document, we were IngenioRx.

Our name may be new, but our commitment to you remains the same.



# Drug and Biologic Pipeline Update

**Q3 2022**

# IngenioRx's quarterly *Drug and Biologic Pipeline Update*

Our Q3 2022 edition highlights emerging therapies in the pharmaceutical pipeline. Read the latest insights on:

- The first potential treatments for hepatitis D virus (HDV) and Friedreich's ataxia, and a second agent for immunoglobulin A (IgA) nephropathy, a rare kidney disease.
- Other significant treatments, including gene therapies and biosimilars, expected in the next several years.
- Recent approvals and pipeline agents for obesity and kidney-related diseases.
- Potential expansions for targeted immunomodulators (TIMs) and agents for spinal muscular atrophy (SMA).

IngenioRx continues to closely monitor the drug and biologic pipeline and provide this free publication as part of our mission to improve health, reduce waste, lower total cost of care for pharmacy and medical, and estimate future cost impact.



Unless otherwise noted, information contained in this document was obtained from the Centers for Disease Control and Prevention (CDC) (cdc.gov), the Food and Drug Administration (FDA) (fda.gov), clinicaltrials.gov, releases from pharmaceutical manufacturers, and UpToDate.com (registration required). Information in this document is accurate as of July 19, 2022.



# Top emerging new therapies

## We expect these products to have significant impact on health plans and members.

# HEPCLUDEX (BULEVIRTIDE)

**Product:**
Hepcludex® (bulevirtide)

**Indication:**
Hepatitis D virus (HDV) treatment

**Estimated FDA approval:**
July 2022

**Therapeutic class:**
Antiviral; entry inhibitor

**Route of administration:**
Subcutaneous injection

**FDA designations:**
Breakthrough; Orphan

**Manufacturer:**
Gilead Sciences

### Condition:

Hepatitis D is a liver infection caused by the hepatitis D virus (HDV). It only occurs in people also infected with the hepatitis B virus (HBV). Infection with hepatitis B and hepatitis D viruses at the same time is coinfection. When infection with HDV occurs after first being infected with HBV, it is superinfection. HDV can be an acute, short-term infection or become a chronic, long-term infection. In immunocompetent adults, more than 95% clear both infections when they are acquired at the same time. HDV becomes a chronic infection in more than 80% of people with superinfection. HDV can cause severe symptoms including fever, vomiting, abdominal pain, dark urine, and jaundice, which may lead to liver damage or death.[1,2]

HDV is the most severe form of viral hepatitis and can have mortality rates as high as 50% within five years in people with cirrhosis. At least 12 million people worldwide are coinfected with HDV and HBV. Coinfection leads to more serious liver disease than HBV alone with a faster progression to fibrosis, cirrhosis, increased risk of liver cancer, and death. There are more than 230,000 people in the U.S. with HDV.[1,2]

### Role in treatment:

There is no vaccine to prevent HDV infection. Prevention of HBV with hepatitis B vaccine may protect against HDV.[1] Hepcludex would be the first FDA-approved treatment for adults with HDV. Its use would be in chronic infection with compensated (asymptomatic) liver disease. It is a novel antiviral that inhibits penetration of HDV into liver cells. Off-label use of pegylated interferon alfa is the only current option for treatment.[3] Treatment of HBV infection would continue during Hepcludex administration.

### Efficacy:

The submission was supported by data from completed and ongoing phase 2 studies and interim results from the ongoing phase 3 MYR301 trial. The primary outcome was combined virological and biochemical response. Treatment for 24 weeks with Hepcludex 2 mg had a statistically significant response compared to the group receiving no treatment. Total duration of treatment across all groups in the study will be 144 weeks.[4] Studies are also ongoing in combination with interferon.[5]

### Safety:

Based on interim results from the phase 3 MYR301 trial, the safety profile of Hepcludex at 24 weeks did not show serious adverse events. The most common adverse events included raised levels of bile salts in the blood and injection site reactions.[4]

*continued »*

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**Manufacturer:**
Gilead Sciences

### Financial impact:

Although the product may be costly, it is unlikely to have a major impact on overall drug spend due to condition rarity. Numbers for HDV infection have declined recently due to HBV vaccination programs.[6] Recently, the CDC drafted new hepatitis B recommendations proposing universal, one-time hepatitis B screening for adults 18 years of age and older.[7] This may identify additional cases of HDV infection.

### IngenioRx view:

Although prevalence is likely low, HDV infection is serious as having HBV and HDV infection increases the risk of liver disease, liver cancer, and death. Current off-label treatment with pegylated interferon alpha products is not very effective. Hepcludex may provide benefit in people with chronic HDV and compensated liver disease.[6] There are some remaining questions regarding long-term outcomes and optimal treatment duration.[8]

# SPARSENTAN

**Product:**
Sparsentan

**Indication:**
Immunoglobulin A (IgA) nephropathy (Berger's disease)

**Estimated FDA approval:**
November 2022

**Therapeutic class:**
Dual endothelin angiotensin receptor antagonist (DEARA)

**Route of administration:**
Oral

**FDA designations:**
Orphan

**Manufacturer:**
Travere Therapeutics

**Condition:**
Immunoglobulin A (IgA) nephropathy, or Berger's disease, is caused by a buildup of IgA leading to inflammation and damage to the kidneys. For some, Berger's disease can progress over several decades to end-stage kidney failure requiring kidney transplant or dialysis. Confirmation of the diagnosis requires a kidney biopsy.[9] Berger's disease is rare with an estimated 100,000 cases in the United States.

**Role in treatment:**
Sparsentan has potential to be the first dual endothelin angiotensin receptor antagonist (DEARA) and the second FDA-approved agent for Berger's disease. Current treatment focuses on preventing or slowing kidney damage by using supportive care, including lifestyle modifications such as diet and exercise and blood pressure control. For people with high amounts of protein in their urine, guidelines recommend off-label treatment with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB).[10] Off-label use of sodium-glucose co-transporter 2 (SGLT2) inhibitors may also be considered. Steroids are reserved for short-term therapy in people who, despite supportive care, remain at high risk of disease progression. Tarpeyo™, approved under the accelerated approval pathway using a surrogate endpoint to predict clinical benefit, is an FDA-approved oral steroid to reduce protein in the urine in adults with primary IgA nephropathy at risk of rapid disease progression.

**Efficacy:**
Sparsentan was submitted for accelerated approval based on an interim analysis from the pivotal PROTECT study evaluating adults with Berger's disease who had protein in their urine despite prior ACEI or ARB therapy. Compared to baseline, significantly more people given sparsentan experienced a reduction in protein in their urine compared to irbesartan, 50% versus 15% respectively, at 36 weeks. The confirmatory analysis, expected in 2023, will evaluate the change from baseline to week 110 in the estimated glomerular filtration rate (eGFR), a measure of kidney function.

**Safety:**
Detailed information has not been announced, but press releases indicate sparsentan is well tolerated.

**Financial impact:**
The price for sparsentan is unknown. Tarpeyo costs approximately $14,000 a month and could be used in combination with sparsentan.[11] Several other late-stage therapies are in development. The global market for Berger's disease is expected to grow to $354M by 2026.[12]

**IngenioRx view:**
If approved, sparsentan will join Tarpeyo as the second FDA-approved agent for Berger's disease. Initial positive data with off-label use of SGLT2 inhibitors in Berger's disease may lead to their use alone or in combination with sparsentan. Sparsentan has a unique mechanism of action and, in trials, was superior to ARB monotherapy in reducing protein in the urine. Like Tarpeyo, sparsentan is seeking accelerated approval using this surrogate endpoint. Confirmatory clinical efficacy, eGFR, results for sparsentan are expected in 2023.

Sparsentan is also in late-stage development for focal segmental glomerulosclerosis (FSGS), another kidney disease. The manufacturer has announced positive interim results and plans to submit for an accelerated approval for FSGS in 2022, pending additional eGFR data.

# OMAVELOXOLONE

**Product:**
Omaveloxolone

**Indication:**
Friedreich's ataxia

**Estimated FDA approval:**
November 2022

**Therapeutic class:**
Inflammation modulator

**Route of administration:**
Oral

**FDA designations:**
Fast track; Orphan; Priority

**Manufacturer:**
Reata Pharmaceuticals

**Condition:**
Friedreich's ataxia is a genetic movement disorder characterized by degeneration of the nervous system. Age of onset is usually between 10 and 15 years. Early symptoms include unsteadiness, difficulty walking due to decreased ability to coordinate voluntary movements, slurred speech, foot deformities, and irregular curving of the spine. Cardiomyopathy causing heart failure or arrhythmias may occur. About one third of people develop diabetes. Ultimately, the disease progresses and affected people typically die in their mid-thirties.[13] Friedreich's ataxia affects an estimated 4,000 diagnosed people in the United States.[14]

**Role in treatment:**
Omaveloxolone would be the first FDA-approved therapy for Friedreich's ataxia. Current treatment is symptomatic and supportive, including walking aids, physical therapy, dietary modification, and medications for heart problems or diabetes.[14]

**Efficacy:**
The submission was supported by data from a 48-week, placebo-controlled phase 2 trial in participants ages 16 to 40 years. The primary outcome was the modified Friedreich's Ataxia Rating Scale (mFARS). Increases in mFARS represent worsening neurological function. People enrolled in the trial were required to have a baseline mFARS between 20 and 80 points. The primary analysis excluded those with a particular foot deformity, pes cavus (abnormally high arch). Pes cavus is reported in about 50% to 70% of people with Friedreich's ataxia and may be more likely in severe disease. At 48 weeks, people treated with omaveloxolone demonstrated a mean decrease in mFARS of 1.55 points compared with those on placebo who had a mean increase in mFARS of 0.85. People younger than 18 years of age saw the greatest results. Significantly positive results were also seen in activities of daily living (FA-ADL) scores.[15,16]

**Safety:**
The most common adverse events seen in both treatment groups in clinical trials were headache, nausea, fatigue, diarrhea, and abdominal pain. Increases in liver enzymes were reported, but these increases were reversed. Most adverse events seen with omaveloxolone were limited to the first 12 weeks, with fewer events reported between weeks 12 and 48. Four adults on omaveloxolone and two on placebo discontinued treatment due to adverse events.[15]

**Financial impact:**
Although the product may be costly, it is unlikely to have a major impact on overall drug spend due to condition rarity.[17]

**IngenioRx view:**
Omaveloxolone would be the first FDA-approved treatment for Friedreich's ataxia. Omaveloxolone works by resolving inflammation through reduction of oxidative stress, an imbalance of antioxidants in the body.[18] It is unclear if this is the most effective pathway to treat Friedreich's ataxia.[17] Additional studies in people with more advanced disease may be needed.[16]

# ETRANACOGENE DEZAPARVOVEC

**Product:**
Etranacogene dezaparvovec

**Indication:**
Hemophilia B

**Estimated FDA approval:**
November to December 2022

**Therapeutic class:**
Gene therapy

**Route of administration:**
Intravenous (IV) infusion

**FDA designations:**
Breakthrough; Orphan; Priority Review

**Manufacturer:**
CSL Behring

**Condition:**
Hemophilia B is a genetic bleeding disorder that occurs when a person does not have enough of the clotting protein, Factor IX (FIX). Severity ranges from few symptoms to severe cases that result in joint damage and even life-threatening, uncontrolled bleeding. There are approximately 5,000 people with hemophilia B in the U.S.[19]

**Role in treatment:**
Current standard of care for people with severe and moderately severe hemophilia B includes using FIX products as preventive therapy and as needed to treat active bleeds. Preventive therapy requires weekly or every-other-week FIX infusions. If approved, etranacogene will introduce the first option for a one-time gene therapy infusion with the goal of decreasing or possibly eliminating the need for preventive FIX therapy, as well as decreasing the number of bleeding events for those with severe disease.

**Efficacy:**
The pivotal HOPE-B trial is evaluating adult males with severe or moderately severe hemophilia B, meaning they have less than 2% of normal FIX activity levels. Eighteen-month results demonstrate increases in FIX activity levels into the mid-to-normal range, significantly fewer bleeding events compared to the year before etranacogene administration, and 98% of participants discontinuing their preventive FIX treatments. The trial evaluated men with and without preexisting antibodies to the viral vector used to deliver the gene therapy. This is important as retreatment is likely not an option for gene therapies delivered by a viral vector. Lingering durability questions regarding how long effects will last and if people will relapse are of great interest.

**Safety:**
The most common side effects with etranacogene are transient elevations in liver enzymes requiring steroids, infusion-reactions, headache, and influenza-like illness. To date, no serious adverse events have been considered related to etranacogene.

**Financial impact:**
The price for etranacogene is unknown. However, analysts anticipate anywhere from $1M to $2M for each person as an estimate for gene therapies in development for hemophilia B.[20]

**IngenioRx view:**
Etranacogene has potential to be the first gene therapy approved for hemophilia B. Competition could come as soon as 2023 with two additional hemophilia B gene therapies in late-stage development. FIX products currently serve as the foundation of treatment for people with hemophilia B. With durability of etranacogene unclear and two competitors on the horizon, it remains to be seen how many people will seek treatment. With a high cost and the clinical data available to date, etranacogene will likely garner significant interest in the medical and health plan communities.

In addition to treatments listed previously, these important drugs and biologics are scheduled to receive FDA approval within the next 12 to 18 months.

**** Key**

**ABT:** add-back therapy

**FGFR2:** fibroblast growth factor receptor 2

**HER2:** human epidermal growth factor receptor 2

**IV:** intravenous

**KRAS:** Kirsten rat sarcoma

**Rolling submission:** when a drug company submits completed sections of its application for review instead of waiting until every section of the application is completed; decision date is assigned when the application is complete

Orphan drug/rare disease; expected to be high cost but with minimal impact to overall drug/medical spend due to low utilization

Potential to significantly increase overall drug/medical spend

New entrant into high-spend/ trending category

No significant impact to incremental spend due to replacement of existing competitors, based on initial analysis

# Other significant product approvals

## We expect these products to reach the market in 2022 to 2023.*

| Drug or biologic manufacturer | Indication/route** | Place in therapy** | Estimated approval date | Impact on overall drug or medical spend |
|---|---|---|---|---|
| **Deucravacitinib** Bristol Myers Squibb | Plaque psoriasis/oral | **First in class:** once daily oral formulation for adults with moderate-to-severe plaque psoriasis | 9/10/2022 |  |
| **Yselty® (linzagolix)** ObsEva | Uterine fibroids/oral | **Addition to class:** will compete with Oriahnn® and Myfembree®; low-dose, non-ABT option | 9/15/2022 |  |
| **Lenti-D™ (elivaldogene auto-temcel)** bluebird bio | Cerebral adrenoleukodystrophy/ IV | **First in class:** will be first gene therapy FDA-approved for this indication | 9/17/2022 |  |
| **Pedmark (sodium thiosulfate)** Fennec Pharmaceuticals | Prevention of ototoxicity and hearing loss induced by cisplatin chemotherapy in children/IV | **Addition to class:** will be first FDA approval for this specific type of chemotherapy toxicity in children | 9/23/2022 |  |
| **Futibatinib** Otsuka | Biliary tract cancer with FGFR2 gene rearrangements/oral | **Addition to class:** targeted therapy after failure of first-line treatment | 9/30/2022 |  |
| **Sparsentan** Bristol Myers Squibb | Immunoglobulin A nephropathy (IgAN)/oral | **First in class:** will be second FDA-approved treatment for this indication | 11/21/2022 |  |
| **Poziotinib** Spectrum Pharmaceuticals | Non-small cell lung cancer, HER2 exon 20 insertion mutations/oral | **First in class:** will be first FDA-approved treatment for this mutation | 11/24/2022 |  |

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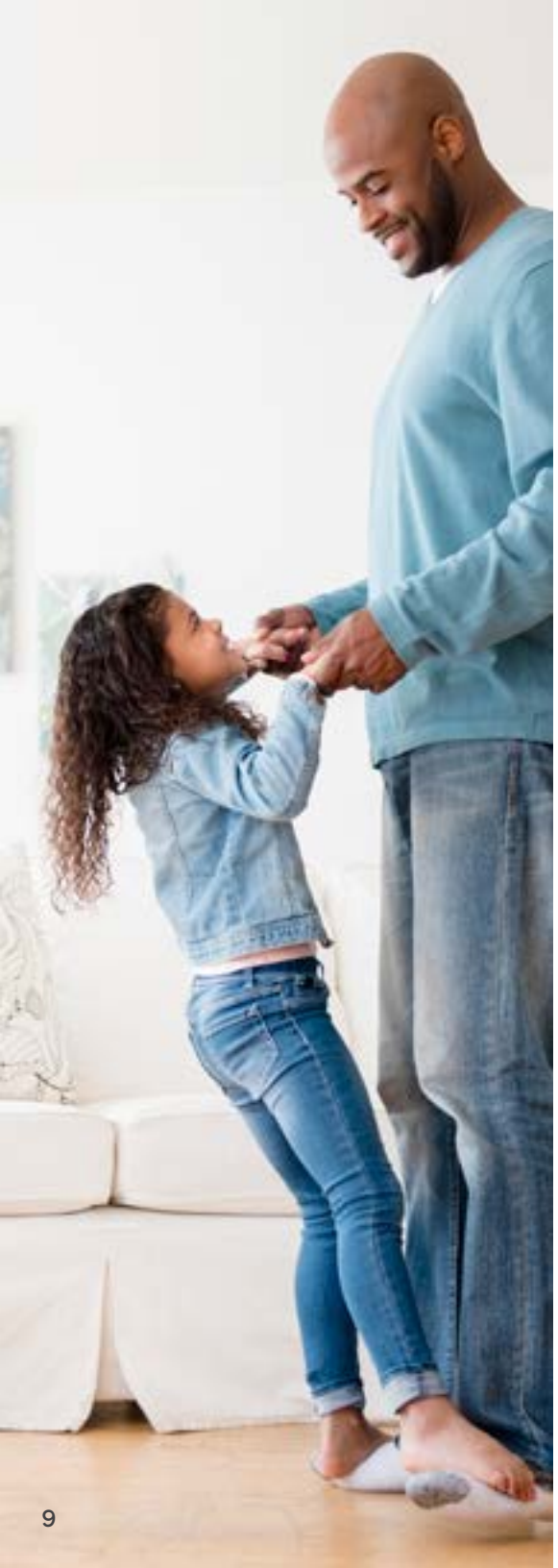
* As of July 19, 2022.



## Other significant product approvals (continued)

| Drug or biologic manufacturer | Indication/route** | Place in therapy** | Estimated approval date | Impact on overall drug or medical spend |
|---|---|---|---|---|
| **Mirvetuximab soravtansine** ImmunoGen | Ovarian cancer/IV | **First in class:** for platinum-resistant disease | 11/28/2022 | |
| **Omaveloxolone** Reata | Friedreich's ataxia/oral | **First in class:** will be first FDA-approved treatment for this indication | 11/30/2022 | |
| **Adagrasib** Mirati Therapeutics | Non-small cell lung cancer, KRAS mutations/oral | **Addition to class:** will compete with Lumakras™ | 12/14/2022 | |
| **Ublituximab** TG Therapeutics | Multiple sclerosis/IV | **Addition to class:** anti-CD20 monoclonal antibody; one-hour administration time | 12/28/2022 | |
| **Lecanemab** Eisai | Alzheimer's disease/IV | **Addition to class:** rolling submission initiated; will compete with Aduhelm™ | 1/6/2023 | |
| **Daprodustat** GlaxoSmithKline | Anemia in chronic renal disease; dialysis dependent and independent/oral | **First in class:** first oral dosing option to compete with erythropoietin stimulating agents (ESAs); 2 similar agents have been denied by FDA | 2/1/2023 | |
| **Omecamtiv mecarbil** Cytokinetics | Chronic heart failure/oral | **First in class:** for heart failure with reduced ejection fraction | 2/28/2023 | |
| **Donanemab** Eli Lilly | Alzheimer's disease/IV | **Addition to class:** rolling submission initiated; will compete with Aduhelm | 2023 | |
| **Roctavian™ (valoctocogene roxaparvovec)** BioMarin | Hemophilia/IV | **First in class:** will be first gene therapy FDA-approved for hemophilia A; questions remain on durability of effect | 2023 | |

The FDA announced in March 2020 that insulins would be redefined as biologics. This enables them to go through a regulatory pathway that will better facilitate the development and serve as reference products for biosimilars. Semglee was the first approved biosimilar to Lantus. An interchangeable version of Semglee is now available.

Currently 37 biosimilars are FDA approved in the United States, including three that were approved in 2022:

Releuko™ (Neupogen® biosimilar), Fylnetra™ (Neulasta® biosimilar), and Alymsys® (Avastin® biosimilar).

# Biosimilar pipeline update

Biosimilars are highly similar to their reference product in terms of structure and function, and they lack clinically meaningful differences in safety and efficacy. Biosimilars may be approved for all or some of the reference products' indications due to patent exclusivity. Prescriptions for biosimilars need to be written for the biosimilar by name. Biosimilars granted interchangeable status are allowed to be substituted for the reference product without the intervention of the prescriber. This is similar to how generic drugs may be substituted for brand-name drugs. Semglee®, a biosimilar to Lantus® (insulin glargine), was granted interchangeable status on July 28, 2021. Cyltezo™, a biosimilar to Humira® 50 mg/mL, was FDA approved in 2017 and subsequently granted interchangeable status on October 15, 2021. Cyltezo is not expected to launch until 2023.

## Select biosimilar products in the pipeline or pending launch

| Type of benefit | Brand name | Brand manufacturer | Biosimilar name | Biosimilar manufacturer | FDA approval* |
|---|---|---|---|---|---|
| **Pharmacy** | Enbrel® | Amgen | Erelzi® | Sandoz | 8/30/2016 |
| **Pharmacy** | Enbrel | Amgen | Eticovo™ | Samsung | 4/25/2019 |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | Abrilada™ | Pfizer | 11/15/2019; seeking interchangeability |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | Amjevita™ | Amgen | 9/23/2016 |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | Cyltezo | Boehringer Ingelheim | 8/25/2017; interchangeable |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | Hadlima™ | Samsung, Merck | 7/23/2019 |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | Hulio® | Fujifilm, Mylan | 7/6/2020 |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | Hyrimoz™ | Sandoz | 10/30/2018 |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | Yusimry™ | Coherus | 12/17/2021 |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | MSB11022 | Fresenius | Pending |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | Yuflyma™ | Celltrion | Pending |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | AVT02 | Alvotech; Teva | Pending; seeking interchangeability |
| **Pharmacy** | Humira (50 mg/mL) | AbbVie | SB5 HC | Samsung Bioepis | Pending; seeking interchangeability |

*continued »*

* Excludes biosimilars that are FDA approved and have launched.

## Biosimilar pipeline update (continued)

| Type of benefit | Brand name | Brand manufacturer | Biosimilar name | Biosimilar manufacturer | FDA approval* |
|---|---|---|---|---|---|
| **Pharmacy** | Lantus | Sanofi | Rezvoglar™ | Eli Lilly | 12/17/2021 |
| **Medical** | Avastin® | Genentech, Roche | Bmab-100 | Biocon, Mylan | Pending |
| **Medical** | Avastin | Genentech, Roche | SB8 | Samsung, Merck | Pending |
| **Medical** | Avastin | Genentech, Roche | FKB238 | Centus; AstraZeneca | Pending |
| **Medical** | Avastin | Genentech, Roche | BAT1706 | Bio-Thera | Pending |
| **Medical** | Avastin | Genentech, Roche | Alymsys | mAbxience | Pending |
| **Medical** | Avastin | Genentech, Roche | CT-P16 | Celltrion | Pending |
| **Medical** | Eylea® | Regeneron | MYL-1701P | Mylan, Momenta | Pending |
| **Medical** | Herceptin® | Genentech, Roche | EG12014 | EirGenix; Sandoz | Pending |
| **Medical** | Lucentis® | Genentech, Roche | Cimerli™ | Coherus, multiple | Pending |
| **Medical** | Neulasta | Amgen | Fylnetra® (TPI-120) | Adello Biologics; Kashiv | 05/26/2022 |
| **Medical** | Neulasta | Amgen | MSB11455 | Fresenius, Dr. Reddy | Pending |
| **Medical** | Neulasta | Amgen | Lapelga Neupeg® | Apotex, Accord | Pending |
| **Medical** | Neulasta | Amgen | Lupifil-P™ | Lupin | Pending |
| **Medical** | Neupogen | Amgen | Grastofil® | Apotex, Accord | Pending |
| **Medical** | Neupogen | Amgen | TX01 | Tanvex | Pending |
| **Medical** | Remicade® | Janssen | Ixifi PF™ | Pfizer | 12/13/2017 |

# Gene therapies in the pipeline

Gene therapy is a novel approach to treatment that introduces genetic material into an individual's body to help fight various diseases. To differentiate gene therapy products, we break them into two broad categories: gene therapy and gene-based therapeutics. The main difference is that gene therapies are usually one-time treatments that aim to treat or cure a genetic disease, while gene-based therapeutics require multiple treatments.

While major advances were made in the field of gene therapy, the FDA has only approved two gene therapies: Luxturna® in 2017 and Zolgensma® in 2019. All FDA-approved gene therapies currently use viral-based therapy, where the infectious parts of viruses are replaced with a gene that can be used to help treat or modify a disease.

## Gene therapies with submitted applications for potential FDA approval in 2022 and 2023†

| Gene therapy | Indication/route* | Expected use | Place in therapy* | Estimated approval date |
|---|---|---|---|---|
| **Zynteglo® (betibeglogene autotemcel; beti-cel (formerly LentiGlobin™)** bluebird bio | Beta-thalassemia/IV | One-time dose; potentially curative | First gene therapy for this indication; will compete with HCT and chronic RBC transfusions | 8/19/2022 |
| **Lenti-D™ (elivaldogene autotemcel; eli-cel)** bluebird bio | Cerebral adrenoleukodystrophy/ IV | One-time dose; potentially curative | First gene therapy for this indication; will compete with HCT | 9/16/2022 |
| **Etranacogene dezaparvovec (AMT-061)** CSL Behring | Hemophilia B/IV | One-time dose; potentially curative | First gene therapy for this indication; will compete with FIX products | November to December 2022 |
| **B-VEC (beremagene geperpavec; KB103)** Krystal Biotech | Epidermolysis bullosa/ topical gel | Once weekly application to wound(s) | First localized gene-based wound therapeutic for people age 1 or older with EB | 6/22/2023 |

*continued »*

*** Key:**

**BCG:** Bacillus Calmette-Guerin

**CRISPR:** clustered regularly interspaced short palindromic repeats

**EB:** epidermolysis bullosa

**FVIII:** factor 8

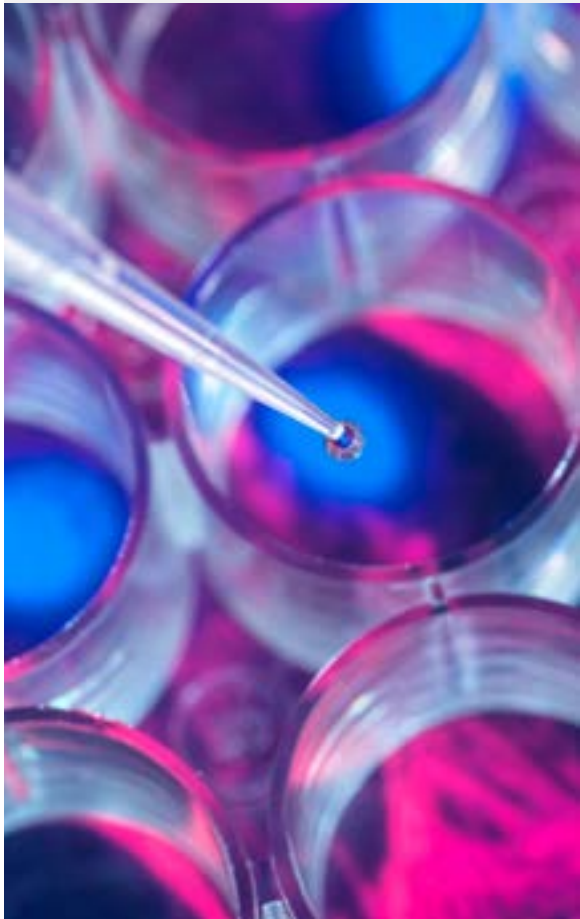
**FIX:** factor 9

**HCT:** hematopoietic cell transplantation

**IV:** intravenous

**NMIBC:** non-muscle invasive bladder cancer

**RBC:** red blood cell



† As of July 19, 2022

## Gene therapies in the pipeline (continued)

### Gene therapies of significant interest with potential FDA submissions in 2023†

| Gene therapy | Indication/route* | Expected use | Place in therapy* | Estimated approval date |
|---|---|---|---|---|
| **D-Fi (FCX-007; dabocemagene autoficel)**<br>Castle Creek Biosciences | Epidermolysis bullosa/ autologous, gene-modified skin grafts | Multiple intradermal treatments to wound(s) | Competing to be second localized gene-based wound therapeutic for people age 2 or older with EB | 2023+ |
| **EB-101**<br>Abeona Therapeutics | Epidermolysis bullosa/ autologous, gene-modified skin grafts | One-time, surgically placed skin graft to wound(s) | Competing to be second localized gene-based wound therapeutic for people age 6 or older with EB | 2023+ |
| **Exagamglogene autotemcel (exa-cel; formerly CTX001)**<br>Vertex and CRISPR Therapeutics | Beta thalassemia anemia/IV<br><br>Sickle cell anemia/IV | One-time dose; potentially curative | Second gene therapy for this indication; potential to compete with beti-cel<br><br>Competing to be first gene therapy for this indication; will compete with HCT and chronic RBC transfusions | 2023 (plans to file late 2022) |
| **Lovotibeglogene autotemcel; lovo-cel (formerly LentiGlobin)**<br>bluebird bio | Sickle-cell anemia/IV | One-time dose; potentially curative | First gene therapy for this indication; will compete with HCT and chronic RBC transfusions | 2023 to 2024 (plans to file 1Q23, even though trials are on hold due to safety concerns) |
| **Roctavian (valoctogene roxaparvovec)**<br>BioMarin | Hemophilia A/IV | One-time dose; potentially curative** | First gene therapy for this indication; will compete with FVIII products and Hemlibra® | 2023 (plans to file September 2022) |
| **Instiladrin® (nadofaragene firadenovec)**<br>FKD Therapies | BCG unresponsive, NMIBC/intravesical | Administered every 3 months for a maximum of 4 instillations | First gene-based therapeutic for NMIBC; will compete with Valstar® and surgery | 2023+ (FDA denied; intends to re-file) |
| **TAVO (tavokinogene telseplasmid)**<br>OncoSec Medical | Advanced melanoma/ intratumoral | Administered on days 1, 5, and 8, every 6 weeks | First gene-based therapeutic for this indication; used in combination with Keytruda® | 2023+ (potential to file with accelerated pathway) |
| **OTL-200**<br>Orchard Therapeutics | Metachromatic leukodystrophy/IV | One-time dose; potentially curative | First gene therapy for this indication; will compete with HCT | 2023 (plans to file late 2022 to early 2023) |

† As of July 19, 2022
** In ongoing studies, factor levels have declined over time introducing doubt in durability of effect.

*continued »*

## Gene therapies in the pipeline (continued)

### Gene therapies of significant interest with potential FDA submissions in 2023†

| Gene therapy | Indication/route* | Expected use | Place in therapy* | Estimated approval date |
|---|---|---|---|---|
| **PTC-AADC (AGIL-AADC)**<br>PTC Therapeutics | Aromatic L-amino acid decarboxylase deficiency/ intracerebral | One-time dose; potentially curative | First gene therapy for this indication | 2023<br>(plans to file 3Q22) |
| **Fidanacogene elaparvovec (PF-06838435)**<br>Pfizer | Hemophilia B/IV | One-time dose; potentially curative | Second gene therapy for this indication; potential to compete with etranacogene and with FIX products | 2023+ |
| **ABO-101**<br>Abeona Therapeutics | Mucopolysaccharidosis IIIA (Sanfilippo Type B)/IV | One-time dose; potentially curative | First gene therapy for this indication; will compete with HCT | 2023+ |
| **ABO-102**<br>Abeona Therapeutics | Mucopolysaccharidosis IIIA (Sanfilippo Type A)/IV | One-time dose; potentially curative | Competing to be first gene therapy for this indication; will compete with HCT | 2023+ |
| **LYS-SAF302**<br>Lysogene | Mucopolysaccharidosis IIIA (Sanfilippo Type A)/ Stereotaxic injection | One-time injection into the brain; potentially curative | Competing to be first gene therapy for this indication; will compete with HCT | 2023+ |
| **OTL-201**<br>Orchard Therapeutics | Mucopolysaccharidosis IIIA (Sanfilippo Type A)/IV | One-time dose; potentially curative | Competing to be first gene therapy for this indication; will compete with HCT | 2023+ |
| **Engensis; donaperminogene seltoplasmid**<br>Helixmith | Diabetic foot ulcers/ intramuscular<br>Diabetic peripheral neuropathy/intramuscular | Multiple injections | First gene-based therapeutic for these indications | 2023+ |
| **Fordadistrogene movaparvovec; PF-06939926**<br>Pfizer | Duchenne muscular dystrophy/IV | One-time dose; potentially curative | First gene therapy for this indication; will compete with Exondys 51, Vyondys 53, and Emflaza® | 2023+ |
| **RP-L201**<br>Rocket Pharmaceuticals | Leukocyte adhesion deficiency-I/IV | One-time dose; potentially curative | First gene therapy for this indication | 2023 to 2024<br>(plans to file 1H23) |
| **RP-L102**<br>Rocket Pharmaceuticals | Fanconi anemia (FA)/IV | One-time dose; potentially curative | First gene therapy for this indication | 2023+ |



† As of July 19, 2022

# Addressing the obesity epidemic

Obesity is a chronic disease that can increase a person's risk of developing type 2 diabetes, heart disease, and certain types of cancer.[21,22] People with a body mass index (BMI) between 25 and 29 are considered overweight and those with a BMI of 30 or greater are considered obese.[21] The CDC estimates that more than 40% of adults and nearly 20% of children in the United States are impacted by obesity today; however, these numbers are expected to continue to rise.[21,22]

## Evolution of treatments for obesity

Lifestyle modifications, including diet, physical activity, and behavioral interventions are considered first-line treatments for management of obesity. When lifestyle intervention alone is not effective, medication, or surgical intervention may be appropriate.

Stimulants, such as phentermine (Adipex-P®, Lomaira™) and diethylpropion, were among the first medications approved by the FDA for treatment of obesity in the late 1950s.[23] As efficacy of these agents wanes over time, they are only indicated for short-term use (8 to 12 weeks).[23] Drugs in this class are commonly associated with adverse effects, such as anxiety, insomnia, heart palpitations, and increased blood pressure, and are classified as controlled substances due to potential for abuse.[23]

Within the last 20 years, the FDA has approved five new medications for the chronic treatment of obesity. These agents produce greater weight loss compared with early obesity treatment options. Guidelines recommend the use of these newer chronic treatments for people with a BMI of 30 or greater as well as those with a BMI between 25 and 30 with at least one comorbid condition, such as hypertension, hyperlipidemia, or heart disease.[23] Selection of chronic treatment should be based on individual factors, such as comorbid conditions, weight loss goal, possible adverse events, preferred route of administration, and dosing frequency.[23]

**Key:**

**GI:** gastrointestinal

**GLP-1:** glucagon-like peptide 1

**SC:** subcutaneous

**NA:** not applicable

**a.** Mean decrease in body weight from baseline to one year (52 to 56 weeks) shown for drugs except Wegovy, where mean reduction in body weight is from baseline to 68 weeks.

**b.** Xenical (orlistat) is available over the counter (OTC) under the brand name Alli® in a lower strength.

**c.** GI upset used to refer to a set of symptoms that may include abdominal pain, constipation, diarrhea, dyspepsia, eructation, flatulence, nausea, or vomiting.

**d.** Data shown for 15 mg/92 mg dose of Qsymia.

**e.** Liraglutide is also approved for type 2 diabetes under brand name Victoza® (SC) at a lower daily dose.

**f.** Semaglutide is also approved for type 2 diabetes under brand names Rybelsus® (oral) and Ozempic® (SC) at a lower daily dose.

### Medications approved for chronic treatment of obesity

| Drug manufacturer | Mechanism of action | Route, dosing frequency | Mean decrease in body weight from baseline[a] | Most common adverse events | Black box warnings |
|---|---|---|---|---|---|
| **Xenical®[b] (orlistat)** Cheplapharm | Inhibits absorption of dietary fats | Oral, 3 times daily | 9.2%[24] | Oily/fatty stool, fecal urgency, and flatulence with discharge | NA |
| **Contrave® (naltrexone/bupropion)** Currax | Appetite regulation and craving reduction | Oral, twice daily | 3.7% to 8.1% | Headache, dizziness, insomnia, and GI upset[c] | Suicidal thoughts and behaviors |
| **Qsymia® (phentermine/topiramate)** Vivus | Appetite regulation and satiety enhancement | Oral, once daily | 9.8% to 10.9%[d] | Dizziness, insomnia, altered taste, and paranesthesia | NA |
| **Saxenda®[e] (liraglutide)** Novo Nordisk | Appetite regulation (GLP1) | SC, once daily | 5.4% to 7.4% | Headache, dizziness, fatigue, GI upset[c] and gastroenteritis | Risk of thyroid c-cell tumors |
| **Wegovy™[f] (semaglutide)** Novo Nordisk | Appetite regulation (GLP1) | SC, once weekly | 9.4% to 16.0% | Headache, dizziness, fatigue, GI upset[c] and gastroenteritis | Risk of thyroid c-cell tumors |

*continued »*

## Addressing the obesity epidemic (continued)

In addition to new medications approved for the chronic treatment of obesity, the FDA approved Imcivree™ (setmelanotide, SC; Rhythm Pharmaceuticals) for obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency in November 2020. POMC, PCSK1, and LEPR deficiency are rare genetic disorders that cause severe-early onset obesity. More recently, Imcivree was approved for treatment of obesity and hunger control in adults and children with Bardet-Biedl Syndrome, another rare genetic disorder.

### Obesity drug pipeline

| Drug manufacturer | Target route | Place in therapy | Phase of development |
|---|---|---|---|
| **Mounjaro™ (tirzepatide)**<br>Eli Lilly | GIP/GLP-1<br>(SC) | Tirzepatide has a dual mechanism of action. It acts as a GLP-1 agonist, like semaglutide, but it is also a GIP agonist.<br>Early-phase studies suggest that tirzepatide can produce greater weight loss than semaglutide (16% to 22.5% reduction from baseline).<br>Tirzepatide was recently approved for use in T2DM as Mounjaro. Should tirzepatide also be approved for obesity, it would have a different brand name. | Phase 3<br>data expected mid-2023 |
| **Rybelsus® (semaglutide)**<br>Novo Nordisk | GLP-1<br>(oral) | Rybelsus contains the same active ingredient as Wegovy but is taken orally once a day.<br>Currently, Rybelsus is approved for treatment of T2DM, but ongoing studies are evaluating its use for treatment of weight management and obesity in persons without diabetes. | Phase 3 |

**Key:**

**GIP:** glucose-dependent insulinotropic polypeptide

**GLP-1:** glucagon-like peptide 1

**SC:** subcutaneous

**T2DM:** type 2 diabetes mellitus

**Key

**COVID-19:** coronavirus disease 2019

**CRL:** complete response letter, was denied by the FDA

**GvHD:** graft versus host disease

**IL:** interleukin

**IV:** intravenous

**JAK:** janus kinase

**PDE-4:** phosphodiesterase-4

**SC:** subcutaneous

**TYK:** tyrosine kinase

**TNFα:** tumor necrosis factor alpha

# Targeted immune modulator pipeline

Targeted immune modulators (TIMs) are drugs or biologics that work by changing how a person's immune system reacts to a given stimulus. Numerous TIMs block different targets, often leading to decreased inflammation and fewer symptoms of disease.

We provide a list of potential new FDA approvals, as well as new indications and formulations for existing TIMs for conditions such as rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis, and alopecia areata.

The TIM pipeline is robust, providing potential for competition among existing products. Summary tables do not capture all agents as TIMs are rapidly emerging as new treatment options in more disease states, such as atopic dermatitis and eosinophilic esophagitis. In addition to agents listed, the introduction of more biosimilars may affect the landscape of this category.

## FDA-submitted applications for new indications, formulations, and products in the TIM pipeline

| Drug or biologic manufacturer | Indication | Target/route** | Estimated future FDA approval dates |
|---|---|---|---|
| **Actemra® (tocilizumab)** Roche | Treatment of COVID-19 in hospitalized adults | IL-6 inhibitor/IV | October 2022* |
| **Bimekizumab** UCB Biosciences | Treatment of adults with moderate-to-severe plaque psoriasis | IL-17A and IL-17F inhibitor/SC | CRL – plans to refile |
| **Deucravacitinib** Bristol Myers Squibb | Treatment of adults with moderate-to-severe plaque psoriasis | TYK-2 inhibitor/oral | September 2022 |
| **Inflectra® (infliximab-dyyb†)** Celltrion | Subcutaneous formulation for the treatment of Crohn's disease | TNFα inhibitor/SC | 2022 |
| | Subcutaneous formulation for the treatment of ulcerative colitis | | 2022 |
| **Rinvoq® (upadacitinib)** AbbVie | Active non-radiographic axial spondyloarthritis | JAK inhibitor/oral | November 2022 |
| **Spesolimab** Boehringer Ingelheim | Treatment of generalized pustular psoriasis (GPP) flares | IL-36 inhibitor/IV | 2022 |

*continued »*

*Actemra was previously granted emergency use authorization for this indication
†Biosimilar

## Targeted immune modulator pipeline (continued)

### Potential new indications, formulations, and products in phase 3 development in the TIM pipeline

| Drug or biologic manufacturer | Indication | Target/route** |
|---|---|---|
| **Bimekizumab**<br>UCB Biosciences | Psoriatic arthritis<br>Axial spondyloarthritis<br>Hidradenitis suppurativa | IL-17A and IL-17F inhibitor/SC |
| **Brazikumab**<br>AstraZeneca | Crohn's disease | IL-23 inhibitor/IV and SC |
| **Cimzia® (certolizumab pegol)**<br>UCB Biosciences | Juvenile idiopathic arthritis | TNFα inhibitor/SC |
| **Cosentyx® (secukinumab)**<br>Novartis | Giant cell arteritis<br>Hidradenitis suppurativa<br>Lupus nephritis | IL-17A inhibitor/SC |
| **CTP-543**<br>Concert Pharmaceuticals | Alopecia areata | JAK inhibitor/oral |
| **Deucravacitinib**<br>Bristol Myers Squibb | Psoriatic arthritis | TYK-2 inhibitor/oral |
| **Entyvio® (vedolizumab)**<br>Takeda Pharmaceuticals | Prophylaxis of GvHD<br>Subcutaneous formulation for ulcerative colitis and Crohn's disease | Integrin receptor antagonist/IV<br>Integrin receptor antagonist/SC |
| **Etrasimod**<br>Pfizer | Ulcerative colitis<br>Crohn's disease | Sphingosine 1-phosphate (S1P) receptor modulator/oral |
| **Filgotinib**<br>Gilead | Ulcerative colitis<br>Crohn's disease | JAK inhibitor/oral |
| **Ilaris® (canakinumab)**<br>Novartis | Non-small cell lung cancer | IL-1 inhibitor/SC |
| **Ilumya® (tildrakizumab-asmn)**<br>Sun Pharmaceutical | Nail psoriasis | IL-23 inhibitor/SC |
| **Imsidolimab**<br>AnaptysBio | Generalized pustular psoriasis | IL-36R inhibitor/IV loading dose followed by SC |
| **Itacitinib**<br>Incyte | Treatment of GvHD | JAK inhibitor/oral |
| **Mirikizumab**<br>Eli Lilly | Ulcerative colitis<br>Crohn's disease | IL-23 inhibitor/IV and SC |

*continued »*

****Key**

**COVID-19:** coronavirus disease 2019

**CRL:** complete response letter, was denied by the FDA

**GvHD:** graft versus host disease

**IL:** interleukin

**IV:** intravenous

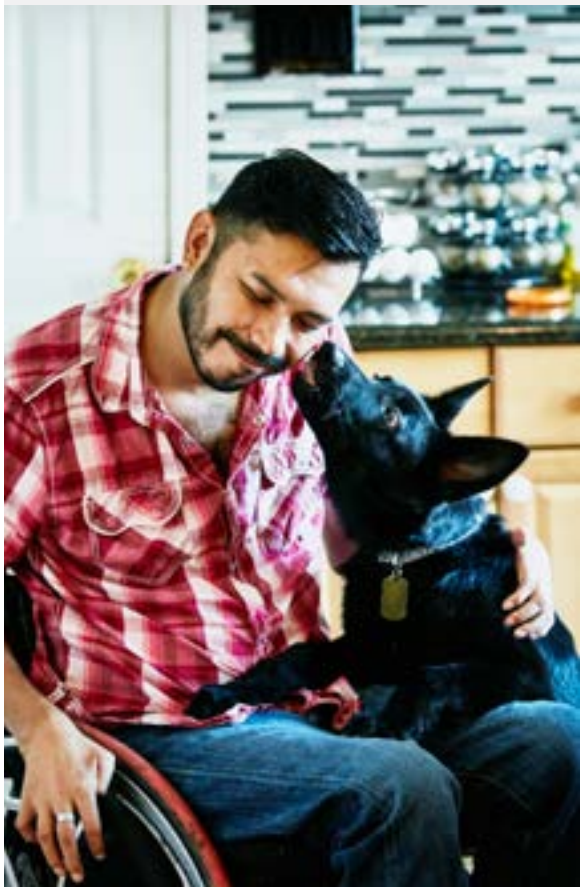
**JAK:** janus kinase

**PDE-4:** phosphodiesterase-4

**SC:** subcutaneous

**TYK:** tyrosine kinase

**TNFα:** tumor necrosis factor alpha



## Targeted immune modulator pipeline (continued)

### Potential new indications, formulations, and products in phase 3 development in the TIM pipeline

| Drug or biologic manufacturer | Indication | Target/route** |
|---|---|---|
| **Olokizumab**<br>UCB Biosciences | Rheumatoid arthritis | IL-6 inhibitor/SC |
| **Olumiant® (baricitinib)**<br>Eli Lilly | Juvenile idiopathic arthritis<br>Uveitis | JAK inhibitor/oral |
| **Otezla® (apremilast)**<br>Amgen | COVID-19 treatment | PDE-4 inhibitor/oral |
| **Otilimab**<br>GlaxoSmithKline | Rheumatoid arthritis | Granulocyte macrophage colony-stimulating factor inhibitor/SC |
| **Rinvoq® (upadacitinib)**<br>AbbVie | Giant cell arteritis<br>Crohn's disease | JAK inhibitor/oral |
| **Ritlecitinib**<br>Pfizer | Alopecia areata | JAK inhibitor/oral |
| **Siliq™ (brodalumab)**<br>Valeant Pharmaceuticals | Systemic sclerosis | IL-17 inhibitor/SC |
| **Skyrizi (risankizumab-rzaa)**<br>AbbVie | Ulcerative colitis | IL-23 inhibitor/SC |
| **Soliris® (eculizumab)**<br>Alexion | Pediatric label expansion for neuromyelitis optica spectrum disorder | Complement protein C5 inhibitor/IV |
| **Spesolimab**<br>Boehringer Ingelheim | Ulcerative colitis | IL-36 inhibitor/IV |
| **Tremfya® (guselkumab)**<br>Janssen | Ulcerative colitis<br>Crohn's disease | IL-23 inhibitor/SC |
| **Ultomiris (ravulizumab-cwvz)**<br>AstraZeneca | COVID-19 treatment<br>Neuromyelitis optica spectrum disorder<br>Transplant-associated thrombotic microangiopathy | Complement protein C5 inhibitor/IV |

# Market trends

## Label expansions for spinal muscular atrophy agents

Spinal muscular atrophy (SMA) is a rare genetic disease affecting the central nervous system, peripheral nervous system, and skeletal muscle, which causes voluntary muscle movement. SMA is characterized by loss of nerve cells in the spinal cord, which affects muscle strength and movement. SMA is the leading genetic cause of death in infants, but it can affect people of all ages. Adult-onset SMA is typically less severe.[25]

There are three FDA-approved treatments for SMA:[26]

- Spinraza® (nusinersen for intrathecal administration into the spinal canal) for newborns and older.
- Zolgensma® (onasemnogene abeparvovec for intravenous infusion), a one-time gene therapy for children less than 2 years of age.
- Evrysdi® (risdiplam oral) for people 2 months of age and older.

There are no new treatments in late-stage development in the United States for SMA. There are, however, two label expansions of interest for FDA-approved agents. Evrysdi recently gained a new indication for presymptomatic newborns under 2 months of age. The goal is to treat young babies with SMA before symptoms arise to help them reach milestones such as standing and walking within typical timeframes of healthy infants.[27] An intrathecal formulation of Zolgensma is in development for people 2 to 17 years of age with SMA type 2. A submission to the FDA is expected to occur in 2025 based on results of the phase 3 STEER trial that just initiated enrollment.[28]

These two label expansions may increase the population of people with SMA who may be treated with these agents.

**Types of SMA:**[29]

**Type 1** is the most common and severe form of SMA. Symptoms begin at birth or within the first 6 months of life.

**Type 2** is an intermediate form of SMA. Symptoms usually start between 6 to 18 months of age.

**Type 3** is a milder form of SMA. Symptoms usually appear around 18 months of age or in early childhood.

**Type 4** is the rarest and the mildest type of SMA. It usually begins in young adulthood.

*continued »*

## Market trends (continued)

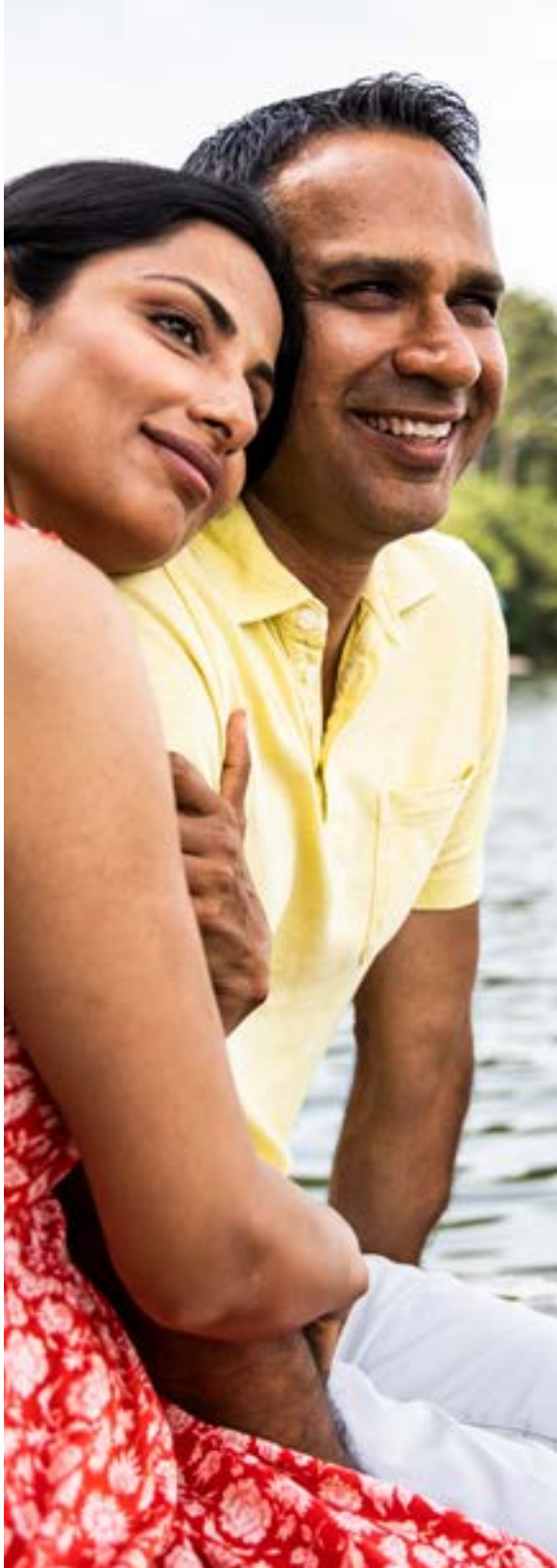
### Growing market and pipeline for kidney-related diseases

**Over the last several years, there has been an abundance of treatments approved for a variety of kidney-related diseases.** These range from highly prevalent forms of chronic kidney disease (CKD) to rare metabolic disorders. Below is a select summary of important recent approvals (2018 to 2022) and late-stage pipeline agents for various kidney-related diseases. In addition to below, other conditions with drugs or biologics in late-stage clinical trials include kidney transplant rejection, renal tubular acidosis, sepsis associated with acute kidney injury (AKI), AKI following cardiac surgery, nephrotic syndrome, and hyperkalemia/hyperphosphatemia in people with CKD.

| Recent FDA approvals | Late-stage pipeline agents |
|---|---|
| **Alport syndrome** | |
| **No FDA-approved treatments for this disease** | **Bardoxolone oral**<br>• Denied by FDA; more data requested[30] |
| **Anemia due to chronic renal failure, dialysis-dependent and dialysis-independent** | |
| **No recent FDA approvals** | **Daprodustat oral**<br>• Would be first in novel class of oral agents for this indication<br>• Expected approval decision 2/1/2023<br>• Two similar agents recently denied by FDA (roxadustat oral and vadadustat oral) |
| **Chronic kidney disease (CKD)-associated pruritus in adults undergoing hemodialysis** | |
| **Korsuva™ (difelikefalin intravenous injection)**<br>• First FDA-approved treatment for this indication | **Haduvio™ (nalbuphine ER oral)** |
| **CKD associated with type 2 diabetes** | |
| **Invokana® (canagliflozin oral)**<br>• First sodium-glucose cotransporter-2 (SGLT2) inhibitor to receive FDA approval for this indication<br>**Kerendia® (finerenone oral)**<br>• Selective nonsteroidal mineralocorticoid receptor antagonist (MRA) option with lower risk of adverse events | **Ozempic (semaglutide subcutaneous injection)**<br>• Would be first glucagon-like peptide-1 (GLP-1) agonist for this indication |
| **CKD in people with and without diabetes** | |
| **Farxiga® (dapagliflozin oral)**<br>• First SGLT2 inhibitor FDA-approved for CKD in people with or without diabetes | **Bardoxolone oral**<br>**Jardiance® (empagliflozin oral)**<br>• Data expected in 2022<br>**KBP-5074 oral**<br>**Kerendia (finerenone oral)[31]** |

*continued »*

| Recent FDA approvals | Late-stage pipeline agents |
|---|---|
| **Focal segmental glomerulosclerosis** | |
| **No FDA-approved treatments for this disease** | **Sparsentan oral**<br>• Expected to submit to FDA in 2022 |
| **Lupus nephritis** | |
| **Lupkynis™ (voclosporin oral)**<br>• First oral agent FDA-approved for this indication | **Cosentyx (secukinumab subcutaneous injection)**<br>**Gazyva® (obinutuzumab intravenous infusion)** |
| **Metabolic acidosis associated with CKD** | |
| **No FDA-approved treatments for this disease** | **Veverimer oral**<br>• Denied by FDA; more data requested |
| **Polycystic kidney disease** | |
| **Jynarque® (tolvaptan oral)**<br>• First FDA-approved treatment for this indication | **Bardoxolone oral** |
| **Primary hyperoxaluria type 1 (PH1)** | |
| **Oxlumo® (lumasiran subcutaneous injection)**<br>• First FDA-approved treatment for this indication | **Nedosiran subcutaneous injection**<br>• For hyperoxaluria types 1, 2, and 3<br>• Expected to submit to FDA in 2022<br>**Oxabact oral**<br>**Reloxaliase oral**<br>• For enteric hyperoxaluria |
| **Primary immunoglobulin A nephropathy (IgAN)** | |
| **Tarpeyo (budesonide delayed release oral)**<br>• First FDA-approved treatment for this indication | **Atrasentan oral**<br>**Iptacopan oral**<br>• Also in trials for C3 glomerulopathy (C3G), including dense deposit disease (DDD) and C3 glomerulonephritis (C3GN)<br>**Narsoplimab intravenous infusion**<br>**Sparsentan oral**<br>• Expected FDA approval decision 11/17/2022[32] |
| **Severe systemic lupus erythematosus (SLE)** | |
| **Saphnelo™ (anifrolumab-fnia intravenous infusion)**<br>• Competitor to Benlysta (belimumab) | **BIIB059 subcutaneous injection**<br>**Dapirolizumab pegol intravenous infusion**<br>**Gazyva (obinutuzumab intravenous infusion)**<br>**Rigerimod subcutaneous injection**<br>**Telitacicept subcutaneous injection** |



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