carelon Rx

Drug and biologic pipeline update Q1 2024

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CarelonRx's quarterly Drug and biologic pipeline update

CarelonRx 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. Information contained in this document is compiled from various publicly available resources and is provided for informational purposes only. This document does not provide information on confidential CarelonRx proprietary clinical programs or management strategies.

Our Q1 2024 update provides summaries of three agents of interest with anticipated approvals this year: marnetegragene autotemcel (RP-L201) for leukocyte adhesion deficiency-type I (LAD-I), fidanacogene elaparvovec for hemophilia B, and ensifentrine for chronic obstructive pulmonary disease (COPD). Other select drugs and biologics in the pipeline, including gene therapies and biosimilars, are also highlighted. An overview of the treatment landscape and pipeline for Duchenne muscular dystrophy (DMD) will be provided. Finally, potential combination influenza and COVID vaccines and a look at Dupixent® and other biologics for chronic obstructive pulmonary disease will be spotlighted.

This document should not be relied on solely for decision-making purposes, and should not be considered clinical, legal, or financial advice. Projections on future drug approvals, availability, and/or pricing are based on information available at the time of publication and are not within the control of CarelonRx.

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, National Institutes of Health (NIH) (nih.gov), and UpToDate.com (registration required). Information in this document is accurate as of February 1, 2024.

Top emerging new therapies

Marnetegragene autotemcel (RP-L201)

Condition:
Leukocyte adhesion deficiency-type I (LAD-I) is a rare disorder caused by mutations in the *ITGB2* gene. People with severe LAD-I experience uncontrolled infections due to their white blood cells inability to move to the site of, and fight, infections. The majority of children with severe LAD-I die within the first two years of life if they do not receive a hematopoietic stem cell (HSC) transplant. LAD-I, including severe and mild-to-moderate severity subtypes, is estimated to affect approximately 800 to 1,000 people in the U.S. In the marnetegragene autotemcel (RP-L201) trial, the severe form of LAD-I was generally characterized by having less than 2% normal surface expression of CD18 on neutrophils (i.e., an essential component of white blood cells).

Role in treatment:
Currently the only treatment known to potentially cure LAD-I is an HSC transplant. This is only an option for children with a matched HSC transplant donor who are well enough to undergo the procedure itself.

Marnetegragene autotemcel (RP-L201) is a one-time personalized therapy that requires removal and modification of each person's own HSCs. RP-L201 uses a lentiviral vector to deliver a functional copy of the *ITGB2* gene. After a chemotherapy-conditioning regimen, the modified HSCs are reinfused.

Efficacy:
A phase 1/2 study evaluating people with severe LAD-I who do not have an eligible matching HSC transplant donor found 100% survival for all nine people at 12 months after RP-L201 infusion.

Safety:
With up to 24 months of follow-up to date, there have been no serious adverse events or deaths considered related to treatment with RP-L201. Most adverse events were due to the chemotherapy conditioning regimen.

Financial impact:
The price of RP-L201 is unknown. However, it will likely be priced similarly to other gene therapies for rare diseases at $3 million or more per one-time treatment.

CarelonRx view:
RP-L201 would be the first gene therapy approved for severe LAD-I, introducing an option for people who do not have a matched HSC donor. While emerging data supports improved survival, it is unclear how long these effects will last.

Product:
Marnetegragene autotemcel

Indication:
Treatment of severe leukocyte adhesion deficiency-type I (LAD-I)

Estimated FDA approval:
March 2024

Therapeutic class:
Gene therapy

Route of administration:
Intravenous

FDA designations:
Orphan; Priority; Rare Pediatric Disease (RPD); Regenerative Medicine Advanced Therapy (RMAT)

Manufacturer:
Rocket Pharmaceuticals

Fidanacogene elaparvovec

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.

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, fidanacogene will compete directly with Hemgenix® (etranacogene dezaparvovec-drlb, infusion; CSL Behring), the first Food and Drug Administration (FDA)-approved gene therapy indicated for the treatment of adults with hemophilia B. These one-time gene therapies are each administered as a single 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 BENEGENE-2 trial is evaluating adult males with severe or moderately severe hemophilia B, meaning they have less than 2% of normal FIX activity levels. Fifteen-month results demonstrate significantly fewer bleeding events with fidanacogene, more specifically a 71% reduction in the annualized bleeding rate (ABR), compared to the six-month lead-in pre-treatment period using only preventive FIX products.

Safety:
Like Hemgenix, fidanacogene use has resulted in transient elevations in liver enzymes requiring steroids. To date, only two serious adverse events have been considered as related to treatment (a duodenal ulcer hemorrhage and anemia), each occurring in the setting of steroid use. No deaths, serious infusion reactions, or blood clots have been reported after fidanacogene administration.

Product:
Fidanacogene elaparvovec

Indication:
Treatment of hemophilia B

Estimated FDA approval:
April 2024

Therapeutic class:
Gene therapy

Route of administration:
Intravenous (IV) infusion

FDA designations:
Breakthrough, Orphan, Regenerative Medicine Advanced Therapy

Manufacturer:
Pfizer

Financial impact:
While the price for fidanacogene is unknown, it will likely garner a similar price as Hemgenix. The wholesale acquisition cost of Hemgenix is $3.5 million per person.[1]

CarelonRx view:
According to its FDA labeling, Hemgenix can only be administered once. It is designed to deliver a copy of a FIX gene using an adeno-associated virus serotype 5-(AAV5) based viral vector. Similarly, fidanacogene will likely be limited to a single administration. Fidanacogene uses a bioengineered AAV viral vector to deliver its FIX gene. While slightly different, both gene therapies use AAV technology to deliver their intended FIX gene therapies. Based on this similarity, can one person theoretically try both gene therapies? It seems unlikely if a person fails treatment with one hemophilia B gene therapy that they would be able to use the other gene therapy due to neutralizing antibodies that develop to the gene therapy vector (AAV) after administration. This question remains unanswered, however, and is an important consideration when deciding which gene therapy to use.

Fidanacogene will compete with Hemgenix as the second gene therapy available for adults with hemophilia B. Lingering durability questions regarding how long effects will last, and if people will relapse, are of great interest. FIX products currently serve as the backbone of treatment for people with hemophilia B. With the durability of high-cost gene therapies unclear, it remains to be seen how many people will seek treatment.

Ensifentrine

Condition:
Chronic obstructive pulmonary disease (COPD) is a serious respiratory condition affecting approximately 16 million Americans. COPD can result in disability and is the sixth-leading cause of death in the U.S. Major risk factors include being age 40 or more, having a history of smoking, having a long-term exposure to lung irritants, and having a genetic condition called alpha-1 antitrypsin (AAT deficiency). The most common symptoms are cough, shortness of breath, shallowness of breath, excessive sputum, and wheezing.

The term COPD references both emphysema and chronic bronchitis, of which most people with COPD have a variable combination. Emphysema results from damage to the lungs that worsens gas exchange and leads to difficulty in releasing air from the body. Chronic bronchitis refers to persistent irritation and inflammation of airways that leads to increased mucus and difficulty breathing. People are diagnosed based on signs and symptoms, personal history, and testing (e.g., lung function tests and spirometry).

Role in treatment:
There is no cure for COPD. Management includes smoking cessation, pharmacologic therapy, and pulmonary rehabilitation. In more severe cases, oxygen therapy may be used, and surgery may be considered. Pharmacologic therapy can improve symptoms, reduce the frequency and severity of exacerbations, and improve function and quality of life.

Initial treatment selection is based on symptom severity and risk of future exacerbations. The most common drug classes used to treat COPD are inhaled bronchodilators (e.g., long-acting beta-agonists [LABAs] and muscarinic antagonists [LAMAs]), which may be given alone, in combination, or with inhaled corticosteroids (ICSs). Of note, fixed-dosed combination inhalers that include a LABA/LAMA, LABA/ICS, LABA/LAMA/ICS are available, which may provide convenience for those using multimodal therapy.

Ensifentrine is a first-in-class agent that provides a novel mechanism of action for the treatment of COPD. The dual inhibition of phosphodiesterase (PDE) 3 and 4 combine to facilitate bronchodilation and anti-inflammatory effects. Based on clinical trial design, ensifentrine could be used as monotherapy or add-on therapy to a LABA or LAMA inhaler in people with moderate-to-severe COPD. With the increased risk of pneumonia associated with inhaled corticosteroid use, ensifentrine may be a preferred alternative for add-on to a LABA or LAMA inhaler.

Ensifentrine's formulation as a nebulized product may be helpful for those who cannot use inhalers. Conversely, it requires a longer treatment time, and may be more difficult to maintain and transport.

Efficacy:
The New Drug Application submitted to the FDA was supported by data from ENHANCE-1 and ENHANCE-2 phase 3 clinical trials. When used as monotherapy or added to LABA or LAMA therapy, ensifentrine demonstrated clinically meaningful improvements in lung function over 24 weeks compared to placebo. Of note, approximately 20% of subjects received inhaled corticosteroids with their LABA or LAMA. A pooled analysis of the ENHANCE trials found ensifentrine substantially reduced the rate and risk of COPD exacerbations compared to placebo.

Product:
Ensifentrine

Indication:
Chronic obstructive pulmonary disease (COPD)

Estimated FDA approval:
June 2024

Therapeutic class:
Dual phosphodiesterase (PDE) 3 and 4 inhibitor

Route of administration:
Inhalation delivered by nebulizer

FDA designations:
None

Manufacturer:
Verona Pharma

Ensifentrine

(continued)

Safety:
Ensifentrine was well-tolerated in ENHANCE trial subjects with minimal adverse events. Overall, it was similar to placebo.

Financial impact:
If approved, ensifentrine will be a first-in-class nebulized agent used as monotherapy or add-on therapy for moderate-to-severe COPD. Peak sales are estimated to reach $500 to $750 million in major markets (US, Europe, and Japan).[2] Ensifentrine is also being studied for use in asthma and cystic fibrosis, and dry powder inhaler and metered dose inhaler formulations are in development. These additional approvals may further expand the agent's use.

CarelonRx view:
The availability of a new drug class for treating COPD is promising. However, questions remain about how ensifentrine may fit best in clinical practice, including which COPD population may benefit most, what line of therapy is most appropriate for its use, and how many people will want to use a nebulized formulation compared with the ease of use of an inhaler. Initially, it will likely be used most often as an alternative to inhaled corticosteroids in second-line therapy. Use may evolve as providers gain more understanding and experience with the agent.

Other significant product approvals

We expect these products to reach the market in 2024:*

Drug or biologic (Manufacturer)	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Donanemab Eli Lilly	Alzheimer's disease/ IV	**Addition to class:** would compete with Leqembi® in early stage disease	First quarter 2024	
Resmetirom Madrigal Pharmaceuticals	Nonalcoholic steatohepatitis (NASH)/oral	**Addition to class:** would be first FDA-approved treatment for this indication	03/17/2024	
OTL-200 Orchard Therapeutics	Metachromatic leukodystrophy/IV	**First in class:** would be first FDA-approved treatment for this indication; gene therapy	03/18/2024	
Aprocitentan Johnson & Johnson	Hypertension, resistant/oral	**First in class:** would be first FDA-approved product specifically for resistant hypertension	03/19/2024	
Sotatercept Merck	Pulmonary arterial hypertension/SC	**First in class:** novel mechanism of action; still uncertain whether this will be self-administered	03/26/2024	
RP-L201 Rocket Pharmaceuticals	Leukocyte adhesion deficiency-type 1/IV	**First in class:** would be first FDA-approved treatment for this indication; gene therapy	03/31/2024	
Odronextamab Regeneron	Diffuse large B-cell lymphoma; Follicular lymphoma/IV	**Addition to class:** binds to both a B-cell tumor protein (CD20) and an immune system T-cell receptor (CD3)	03/31/2024	

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

** Key

IM: intramuscular

IV: intravenous

LRTD: lower respiratory tract disease

SC: subcutaneous

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 current or future high-spend/trending category

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

Other significant product approvals (continued)

Drug or biologic (Manufacturer)	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
EB-101 Abeona Therapeutics	Dystrophic epidermolysis bullosa (DEB)/ surgically placed skin graft	**Addition to class:** would be second localized gene-based wound therapeutic for this indication; will compete with Vyjuvek™; uses viral vector (adeno-associated virus)	Second quarter 2024	
mRNA-1345 Moderna	Prevention of LRTD caused by respiratory syncytial virus (RSV) in people age 60 years and older/IM	**Addition to class:** would be third RSV vaccine for older adults	04/05/2024	
Anktiva (nogapendekin alfa inbakicept) ImmunityBio	Bladder cancer/ intravesical	**First in class:** another option for individuals unresponsive to Bacillus Calmette-Guérin (BCG)	04/23/2024	
Fidanacogene elaparvovec Pfizer	Hemophilia B/IV	**Addition to class:** would compete with Hemgenix® as the second gene therapy for hemophilia B	04/27/2024	
Mavorixafor X4 Pharmaceuticals	Warts, Hypogammaglobulinemia, Immunodeficiency, and Myelokathexis (WHIM) syndrome/ oral	**Addition to class:** would be first FDA-approved treatment for this indication	04/30/2024	
Rivoceranib Elevar Therapeutics	Liver cancer, first-line/IV	**Addition to class:** tyrosine kinase inhibitor for use in combination with camrelizumab, also under FDA review	05/16/2024	
Camrelizumab Elevar Therapeutics	Liver cancer, first-line/IV	**Addition to class:** programmed cell death protein 1 (PD-1) inhibitor for use in combination with rivoceranib, also under FDA review	05/16/2024	

Other significant product approvals (continued)

Drug or biologic (Manufacturer)	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Imetelstat Geron Corporation	Myelodysplastic syndrome (MDS)/IV	**First in class:** for those who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESAs)	06/16/2024	
Ensifentrine Verona Pharma	Chronic obstructive pulmonary disease (COPD)/nebulization	**First in class:** moderate to severe COPD; bronchodilator and anti-inflammatory properties	06/26/2024	
Crovalimab Roche	Paroxysmal nocturnal hemoglobinuria (PNH)/IV; SC	**Addition to class:** first dose is intravenous infusion; maintenance dosing is self-administered SC injection	07/27/2024	
Danicopan AstraZeneca	Paroxysmal nocturnal hemoglobinuria (PNH)/oral	**First in class:** add-on therapy with Soliris® or Ultomiris® in people who also have clinically evident extravascular hemolysis	07/27/2024	
KarXT (xanomeline tartrate/ trospium chloride)	Schizophrenia/oral	**Addition to class:** works on negative symptoms of schizophrenia	09/28/2024	
Deuruxolitinib Sun Pharmaceuticals	Alopecia areata in adults, moderate to severe disease/topical	**Addition to class:** would complete with Olumiant® and Litfulo®	10/06/2024	

*As of February 1, 2024

Currently, 45 biosimilar products are FDA-approved in the United States, including three approved in the second half of 2023: Tofidence™ (tocilizumab-bavi), Tyruko® (natalizumab-sztn), and Wezlana™ (ustekinumab-auub).

Biosimilar products are highly similar to their reference product in terms of structure and function and lack clinically meaningful differences in terms of safety and efficacy. Biosimilar products may be approved for all or some of the reference product indications due to patent exclusivity. Prescriptions for biosimilar products need to be written for the biosimilar by name. Biosimilar products that are 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.

In October 2023, the FDA announced new guidance to align the biosimilarity statements included in product labeling regardless of a product's interchangeability status. The update may help to address incorrect perceptions that interchangeable biosimilars are safer or more effective than biosimilars that are not approved as interchangeable.

The updated guidance comes alongside results of research published by the FDA Center for Drug Evaluation and Research (CDER) and the Division of Biometrics on the safety of switching between biosimilar products and the corresponding reference product. Data for over 5,000 people who had been switched between one of 21 biosimilar products and a corresponding reference product in trials were analyzed. The researchers concluded that there was no difference in the safety profiles or immunogenicity rates.[3]

Biosimilar pipeline update

The table below presents key biologic products that have biosimilar competition in phase 3 clinical trials. Some of these reference biologic products have existing FDA-approved and launched biosimilar competition. FDA approval of additional biosimilars in phase 3 clinical trials would allow for more options.

Biosimilar products awaiting launch

Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval*
Actemra® IV	Roche; Chugai; Genentech	Tyenne®	Fresenius Kabi	Pending
Actemra IV	Roche; Chugai; Genentech	Tofidence	Bio-Thera Solutions; Biogen	09/29/2023
Actemra SC	Roche; Genentech; Chugai	Tyenne	Fresenius Kabi	Pending
Avastin®	Genentech; Roche	Avzivi®	Bio-Thera Solutions; Sandoz	12/07/2023
Avastin	Genentech; Roche	FKB238	Centus Biotherapeutics; AstraZeneca; Fujifilm Kyowa Kirin	Pending
Enbrel®	Amgen; Immunex	Erelzi™	Sandoz	08/30/2016
Enbrel	Amgen; Immunex	Eticovo™	Samsung Bioepis	04/25/2019
Eylea®	Regeneron	Yesafili	Momenta; Mylan; Janssen; Biocon; Viatris	Pending
Eylea	Regeneron	ABP 938	Amgen	Pending
Eylea	Regeneron	CT-P42	Celltrion	Pending
Eylea	Regeneron	FYB203	Formycon; Santo Holding; Bioeq AG; Klinge Pharma; Coherus BioSciences	Pending
Herceptin®	Roche; Genentech	Zercepac	Henlius; Accord	Pending

*Excludes biosimilars that are FDA-approved and have launched
IV: Intravenous; SC: Subcutaneous

Biosimilar products awaiting launch (continued)

Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval*
Humalog®	Eli Lilly	GL-LIS	Gan & Lee; Sandoz	Pending
Humalog Pen	Eli Lilly	GL-LIS	Gan & Lee; Sandoz	Pending
Humalog U-100 KwikPen	Eli Lilly	GL-LIS	Gan & Lee; Sandoz	Pending
Humira® (100 mg/mL)	AbbVie	AVT02	Alvotech; Teva; Alvogen	Pending
Humira (100 mg/mL)	AbbVie	Hadlima™ HC	Samsung Bioepis; Organon	Pending
Humira (100 mg/mL)	AbbVie	Adalimumab AbbVie	AbbVie	11/03/2023
Humira (50 mg/mL)	AbbVie	Abrilada™	Pfizer	11/15/2019
Humira (50 mg/mL)	AbbVie	Hyrimoz®	Sandoz; Cordavis	10/30/2018
Lantus Solostar®	Sanofi	GL-GLA	Gan & Lee; Sandoz	Pending
Lantus Solostar	Sanofi	Rezvoglar™	Eli Lilly	12/17/2021
Lucentis®	Roche; Genentech	XlucaneTM	Xbrane; Stada	Pending
Neulasta®	Amgen	Lupifil-P	Lupin	Pending
Neulasta	Amgen	Lapelga®	Apotex; Accord; Intas	Pending
Neulasta Onpro®	Amgen; Insulet	Udenyca® Onbody	Coherus BioSciences	12/26/2023
Neupogen®	Amgen	TX01	Tanvex	Pending
Neupogen	Amgen	Grastofil	Apotex; Accord; Intas	Pending

*Excludes biosimilars that are FDA-approved and have launched
IV: Intravenous; SC: Subcutaneous

Biosimilar products awaiting launch (continued)

Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval*
Novolog® (10 mL vial)	Novo Nordisk	GL-ASP	Gan & Lee; Sandoz	Pending
Novolog FlexPen®	Novo Nordisk	GL-ASP	Gan & Lee; Sandoz	Pending
Novolog FlexTouch®	Novo Nordisk	GL-ASP	Gan & Lee; Sandoz	Pending
Novolog PenFill®	Novo Nordisk	GL-ASP	Gan & Lee; Sandoz	Pending
Prolia®	Amgen	GP2411	Sandoz; Hexal	Pending
Rituxan®	Roche; Biogen; Genentech	DRL RI	Dr. Reddy's; Fresenius Kabi	Pending
Soliris®	Alexion; AstraZeneca	ABP 959	Amgen	Pending
Stelara® IV	Janssen	Wezlana	Amgen	10/31/2023
Stelara IV	Janssen	SB17	Samsung Bioepis; Sandoz	Pending
Stelara IV	Janssen	CT-P43	Celltrion	Pending
Stelara SC	Janssen	Wezlana	Amgen	10/31/2023
Stelara SC	Janssen	SB17	Samsung Bioepis; Sandoz	Pending
Stelara SC	Janssen	CT-P43	Celltrion	Pending
Tysabri IV	Biogen; Royalty Pharma	Tyruko	Polpharma; Sandoz	08/24/2023
Xgeva®	Amgen	GP2411	Sandoz; Hexal	Pending

*Excludes biosimilars that are FDA-approved and have launched
IV: Intravenous; SC: Subcutaneous

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 following gene therapies and gene-based therapeutics are scheduled to receive an FDA decision in the next 12 months, or we expect them to file a biologics license application (BLA) with the FDA in 2024 or 2025.

Gene and gene-based therapies with submitted applications for potential FDA approval in 2023-2024†

Gene therapy/ gene-based therapy	Indication/route*	Expected use	Place in therapy*	Estimated approval date
Casgevy™ (exagamglogene autotemcel (exa-cel; formerly CTX001) Vertex and CRISPR Therapeutics	Beta-thalassemia anemia/IV	One-time dose	Second gene therapy for this indication; will compete with Zynteglo®. Uses gene editing.	FDA-approved (01/17/2024)
	Sickle cell anemia/IV		One of the first two gene therapies approved for this indication; will compete with HCT, chronic RBC transfusions, and Lyfgenia® gene therapy. Uses gene editing.	FDA-approved (12/08/2023)
Lyfgenia (lovotibeglogene autotemcel; lovo-cel (formerly LentiGlobin) bluebird bio	Sickle cell anemia/IV	One-time dose	One of the first two gene therapies approved for this indication; will compete with HCT, chronic RBC transfusions, and Casgevy gene therapy. Uses viral vector (lentivirus).	FDA-approved (12/08/2023)
Atidarsagene autotemcel (OTL-200) Orchard Therapeutics	Metachromatic leukodystrophy/IV	One-time dose	First gene therapy for this indication; will compete with HCT. Uses viral vector (lentivirus).	03/18/2024 (priority review)
Marnetegragene autotemcel (RP-L201) Rocket Pharmaceuticals	Leukocyte adhesion deficiency-1/IV	One-time dose	First gene therapy for this indication. Uses viral vector (lentivirus).	03/31/2024 (priority review)

*Key

BLA: biologics license application

DNA: deoxyribonucleic acid

EB: epidermolysis bullosa

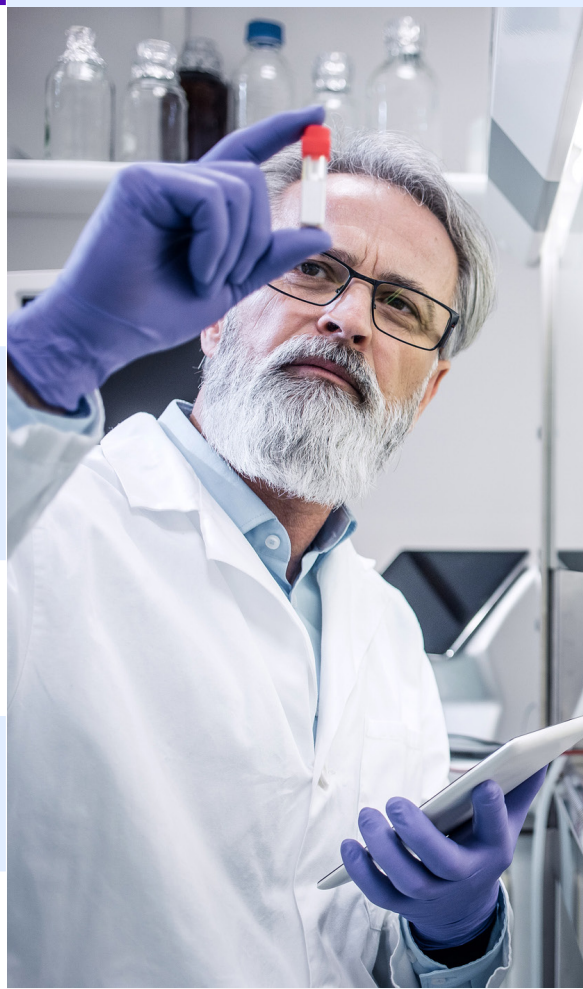
FVIII: factor 8

FIX: factor 9

HCT: hematopoietic cell transplantation

IV: intravenous

RBC: red blood cell



Gene and gene-based therapies of significant interest with potential FDA submissions in 2023-2024† (continued)

Gene therapy/ gene-based therapy	Indication/route*	Expected use	Place in therapy*	Estimated approval date
Fidanacogene elaparvovec (PF-06838435) Pfizer	Hemophilia B/IV	One-time dose	Second gene therapy for this indication; will compete with Hemgenix® and with FIX products. Uses viral vector (adeno-associated virus).	04/27/2024
Prademagene zamikeracel (Pz-cel; EB-101) Abeona Therapeutics	Dystrophic epidermolysis bullosa (DEB)/ surgically placed skin-graft	One-time surgically placed gene-modified skin graft	Competing to be the second localized gene-based wound therapeutic for people age 6 years and older with DEB; will compete with Vyjuvek™. Uses viral vector (adeno-associated virus).	05/25/2024 (priority review)

Gene and gene-based therapies of significant interest with potential FDA submissions in 2024-2025†

Gene therapy/ gene-based therapy	Indication/route*	Expected use	Place in therapy*	Estimated approval date
Eladocagene exuparvovec (PTC-AADC; AGIL-AADC) PTC Therapeutics	Aromatic L-amino acid decarboxylase deficiency/ intracerebral	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024 (plans to file in 2024)
RP-L102 Rocket Pharmaceuticals	Fanconi anemia (FA)/IV	One-time dose	First gene therapy for this indication. Uses viral vector (lentivirus).	2024 (plans to file in 2024)
Fordadistrogene movaparvovec Pfizer	Duchenne muscular dystrophy/IV	One-time dose	Second gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024 (plans to file in 2024)
Dirloctogene samoparvovec (SPK-8011) Spark Therapeutics	Hemophilia A/IV	One-time dose	Competing with giroctocogene to be second gene therapy for hemophilia A; will compete with FVIII products, Hemlibra®, and Roctavian™. Uses viral vector (adeno-associated virus).	2024-2025 (potential to file in 2024)

Gene and gene-based therapies of significant interest with potential FDA submissions in 2024-2025† (continued)

Gene therapy/ gene-based therapy	Indication/route*	Expected use	Place in therapy*	Estimated approval date
RGX-121 Regenxbio	Mucopolysaccha-ridosis II (MPS II; Hunter syndrome)/ intracisternal or intracerebroventric-ular injection	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025 (plans to file in 2024)
Giroctocogene fitelparvovec (PF-07055480; SB-525) Pfizer and Sangamo Therapeutics	Hemophilia A/IV	One-time dose	Competing with SPK-8011 to be second gene therapy for hemophilia A; will compete with FVIII products, Hemlibra, and Roctavian. Uses viral vector (adeno-associated virus).	2024-2025 (plans to file in 2H24)
Botaretigene sparoparvovec (AAV-RPGR) Athena Vision; MeiraGTx Ltd.; Janssen Pharma	X-linked retinitis pigmentosa (XLRP)/ subretinal injection	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025 (potential to file in 2024)
Cretostimogene grenadenorepvec (CG0070) Novartis	Non-muscle invasive bladder cancer (NMIBC)/intravesical	Multiple dosing	Second gene-based therapeutic; would compete with Adstiladrin®. Uses viral vector (adeno-associated virus).	2024-2025 (plans to file late 2024 or early 2025)
DTX401 Ultragenyx Pharmaceutical	Glycogen storage disease type Ia/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025 (potential to file in 2024)
RGX-111 Regenxbio	Mucopolysaccharido-sis I (MPS I; Hurler Syndrome)/intracere-broventricular infusion	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025 (potential to file in 2024)

Gene and gene-based therapies of significant interest with potential FDA submissions in 2024-2025† (continued)

Gene therapy/ gene-based therapy	Indication/route**	Expected use	Place in therapy	Estimated approval date
RP-A501 Rocket Pharmaceuticals	Danon disease/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025 (potential to file in 2024)
UX701 Ultragenyx	Wilson disease/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025 (potential to file in 2024)
ABO-102 Abeona Therapeutics	Mucopolysaccharidosis IIIA (Sanfilippo Type A)/IV	One-time dose	Competing with OTL-201 to be first gene therapy for this indication; will compete with HCT. Uses viral vector (adeno-associated virus).	2024+
Dabocemagene autoficel (D-Fi; FCX-007) Castle Creek Biosciences	Dystrophic epidermolysis bullosa (DEB)/intradermal injections	Multiple intradermal injections of gene-modified cells	Competing to be the second localized gene-based wound therapeutic for people age 2 years and older with DEB; will compete with Vyjuvek. Uses viral vector (lentivirus).	2024+
Engensis; donapermino-gene seltoplasmid Helixmith	Diabetic peripheral neuropathy and diabetic foot and other ulcers/ intramuscular injections	Intramuscular injections (multiple doses)	First gene-based therapy for these indications. Uses non-viral vector (plasmid DNA).	2024+
OTL-201 Orchard	Mucopolysaccharidosis IIIA (Sanfilippo Type A)/IV	One-time dose	Competing with ABO-102 to be first gene therapy for this indication; will compete with HCT. Uses viral vector (lentivirus).	2024+
TAVO (tavokinogene telseplasmid) OncoSec Medical	Metastatic melanoma/ intratumoral injections	Intratumoral injections (multiple doses)	First gene therapy for this indication. Uses non-viral vector (plasmid DNA).	2024+

Gene and gene-based therapies of significant interest with potential FDA submissions in 2024-2025† (continued)

Gene therapy/ gene-based therapy	Indication/route**	Expected use	Place in therapy	Estimated approval date
AGTC-501 Beacon Therapeutics	X-linked retinitis pigmentosa (XLRP)/ intraocular injection	One-time dose	Second gene therapy for this indication; will compete with botaretigene if FDA-approved. Uses viral vector (adeno-associated virus).	2025-2026 (potential to file in 2025)
DTX301 Ultragenyx Pharmaceutical	Ornithine transcarbamylase (OTC) deficiency/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2025-2026 (potential to file in 2025)
Generx® (alferminogene tadenovec) Gene Biotherapeutics	Angina/ intracoronary infusion	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2025-2026 (potential to file in 2025)
VTX-801 Vivet Therapeutics and Pfizer	Wilson disease/IV	One-time dose	Second gene therapy for this indication; will compete with UX701 if FDA-approved. Uses viral vector (adeno-associated virus).	2025-2026 (plans to file in 2025)
Zolgensma® (onasemnogene abeparvovec) Novartis	Spinal muscular atrophy (SMA) Type 2/ intrathecal infusion	One-time dose	Potential expanded indication for Zolgensma to include children age 2 to 18 years with SMA Type 2; will compete with Spinraza® and Evrysdi®. Uses viral vector (adeno-associated virus).	2025-2026 (plans to file in 2025)
ABBV-RGX-314 REGENXBIO	Neovascular age-related macular degeneration (wet AMD) and diabetic retinopathy/ subretinal and/or suprachoroidal injection	One-time dose	First gene therapy for this indication; will compete with treatments requiring multiple intravitreal injections such as Eylea® and Vabysmo®. Uses viral vector (adeno-associated virus).	2026 (plans to file in late 2025 or 2026)

† As of February 1, 2024

Duchenne muscular dystrophy (DMD) landscape and pipeline

Duchenne muscular dystrophy (DMD) is a genetic disease affecting an estimated 12,000 people, mostly boys, in the U.S. Over time, people with DMD experience progressive muscle weakness which ultimately leads to death, usually by early adulthood.

In 2023, two new products received FDA approval for people with DMD. Agamree (vamorolone) is a corticosteroid approved for people age 2 years and older and will compete with Emflaza and the off-label use of prednisone. Elevidys (delandistrogene moxeparvovec), the first gene therapy treatment approved for ambulatory people age 4 years to 5 years, is administered as a one-time intravenous infusion and carries a price tag of $3.2 million per person.

Current treatment options include oral corticosteroids which may be used to help manage symptoms, such as muscle weakness, in people with DMD. Corticosteroids can be combined with other FDA-approved agents with different mechanisms of action for DMD such as injectable exon-skipping agents and the gene therapy Elevidys. Importantly, exon-skipping agents and Elevidys were FDA-approved using an accelerated pathway, Therefore, continued FDA approval is contingent upon verification of a clinical benefit in people with DMD.

In October 2023, the manufacturer announced that Elevidys' confirmatory trial did not meet its primary efficacy endpoint. The failure of a confirmatory trial could result in removal of Elevidys from the market. Interestingly, based on statistically significant secondary endpoints, the manufacturer also announced that overall, these results support submission of a potential expanded indication for Elevidys to include all people with DMD. An application for this expansion was submitted with an estimated decision date of May 6, 2024. It is unclear how the FDA will handle the failure of the confirmatory trial.

Looking to this year and beyond, CarelonRx is closely monitoring the pipeline, including the following late-stage products in development for DMD.

Duchenne muscular dystrophy (DMD) pipeline: agents in late stage development

Drug, biologic, or gene therapy (Manufacturer)	Route (frequency)	Place in therapy	Estimated FDA approval date (stage of development)	Estimated peak-year sales potential[2]
Givinostat Italfarmaco	Oral (twice daily)	**First in class:** • Histone deacetylase (HDACs) enzyme inhibitor; pivotal trial evaluating ambulant boys age 6 years to 17 years with DMD. • Will be used in addition to other DMD therapies.	03/21/2024 (submitted)	$90M to $120M
Fordadistrogene movaparvovec Pfizer	Intravenous infusion (single, one-time dose)	**Addition to class:** • Second gene therapy for this indication; pivotal trial evaluating one-time dose in ambulatory boys age 4 years to 7 years with DMD; uses viral vector (adeno-associated virus). • Will compete with the first gene therapy Elevidys, which also uses a viral vector (adeno-associated virus).	2024 (phase 3)	$1B to $1.3B
CAP-1002 Capricor	Intravenous infusion (every 3 months)	**First in class:** • Immunomodulatory cell therapy; trials evaluating ambulatory and non-ambulatory boys and young men age 10 years and older with DMD; uses human allogeneic cardiosphere-derived cells. • Will be used in addition to other DMD therapies.	2025 (phase 3)	Unknown

B=billion; M=million

Market trends

Combination seasonal flu and COVID vaccines

Vaccinations are an important part of routine healthcare. Maximizing vaccine uptake can be a challenge, though. According to the Centers for Disease Control and Prevention (CDC) at least three out of every four adults in the U.S. are missing one or more recommended routine vaccines. One potential strategy for increasing vaccination rates is the development of more convenient combination products designed to reduce the number of injections that need to be administered. One example is the ongoing development of several combination seasonal flu and COVID vaccines. The table below provides insight on these products in the pipeline. Future phase 3 data will provide a better understanding of the efficacy and safety of this combination approach. If approved, the first one would likely be available as early as 2025.

Product (Manufacturer)	Early efficacy and safety data	FDA status
mRNA-1083 (Moderna)	• Phase 1/2 data demonstrated immune responses similar to each company's standard flu shots and COVID-19 vaccines. • Local and systemic adverse reactions were also similar to standalone products. No new concerns were identified.	Phase 3 trial initiated; potential approval in 2025.
BNT162b2+BNT161 (BioNTech/Pfizer)		Phase 3 trial will be initiated soon; would likely be second COVID-flu combination vaccine approved. No information on FDA submission timeline.
COVID-Influenza combination (CIC) (Novavax)		Phase 3 trial will be initiated soon; no information on FDA submission timeline.

Biologics for chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a chronic disease caused by damage, such as smoking, to the lungs. People with COPD have difficulty breathing and often a chronic cough. Exacerbations, or symptom flare-ups making it even harder to breathe, can be caused by triggers such as poor air quality and infections. Severe exacerbations can result in hospitalization or death.

COPD is treated based on disease severity with the overarching goal to reduce symptoms and frequency of exacerbations. Pharmacologic treatments include inhaled corticosteroids, bronchodilators, and antimuscarinics. For severe COPD, treatment with two or three different inhaled pharmacologic agents is recommended. When inhaled therapies do not adequately control COPD symptoms, oral treatments with steroids, roflumilast, and azithromycin may be considered.

Treatment options for people with COPD who do not respond to two or three different inhaled pharmacologic agents will likely expand to include biologics. Six biologics in late-stage development for moderate-to-severe COPD are highlighted in the following table. Dupixent®, Nucala, and Fasenra®, are being studied for a subtype of severe COPD in people who also have elevated eosinophils, a type of white blood cell. Notably, Dupixent is the closest to potential FDA approval in 2024. Analysts expect the global COPD market, including biologics, to grow, reaching nearly $24 billion in sales by 2032.[2]

COPD pipeline: biologics in late-stage development

Drug or biologic (Manufacturer)	Route (frequency)	Target	Place in therapy	Estimated FDA approval date (stage of development)	Estimated peak-year, major market sales potential for COPD[2]
Dupixent (dupilumab) Sanofi & Regeneron	SC (every 2 weeks)	Inhibits IL-4 and IL-13 by binding to a shared subunit, IL-4Ra	• Seeking approval for adults with moderate-to-severe COPD with eosinophilic phenotype and history of exacerbations. • In pivotal trials, Dupixent significantly reduced exacerbations compared to placebo when added to maximal standard-of-care inhaled therapy.	2024 (phase 3)	$90M to $120M
Nucala (mepolizumab) GlaxoSmithKline	SC (every 4 weeks)	IL-5 inhibitor	• Seeking approval for adults with moderate-to-severe COPD with eosinophilic phenotype and history of exacerbations. • Trial results are expected in the second half of 2024.	2025 (phase 3)	$250M to $500M
Fasenra (benralizumab) AstraZeneca	SC (every 8 weeks)	IL-5 inhibitor	• Seeking approval for adults with moderate-to-severe COPD with eosinophilic phenotype and history of exacerbations. • Trial results are expected in 2025.	2025-2026 (phase 3)	$100M to $250M
Itepekimab Sanofi & Regeneron	SC (every 2 to 4 weeks)	IL-33 inhibitor	• Seeking approval for adults with moderate-to-severe COPD who are having recurring exacerbations. • Trial results are expected in 2025.	2025-2026 (phase 3)	>$1B
Tozorakimab AstraZeneca	SC	IL-33 inhibitor		2025-2026 (phase 3)	>$1B
Astegolimab Roche	SC (every 2 to 4 weeks)	IL-33 inhibitor		2026-2027 (phase 3)	Unknown

COPD= chronic obstructive pulmonary disease; SC= subcutaneous injection; IL= interleukin; M= million; B= billion

References

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