carelon Rx

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

**Q4 2022**

ingenio Rx™

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

Our Q4 2022 edition highlights emerging therapies in the pharmaceutical pipeline. Read the latest insights on:

- Three agents with the potential to reach the market next year for beta thalassemia and sickle cell disease, atopic dermatitis, and dry age-related macular degeneration (AMD).
- Other significant treatments, including gene therapies and biosimilars, expected in the next few years.
- Overviews of attention-deficit hyperactivity disorder (ADHD), intravenous products seeking new subcutaneous formulations, and the Food and Drug Administration (FDA) Regenerative Medicine Advanced Therapy (RMAT) designation.

IngenioRx continues to closely monitor the drug and biologic pipeline and provides 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 November 20, 2022.

# Top emerging new therapies

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

# PEGCETACOPLAN

**Product:**
Pegcetacoplan

**Indication:**
Geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

**Estimated FDA approval:**
February 2023

**Therapeutic class:**
C3 complement inhibitor

**Route of administration:**
Intravitreal injection

**FDA designations:**
Fast track; Priority

**Manufacturer:**
Apellis Pharmaceuticals

**Condition:**
AMD is an eye disease and is a leading cause of irreversible vision loss in adults over age 60. Risk increases with age and AMD affects approximately 11 million people in the United States.[1] The retina is a thin tissue that lines the inside back layer of the eye. It turns light into nerve impulses that are then sent to the brain for visual recognition. The macula is the center of the retina and is responsible for the ability to drive, read, and see fine details. If macula cells deteriorate, this central or straight-ahead vision may be gradually lost.

There are two types of AMD, wet and dry. They are defined based on physical changes affecting the retina. Dry AMD accounts for approximately 85% to 90% of all AMD cases and severity is classified in stages. Approximately 1 million people in the United States have progressed to the most advanced stage of dry AMD, geographic atrophy (GA).

**Role in treatment:**
Pegcetacoplan would be the first FDA-approved therapy for dry AMD. Current treatment for early disease is a healthy diet high in antioxidants to support macula cells and nutritional supplements may be given as disease progresses.[2] Pegcetacoplan is also available as Empaveli® subcutaneous injection for treatment of paroxysmal nocturnal hemoglobinuria (PNH).

**Efficacy:**
Based on positive data from a phase 2 trial demonstrating a statistically significant reduction in GA lesion growth, two phase 3 trials were conducted.[3] The first met the primary endpoint of change in the total area of GA lesions at 12 months. The second did not meet that endpoint. However, the FDA accepted the submission based on pooled data. Data at 24 months continued to show a benefit in reduction of GA lesions but did not show a benefit on the secondary endpoint of visual function. An additional 36-month long extension trial is planned.

**Safety:**
Pegcetacoplan demonstrated a favorable safety profile. At 18 months, combined new-onset exudations (leaky blood vessels growing behind the macula, also known as wet AMD) occurred in 9.5%, 6.2%, and 2.9% of participants in the pegcetacoplan monthly, every other month, and placebo groups. Infectious endophthalmitis (inflammation of intraocular fluids) and intraocular inflammation are consistent with other intravitreal therapies.[4]

**Financial impact:**
Pegcetacoplan approval is expected next year. A second complement inhibitor for treatment of dry AMD will likely be approved in 2024. Market penetration for these agents is expected to be moderate due to the likelihood they will be approved to slow disease progression rather than improve visual symptoms. Sales of approximately $2 billion are expected in the United States and Europe in 2030.[5]

**IngenioRx view:**
Pegcetacoplan would be the first FDA-approved treatment for late-stage dry AMD. Long-term efficacy and safety data are still pending. Questions remain on whether people are likely to seek treatment before their vision is affected.[5]

# LEBRIKIZUMAB

**Product:**
Lebrikizumab

**Indication:**
Moderate-to-severe atopic dermatitis

**Estimated FDA approval:**
November 2023

**Therapeutic class:**
Interleukin-13 (IL-13) inhibitor

**Route of administration:**
Subcutaneous injection

**FDA designations:**
Fast Track

**Manufacturer:**
Eli Lilly

**Condition:**
Atopic dermatitis (AD), the most common type of eczema, is an inflammatory skin disease that causes red, itchy, and sometimes painful rashes.[6] Disease severity ranges from mild isolated flare-ups to severe widespread disease that can significantly affect quality of life, including ability to sleep. Approximately one in 10 people in the United States have AD.[6]

**Role in treatment:**
Topical steroids and emollients are the usual treatment for AD. For mild disease, these agents are often used with other topical medicines such as tacrolimus ointment, pimecrolimus cream, Eucrisa™ ointment, or Opzelura™ cream. When topicals are inappropriate or do not adequately control symptoms, people may add phototherapy and systemic agents. Adbry™ and Dupixent® are indicated for the treatment of moderate-to-severe AD and are administered through subcutaneous injections every two or four weeks depending on a person's age, weight, and response to therapy. Cibinqo™ and Rinvoq® are once daily oral janus kinase (JAK) inhibitors indicated for the treatment of people with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic therapies, including biologics like Adbry and Dupixent, or when those therapies are inadvisable.

Based on clinical trial design, mechanism of action, and safety profile, lebrikizumab will likely compete most closely with Adbry, an IL-13 inhibitor, and Dupixent, an IL-4/IL-13 inhibitor as another systemic treatment for moderate-to-severe AD when topical therapies do not adequately control the disease.

**Efficacy:**
After four months of treatment with lebrikizumab administered every two weeks, significantly more people age 12 years and older, approximately one out of every four to five people, achieved clear or almost clear skin (i.e., responders) compared to the placebo. In addition, 52-week trial extension data could support two maintenance dosing regimens for lebrikizumab responders, either every two weeks or every four weeks. While there are no direct head-to-head trials comparing lebrikizumab to Dupixent, efficacy appears similar when given every two weeks compared to the placebo.

In a separate combination therapy trial where all people received background treatment with topical steroids, lebrikizumab given every two weeks again was superior to the placebo in the number of responders after four months of treatment.

**Safety:**
The most common adverse reactions with lebrikizumab were conjunctivitis (with an incidence of approximately 8%), nasopharyngitis, and headache. Therapy with other IL-13 inhibitors, Adbry and Dupixent, had similar rates of conjunctivitis.

**Financial impact:**
The approximate monthly cost for an adult maintenance dose of Adbry is between $2,000 and $4,000, depending on dosing frequency, and Dupixent is $4,100.[7] While the price of lebrikizumab is unknown, it will likely be priced to compete with these therapies.

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# LEBRIKIZUMAB

**Product:**
Lebrikizumab

**Indication:**
Moderate-to-severe atopic dermatitis

**Estimated FDA approval:**
2023

**Therapeutic class:**
Interleukin-13 (IL-13) inhibitor

**Route of administration:**
Subcutaneous injection

**FDA designations:**
Fast Track

**Manufacturer:**
Eli Lilly

**IngenioRx view:**
If approved, lebrikizumab will compete closely with Adbry and Dupixent as the third interleukin inhibitor approved for the treatment of moderate-to-severe AD. While these may carry similar indications for AD, it is important to consider FDA-approved ages and maintenance dosing injection frequency. Dupixent is approved for people age six months and older with AD. For most people age 12 years and older, Dupixent would be administered every two weeks for AD. Adbry is approved only for adults with AD and can be administered every two weeks, or for people who are initial responders after the first four months of treatment and weigh less than 100 kilograms, who then receive the drug every four weeks. Lebrikizumab trials included people age 12 years and older and could get an indication for either every two weeks or once-monthly dosing for lebrikizumab initial responders, introducing a potential advantage compared to Dupixent.

# EXAGAMGLOGENE AUTOTEMCEL (EXA-CEL)

**Product:**
Exagamglogene autotemcel (exa-cel, formerly CTX001™)

**Indication:**
Transfusion-dependent beta thalassemia (TDT); Severe sickle cell disease (SCD)

**Estimated FDA approval:**
2023

**Therapeutic class:**
Gene therapy

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

**FDA designations:**
Fast Track; Orphan; Rare Pediatric Disease; Regenerative Medicine Advanced Therapy (RMAT)

**Manufacturer:**
Vertex and CRISPR Therapeutics

**Condition:**
Beta thalassemia and sickle cell disease (SCD) are two of the most common inherited blood disorders, each a result of mutations in the hemoglobin (Hb) gene. SCD affects approximately 100,000 Americans, while symptomatic cases of beta thalassemia occur in an estimated one in 100,000 people worldwide, affecting approximately 1,300 Americans.[8,9] Severity and symptoms for each disease varies.

SCD causes abnormal C-shaped or sickled red blood cells (RBCs) that are sticky and die early. People with severe SCD can have complications such as anemia, a condition when the body does not get enough oxygen (in the case of SCD, because the number of RBCs are too low), blood clots, infections, and pain crises, also called vaso-occlusive episodes (VOE), which occur when sickled RBCs get stuck and cause a blockage of blood flow.

Beta thalassemia causes defective RBCs that have little or no Hb, the protein responsible for oxygen transport. Transfusion-dependent beta thalassemia (TDT), the most severe form of beta thalassemia, is generally caused by ineffective development of RBCs, resulting in anemia that requires treatment with chronic red blood cell infusions.

**Role in treatment:**
Red blood cells are formed in the bone marrow by stem cells. Currently, the only potential cure for either beta thalassemia or SCD is a hematopoietic stem cell (HSC) transplant. HSC transplantation introduces new stem cells into a person's bone marrow and, in doing so, produces normal red blood cells. This procedure is usually only an option for younger people who have a matched donor, often a family member. TDT and anemia in SCD are treated using chronic RBC infusions. Additional treatment options are available such as hydroxyurea, Adakveo®, Oxbryta®, and Endari™ for SCD, and Reblozyl® for TDT.

Exagamglogene autotemcel (exa-cel) is a personalized, one-time therapy that requires extraction, genetic modification, and reinfusion of a person's own HSC after myeloablation, a process that drastically reduces bone marrow activity. Genetic modification is aimed at restoring, at least partially, the ability of a person with SCD or TDT to produce normal or non-affected RBCs. After infusion, people need to be monitored to determine if the genetically modified HSC are producing the desired form of fetal Hb. If approved, exa-cel would compete with another gene therapy, Zynteglo®, which was approved this year for TDT. Exa-cel would be the first gene therapy approved for SCD.

**Efficacy:**
Exa-cel is being evaluated in two open-label, single-arm studies in people age 12 years and older with either TDT or severe SCD, defined as having two or more severe VOEs per year in the two years prior to enrolling. Interim results found 95% of 44 people with TDT did not require any RBC transfusions during their initial follow-up, which ranged between one and 37 months, after receiving exa-cel. As of June 2022, all 31 of the severe SCD participants remained free of VOEs, with initial follow-up ranging between two and 32 months, after receiving exa-cel. We are waiting on additional data to determine durability of effect of exa-cel — that is, how long a sufficient quantity of normal RBCs is produced after gene therapy, in a manner that prevents relapse of disease. It is not known whether exa-cel can be administered more than once.

Two additional open-label pediatric studies are under way, evaluating exa-cel in people age two to 11 years with either TDT or severe SCD.

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# EXAGAMGLOGENE AUTOTEMCEL (EXA-CEL)

**Product:**
Exagamglogene autotemcel (exa-cel, formerly CTX001™)

**Indication:**
Transfusion-dependent beta thalassemia (TDT); Severe sickle cell disease (SCD)

**Estimated FDA approval:**
2023

**Therapeutic class:**
Gene therapy

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

**FDA designations:**
Fast Track; Orphan; Rare Pediatric Disease; Regenerative Medicine Advanced Therapy (RMAT)

**Manufacturer:**
Vertex and CRISPR Therapeutics

**Safety:**
Two TDT and zero severe SCD participants experienced serious adverse events (SAEs) considered related to exa-cel, all of which have resolved. Three SAEs (life-threatening immune activation, acute respiratory distress syndrome, and headache) occurred in one person and idiopathic pneumonia syndrome occurred in a second person. Most of the other side effects were considered related to the myeloablative process.

**Financial impact:**
While the cost of exa-cel is unknown, it could have a significant price similar to gene therapies like Zolgensma®, which is priced at $2 million per person.[7] Because people living with TDT and severe SCD are already managing their disease with other therapies, including some who are eligible for curative treatment with HSC transplantation, it is unclear how many will choose to use gene therapy.

**IngenioRx view:**
Exa-cel is being developed for the treatment of people with TDT or severe SCD. If approved, exa-cel will likely be the first gene therapy for SCD and, potentially, the second gene therapy for TDT. Exa-cel would compete closely with Zynteglo, which uses a similar treatment process to extract and administer therapy. While the clinical significance is unknown, one major difference between exa-cel and Zynteglo is the type of gene modification technology being used to deliver the intended gene. Zynteglo is delivered using a lentiviral vector while exa-cel uses gene editing technology, specifically a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) platform. Exa-cel has the potential to be the first gene therapy approved that uses gene editing (CRISPR) technology. Similar to other gene therapies, the durability of effect of exa-cel remains unknown as does the question of whether exa-cel can be given more than one time.

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**

**BCG:** Bacillus Calmette-Guérin

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

**IV:** intravenous

**KRAS:** Kirsten rat sarcoma

**SC:** subcutaneous

**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 late 2022 to 2023:*

| Drug or biologic manufacturer | Indication/route** | Place in therapy** | Estimated approval date | Impact on overall drug or medical spend |
|---|---|---|---|---|
| **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 |  |
| **Etranacogene dezaparvovec** CSL Behring | Hemophilia B/IV | **First in class:** will be first gene therapy for hemophilia B; questions remain about durability of effect | November to December 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 |  |
| **Palovarotene** Clementia | Fibrodysplasia ossificans progressiva/oral | **First in class:** will be first FDA-approved treatment for this indication | 12/29/2022 |  |
| **Lecanemab** Eisai | Alzheimer's disease/IV | **Addition to class:** rolling submission initiated; will compete with Aduhelm™ | 1/6/2023 |  |
| **Donanemab** Eli Lilly | Alzheimer's disease/IV | **Addition to class:** rolling submission initiated; will compete with Aduhelm | Between 1/20/2023 and 2/20/2023 |  |
| **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); two similar agents have been denied by FDA | 2/1/2023 |  |

* As of November 20, 2022

*continued »*

## Other significant product approvals (continued)

| Drug or biologic manufacturer | Indication/route** | Place in therapy** | Estimated approval date | Impact on overall drug or medical spend |
|---|---|---|---|---|
| **Beremagene geperpavec** Krystal Biotech | Dystrophic epidermolysis bullosa/topical | **First in class:** will be first localized gene-based wound therapeutic for individuals age one year and older for this indication; once weekly administration | 2/17/2023 | |
| **Sparsentan** Bristol Myers Squibb | Immunoglobulin A nephropathy (IgAN)/oral | **First in class:** will be second FDA-approved treatment for this indication | 2/17/2023 | |
| **Pegcetacoplan** Apellis | Geographic atrophy secondary to age-related macular degeneration/ intravitreal | **Addition to class:** will be first FDA-approved treatment for this indication; SC formulation approved under trade name Empaveli® for paroxysmal nocturnal hemoglobinuria | 2/26/2023 | |
| **Omecamtiv mecarbil** Cytokinetics | Chronic heart failure/oral | **First in class:** for heart failure with reduced ejection fraction | 2/28/2023 | |
| **Omaveloxolone** Reata | Friedreich's ataxia/oral | **First in class:** will be first FDA-approved treatment for this indication | 2/28/2023 | |
| **Nogapendekin alfa inbakicept** ImmunityBio | Bladder cancer/ intravesical | **First in class:** another option for individuals unresponsive to BCG | 5/23/2023 | |
| **Zynquista™ (sotagliflozin)** Lexicon | Heart failure in diabetes, reduced and preserved ejection fraction/oral | **First in class:** will compete with Jardiance® and Farxiga® in heart failure | 5/31/2023 | |
| **NovaTears (perfluorohexyloctane)** Bausch Health | Dry eyes/ophthalmic | **First in class:** preservative-free eye lubricant and tear-film stabilizer | 6/20/2023 | |
| **Roctavian™ (valoctocogene roxaparvovec)** BioMarin | Hemophilia/IV | **First in class:** will be first gene therapy FDA-approved for hemophilia A; questions remain about durability of effect | March 2023 | |

The FDA requires all approved biological products, including reference, biosimilar, and interchangeable products, to be evaluated for safety and efficacy to determine whether the benefits outweigh any known potential risks.

Reference biologics undergo several phases of clinical studies to establish safety and effectiveness before they are approved by the FDA. Clinical trials begin with early, small-scale, Phase 1 studies and move toward late-stage, large scale, Phase 3 studies. After the biologic has entered the market, post-marketing monitoring continues to assess the safety, efficacy, and clinical benefit in a larger population.

# Biosimilar pipeline update

Biosimilars are highly similar to their reference product in terms of structure and function and lack clinically meaningful differences in terms of 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 interchangeability are allowed to be substituted for their reference biologic without the intervention of the prescriber. This is similar to how generic drugs may be substituted for brand-name drugs.

Unlike reference biologics, biosimilar products are not required to submit evidence to establish safety and efficacy. However, a biosimilar manufacturer must submit clinical trial data establishing biosimilarity with the reference product.

The table below presents key biologic products that have biosimilar competition in Phase III clinical trials. Some reference biologic products already have been FDA-approved and launched biosimilar competition, and FDA approval of additional biosimilars would allow for more options.

## Biologic products with biosimilars in Phase III clinical trials

| Reference biologic | Therapeutic use | FDA-approved biosimilar | Launched biosimilar |
|---|---|---|---|
| **Xolair®** | Asthma | No | No |
| **Soliris®** | Blood modifying | No | No |
| **Prolia®** | Bone conditions | No | No |
| **Perjeta®** | Cancer | No | No |
| **Rituxan®** | Cancer | Yes | Yes |
| **Herceptin®** | Cancer | Yes | Yes |
| **Epogen®/Procrit®** | Erythropoiesis-stimulating agent (ESA) | Yes | Yes |
| **Eylea®** | Eye conditions | No | No |
| **Lucentis®** | Eye conditions | Yes | Yes |
| **Actemra®** | Inflammatory conditions | No | No |
| **Enbrel®** | Inflammatory conditions | Yes | No |
| **Humira®*** | Inflammatory conditions | Yes | No |
| **Remicade®** | Inflammatory conditions | Yes | Yes |
| **Simponi®/ Simponi Aria®** | Inflammatory conditions | No | No |
| **Stelara® (IV and SC)®*** | Inflammatory conditions | No | No |
| **Lantus®*/ Lantus® Solostar®** | Insulin | Yes | Yes |
| **Novolog® products** | Insulin | Yes | Yes |

*Biosimilar seeking interchangeable status

# Gene therapies in the pipeline

Gene therapy is a novel approach to treatment that introduces genetic material into a person'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.

The FDA has approved four gene therapies: Skysona® in September 2022, Zynteglo® in August 2022, Zolgensma® in 2019, and Luxturna® in 2017. 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 and gene-based therapies with submitted applications for potential FDA approval in 2022 and 2023†

| Gene therapy | Indication(s)/route* | Expected use | Place in therapy* | Estimated approval date |
|---|---|---|---|---|
| **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 |
| **Beremagene geperpavec (B-VEC)** Krystal Biotech | Epidermolysis bullosa (EB)/topical gel | One-time dose; potentially curative | First gene therapy for this indication; will compete with HCT | 2/17/2023 |
| **Exagamglogene autotemcel (exa-cel; formerly CTX001)** Vertex and CRISPR Therapeutics | Beta-thalassemia anemia/IV<br>Sickle cell anemia/IV | One-time dose; potentially curative | Second gene therapy for this indication; potential to compete with Zynteglo<br>Competing to be first gene therapy for this indication; will compete with HCT and chronic RBC transfusions | 2023 (plans to file in late 2022) |
| **Roctavian (valoctogene roxaparvovec)** BioMarin | Hemophilia A/IV | One-time dose; potentially curative; however, in ongoing studies, factor levels have declined over time, introducing doubt regarding durability of effect | First gene therapy for this indication; will compete with FVIII products and Hemlibra® | March 2023 (filed in September 2022) |
| **Lovotibeglogene autotemcel; lovo-cel (formerly LentiGlobin)** bluebird bio | Sickle cell anemia/IV | One-time dose; potentially curative | Competing to be first gene therapy for this indication; will compete with HCT and chronic RBC transfusions | 2023 to 2024 (plans to file the first quarter of 2023) |

† As of November 20, 2022

*continued »*

*** Key:**

**BCG:** Bacillus Calmette-Guérin

**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

# Gene therapies in the pipeline (continued)

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

| Gene therapy | Indication(s)/route* | Expected use | Place in therapy* | Estimated approval date |
|---|---|---|---|---|
| **RP-L201**<br>Rocket Pharmaceuticals | Leukocyte adhesion deficiency-I/IV | One-time dose; potentially curative | First gene therapy for this indication | 2023 to 2024 (plans to file in the first half of 2023) |
| **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 two years 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 six years or older with EB | 2023+ |
| **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) |
| **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 (plans to file 2022) |
| **Delandistrogene moxeparvovec (SRP-9001)**<br>Sarepta and Roche | 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 to 2024 (plans to initiate filing in the second half 2022) |
| **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 | 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+ |

† As of November 20, 2022

*continued »*

## Gene therapies in the pipeline (continued)

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

| Gene therapy | Indication(s)/route* | Expected use | Place in therapy* | Estimated approval date |
|---|---|---|---|---|
| **Fidanacogene elaparvovec (PF-06838435)** 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+ |
| **Instiladrin® (nadofaragene firadenovec)** FKD Therapies | BCG unresponsive, NMIBC/intravesical | Administered every three months for a maximum of four instillations | First gene-based therapeutic for NMIBC; will compete with Valstar® and surgery | 2023+ (FDA-denied; intends to re-file) |
| **TAVO (tavokinogene telseplasmid)** OncoSec Medical | Advanced melanoma/ intratumoral | Administered on days 1, 5, and 8 every six weeks | First gene-based therapeutic for this indication; used in combination with Keytruda® | 2023+ (potential to file with accelerated pathway) |
| **RP-L102** Rocket Pharmaceuticals | Fanconi anemia (FA)/IV | One-time dose; potentially curative | First gene therapy for this indication | 2023+ |



† As of November 20, 2022

# Analysis: Regenerative Medicine Advanced Therapy (RMAT)

The Center for Biologics Evaluation and Research (CBER) created the RMAT designation. It was enacted in the 21st Century Cures Act on December 13, 2016. It is intended to speed the review of regenerative medicines, which are defined as:

- Cell therapies
- Tissue-based products
- Gene therapies
- Combination products (biologic-device, biologic-drug, or biologic-device-drug) when the primary mechanism of action is due to the biological product

To qualify, a product must treat, modify, or cure a serious disease or condition. It also needs to show preliminary evidence that it has the potential to address an unmet medical need. This would allow a product to be submitted to the FDA without conducting late-stage clinical trials.

RMAT is similar to the FDA's Breakthrough Designation with the primary difference being that an RMAT product must meet criteria for being a regenerative medicine. In contrast, a small molecule drug may qualify for Breakthrough status. In addition, the RMAT designation does not require evidence that the product may offer a substantial improvement over available treatments. It only requires evidence of potential to address an unmet medical need. It is possible for a therapy to receive RMAT designation along with other FDA designations to further expedite the approval process.[10,11]

To date, only the following three therapies with an RMAT designation have received FDA approval.

| Product | Approval | Indication |
|---|---|---|
| **Rethymic® (allogeneic processed thymus tissue)** | 10/8/2021 | Immune reconstitution in children with congenital athymia |
| **StrataGraft® (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat)** | 6/15/2021 | Promote durable wound closure and regenerative healing in the treatment of adults with debrided thermal burns that contain intact dermal elements, and for which surgical intervention is clinically indicated |
| **Breyanzi® (lisocabtagene maraleucel)** | 2/5/2021 | Chimeric antigen receptor (CAR) T-cell therapy for the treatment of adults with relapsed or refractory large B-cell lymphoma after at least two prior therapies |

### Breakdown of RMAT submissions

The 21st Century Cares Act provides the National Institutes of Health (NIH) with tools to advance biomedical research.

| Year | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|
| Total requests | 31 | 47 | 37 | 34 | 24 | 21 |
| Granted | 11 | 18 | 17 | 13 | 8 | 9 |
| Denied | 18 | 27 | 18 | 21 | 14 | 6 |
| Withdrawn | 2 | 2 | 2 | 0 | 2 | 1 |
| Approved | 0 | 0 | 0 | 0 | 3 | 0 |

# Market trends

## Attention deficit hyperactivity disorder and misuse and abuse of treatments

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder usually diagnosed in childhood. Children with ADHD may have trouble paying attention or controlling impulsive behaviors or be overly active. Adults can also be diagnosed with ADHD, but only if several symptoms were present in childhood. Symptoms vary and can interfere with many aspects of life, including school, home, work, and relationships. The number of children in the United States with a diagnosis of ADHD has changed over time. Data from 2016 to 2019 estimated that 6 million (10%) children, age 3 to 17 years, had been diagnosed with ADHD. Most children with ADHD continue to experience symptoms as adults.[12]

Treatment options for ADHD include behavioral therapy, skills training, educational supports, and medication. Prescription stimulants (e.g., amphetamine and methylphenidate) are the most widely used and effective medications for ADHD. Stimulants are controlled substances and have black box warnings due to their high potential for abuse and dependence. Non-stimulants are useful alternatives for individuals who cannot tolerate or do not respond to stimulants, and if there is concern for stimulant misuse, abuse, or diversion.[12]

The misuse and abuse of Rx stimulants is a major public health concern in the U.S., with 4.9 million abusers yearly.[13]

- Rx stimulants are often obtained through diversion, mostly from friends or family who have legitimate prescriptions. Diversion is the unlawful transfer of Rx drugs from their legal medical purpose to the illegal marketplace.[14]
- In 2019, 6% of college-aged people, ages 18 to 25 years, misused Rx stimulants.[14]
- Primary motivations for misusing Rx stimulants are to increase alertness and concentration, to help with academic studies, and to enhance performance. However, there is a lack of evidence to support improved academic performance in those without ADHD.[13,14,15]

Commonly misused and abused ADHD stimulants are Adderall® and Ritalin®.[13] Most misuse and abuse involves oral administration; however, Rx stimulants can also be administered non-orally (snorting/inhaling, smoking, or injecting). Non-oral use can increase the risk of serious side effects, including development of substance use disorder (SUD) and death.[14] Stimulants (20.6%) are among the top three deadliest drugs involved in overdoses in the U.S. after opioids (67.8%) and cocaine (21.2%).[16]

Preventing misuse, abuse, and diversion of Rx stimulants will require collaboration across the healthcare industry, schools, and communities. See Table 1 for potential prevention strategies.

*continued »*

## Table 1: Strategies to prevent misuse, abuse, and diversion of Rx stimulants

| Prescribers[14,15] | Pharmacists[17,18] | Schools and communities[14,18] |
|---|---|---|
| • Confirm diagnosis before prescribing stimulants<br>• Assess risk factors and screen for SUD<br>• Prescribe ER formulations instead of IR (higher abuse potential)<br>• Counsel people receiving Rx medication and parents (appropriate use, safe storage and disposal, consequences of misuse, abuse, and diversion)<br>• Monitor medication use (refill requests, pill counts, PDMPs)<br>• Consider medication contracts<br>• Consider non-stimulants | • Counsel people receiving Rx medication and parents (appropriate use, safe storage, and disposal)<br>• Participate in PDMPs<br>• Provide year-round drug disposal bins (pharmacies) | • Educate on myths of perceived benefits and consequences of misuse, abuse, and diversion<br>• Provide academic resources (tutoring, healthy study habits)<br>• Participate in DEA's National Rx Drug Take Back Day<br>• Provide year-round drug disposal bins (police departments) |

**Key**

**Rx:** prescription

**CR:** controlled-release

**DEA:** Drug Enforcement Administration

**ER:** extended-release

**FDA:** Food and Drug Administration

**IR:** immediate-release

**PDMP:** prescription drug monitoring program

**SNRI:** selective norepinephrine reuptake inhibitor

**SUD:** substance use disorder

## Table 2: Abuse-deterrent stimulant and non-stimulant agents in the pipeline for ADHD

| Drug name | Manufacturer | Route | FDA status | Comments |
|---|---|---|---|---|
| **ABV-1505**[19] | ABVC Biopharma | Oral | Phase 2 | • Non-stimulant (norepinephrine transporter inhibitor)<br>• Plant-based drug for adult ADHD<br>• Would compete with other non-stimulants such as the SNRIs, Strattera®, and Qelbree® |
| **AR 19** (amphetamine sulfate IR) | Arbor Pharmaceuticals | Oral | Suspended | • Stimulant designed to resist manipulation for non-oral use<br>• FDA Advisory Committee voted against approval due to safety risks outweighing potential benefit<br>• Would compete with other amphetamine IR products |
| **Centanafadine** | Otsuka Pharmaceuticals | Oral | Phase 3 | • Non-stimulant (serotonin-norepinephrine-dopamine triple reuptake inhibitor)<br>• Would compete with other non-stimulants such as the SNRIs, Strattera, and Qelbree |
| **Nolazol®** (mazindol CR)[20] | NLS Pharmaceutics | Oral | Phase 2 | • Non-stimulant (triple monoamine reuptake inhibitor and partial orexin-2 receptor agonist)<br>• Mazindol IR (Sanorex®) was previously FDA-approved for obesity but is no longer available due to discontinuation by the manufacturer<br>• Mazindol ER (Quilience®) is in phase 2 development for narcolepsy<br>• Would compete with other non-stimulants such as the SNRIs, Strattera, and Qelbree |

# Market trends (continued)

## Shift from intravenous to subcutaneous formulations

A recent trend in the pharmaceutical pipeline is the development of new subcutaneous (SC) formulations for existing intravenous formulations. There are more than 330 SC biologics in the pipeline. There are also various FDA-approved therapies that are administered by intravenous infusion (IV) but are being reformulated for SC administration.

Protein-based therapies often need to be given in large quantities and become highly viscous when reformulated for SC delivery. Manufacturers are working to overcome these challenges and make products user-friendly by developing novel delivery technology and devices.[21]

The shift to SC therapies is attractive due to the potential for self-administration. Other benefits include shorter administration times and fewer infusion-related adverse events. These factors may translate to reduced healthcare costs and improved adherence.[22]

In recent years, SC versions of IV therapeutics have gained FDA approval for various agents, including Herceptin® (oncology), Rituxan® (oncology), Darzalex® (oncology), Benlysta (systemic lupus erythematosus and lupus nephritis), Ultomiris® (paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome), Actemra® (inflammatory disorders), and Orencia® (inflammatory disorders). Below are several FDA-approved products that have SC formulations being developed by the manufacturer.

## FDA-approved products seeking SC formulation approvals

| Name | Manufacturer | Development status | Indication |
|---|---|---|---|
| **Entyvio®** (vedolizumab subcutaneous) | Takeda Pharmaceuticals | 2023 (previously denied; plans to resubmit) | Moderate-to-severe ulcerative colitis |
| **Inflectra®** (infliximab-dyyb biosimilar subcutaneous) | Celltrion | 2022 (submitted) | Inflammatory bowel disease |
| **Tecentriq®** (atezolizumab subcutaneous) | Roche | Plans to submit in 2023 | Non-small cell lung cancer (NSCLC) |
| **Vyvgart™** (efgartigimod alfafcab subcutaneous) | Argenx | Plans to submit in 2022 | Myasthenia gravis |

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