carelon Rx

Drug and biologic pipeline update Q2 2024

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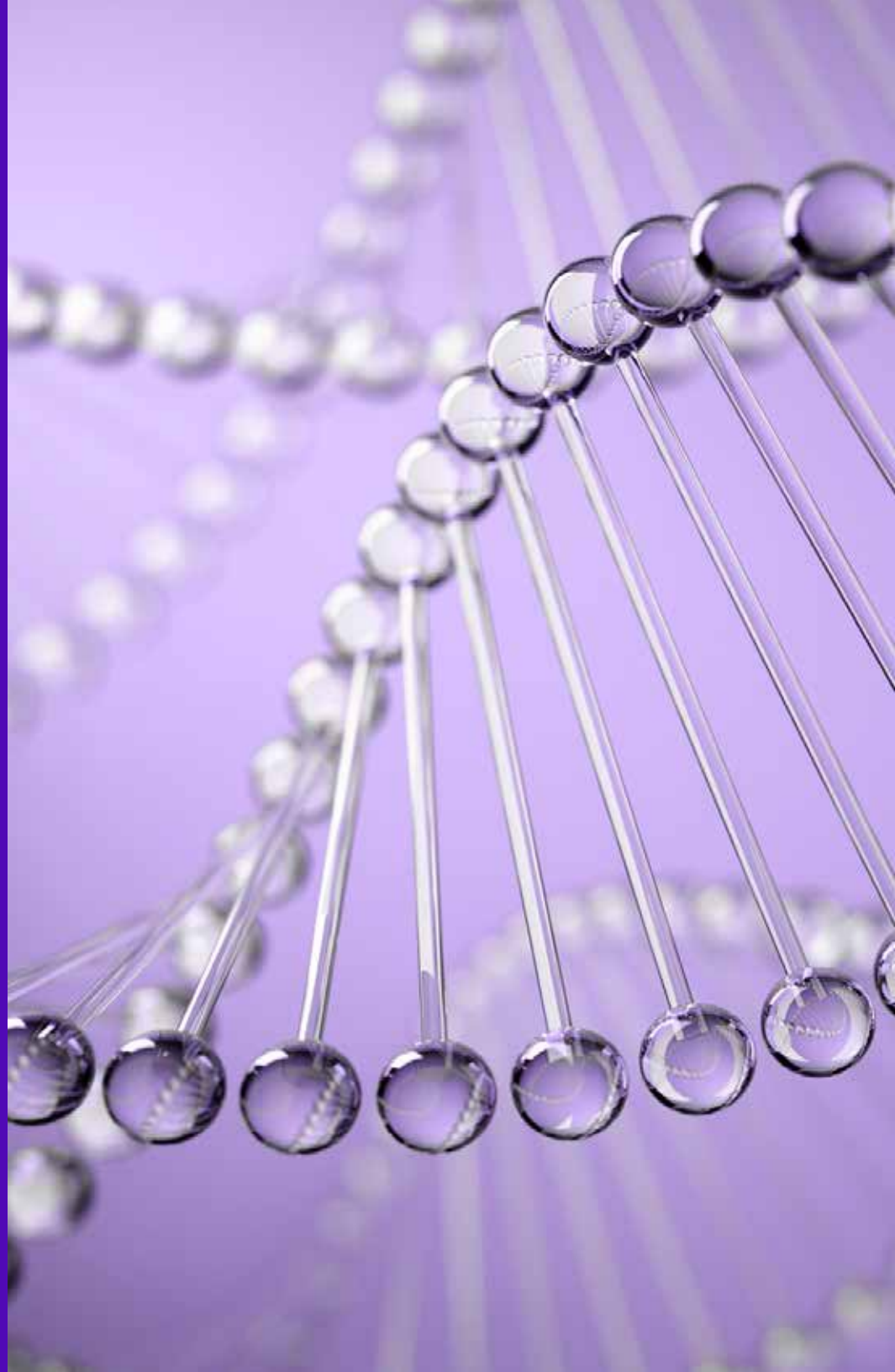
CarelonRx's quarterly Drug and biologic pipeline update

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 Q2 2024 update provides summaries of three agents of interest with anticipated approvals this year: marstacimab for hemophilia A and B, seladelpar and elafibranor for primary biliary cholangitis, and midomafetamine for post-traumatic stress disorder (PTSD). Other select drugs and biologics in the pipeline, including gene therapies and biosimilars, are also highlighted. An overview of Food and Drug Administration (FDA) approvals in 2023 will be provided. Other topics this quarter include nomenclature changes for nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) and an overview of atopic dermatitis treatment, including recently approved clinical guidelines and the current pipeline landscape.



Marstacimab

Condition:
Hemophilia is a rare but serious bleeding disorder occurring in about 1 of every 5,000 male births. While it can develop later in life, hemophilia is usually an inherited disease where the blood is unable to clot properly due to a lack of clotting factors. Symptoms include bleeding in the joints, skin, muscle, or soft tissue following an injury or surgery. Bleeding can also occur spontaneously. Recurrent or prolonged bleeding can lead to chronic joint disease and pain, seizures, paralysis, or even death.

There are two types of hemophilia, defined by the clotting factor in which the individual is deficient. People with hemophilia A lack clotting factor VIII (FVIII) whereas hemophilia B refers to a deficiency in factor IX (FIX). The degree of factor deficiency determines the severity of disease, with severe hemophilia occurring when factor levels are less than 1%. FVIII or FVIX levels greater than 40% are considered normal. In general, the number of spontaneous bleeds increases as the factor level decreases.

Role in treatment:
There is no cure for hemophilia. Management includes replacing the missing factor using plasma-derived or recombinant clotting factor concentrates. Replacement may be done as needed; this is known as on-demand therapy. For those with more severe disease, factor concentrates may be given prophylactically to reduce the risk of spontaneous bleeding and long-term complications. However, limitations to prophylactic use include intravenous (IV) injections 1-3 times weekly, risk of infection, variable factor activity, and the risk of developing inhibitors.

About 20% of people with hemophilia A and 3% of those with hemophilia B develop inhibitors, which are antibodies that stop the clotting factors from being able to clot the blood and stop the bleeding. Standard replacement factor is no longer an effective option in those individuals. Hemlibra® (emicizumab, subcutaneous) is given once weekly for prophylaxis in people with hemophilia A with or without FVIII inhibitors. For treatment of bleeding events in those with hemophilia A or B and inhibitors, bypass agents such as FEIBA (anti-inhibitor coagulant complex [human], intravenous), NovoSeven® (factor VIIa [recombinant], intravenous) or SEVENFACT® (factor VIIa [recombinant], intravenous) are used.

Marstacimab is a first-in-class agent that provides a novel mechanism of action for hemophilia. It is a human monoclonal immunoglobulin that targets the tissue factor pathway inhibitor responsible for preventing clots. If approved, marstacimab would be the first once-weekly subcutaneous prophylactic option for hemophilia B without inhibitors and would join Hemlibra as another option for hemophilia A without inhibitors.

Product:
Marstacimab

Indication:
Prophylactic treatment of hemophilia A or B without inhibitors

Estimated FDA approval:
4Q 2024

Therapeutic class:
Tissue factor pathway inhibitor

Route of administration:
Subcutaneous

FDA designations:
Fast Track; Orphan

Manufacturer:
Pfizer

Marstacimab

(continued)

Efficacy:
The open-label, phase 3 BASIS trial assessed adolescents and adults with severe hemophilia A or moderately severe to severe hemophilia B with or without inhibitors. Only data from individuals without inhibitors is available currently. Of those who received routine prophylaxis, a reduction in mean annualized bleeding rate (ABR) from 7.85 to 5.08 was seen following 12 months of marstacimab. Those who received on-demand factor replacement had a reduction in mean ABR from 38.00 to 3.18. Consistent reductions in mean ABR were observed for up to 16 months of additional marstacimab use.

Safety:
Marstacimab was well-tolerated in the BASIS trial. No deaths or thromboembolic events have been reported.

Financial impact:
If approved, marstacimab will be a first-in-class prophylactic treatment option for hemophilia A or B without inhibitors.[1] Peak sales are estimated to reach $250 to 500 million in major markets (US, Europe, and Japan).

CarelonRx view:
While individuals with hemophilia are always seeking new options to decrease their disease burden, it remains unclear where marstacimab will best fit in clinical practice. Expanded use in younger children or those with inhibitors may gain approval later.

Elafibranor and Seladelpar

Peroxisome proliferator-activated receptor (PPAR) agonists for primary biliary cholangitis (PBC): elafibranor and seladelpar

Condition:
Primary biliary cholangitis (PBC), previously referred to as primary biliary cirrhosis, is a rare, chronic, progressive, autoimmune, cholestatic liver disease that eventually leads to cirrhosis and liver failure. In the beginning stages, most people are asymptomatic. Over time people may experience itchy skin, feeling tired, and other symptoms related to liver failure. The rate of progression varies widely and may extend over decades. The prevalence of PBC in the United States has been estimated around 130,000 people, with the majority being women.

Role in treatment:
Guidelines recommend ursodiol as first-line treatment for all people diagnosed with PBC who have abnormal liver biochemistries, such as elevated alkaline phosphatase (ALP). The two pipeline agents, elafibranor and seladelpar, would compete with the current FDA-approved product Ocaliva® (obeticholic acid oral) as second-line treatment options — either as add-on therapy with ursodiol, or as monotherapy if a person is unable to tolerate ursodiol. Elafibranor and seladelpar have unique mechanisms of action compared to Ocaliva, a farnesoid X receptor agonist, and are likely to compete closest with one another as peroxisome proliferator-activated receptor (PPAR) agonists. While combination therapy with Ocaliva has not been evaluated in trials, it is possible that in clinical practice combining therapies with different mechanisms of action may be considered.

Efficacy:
The PPAR agonists, elafibranor and seladelpar, were evaluated in similarly designed, separate, placebo-controlled phase 3 trials. Participants entering these studies were either unable to tolerate ursodiol or already on a stable dose of ursodiol. Despite treatment with ursodiol, people with elevated levels of liver biomarkers at baseline, such as ALP and total bilirubin, were then randomized to add either elafibranor or seladelpar once daily to their PBC treatment regimen. Efficacy of treatment was assessed after 12 months by evaluating a combination of the change in ALP and total bilirubin lab values, a proposed biomarker surrogate endpoint in PBC trials. Both agents are seeking accelerated approval using this surrogate biomarker, while the potential clinical benefits are still being evaluated in ongoing trials.

The primary efficacy endpoint — improvement in liver biomarker lab values — was met for both agents compared to placebo after 12 months. Approximately one in three people treated in trials with either elafibranor or seladelpar achieved this endpoint.

Product:
Elafibranor

Indication:
Treatment of adults with primary biliary cholangitis (PBC) either in combination with ursodeoxycholic acid (UDCA; ursodiol) with an inadequate response to ursodiol, or as monotherapyin those unable to tolerate ursodiol.

Estimated FDA approval:
Elafibranor: June 2024

Therapeutic class:

Dual peroxisome proliferator-activated receptor alpha/delta (PPAR α,δ) agonist.

Route of administration:
Oral

FDA designations:
Breakthrough Therapy; Orphan; Priority Review

Manufacturer:
Ipsen and Genfit

Elafibranor and Seladelpar

(continued)

Safety:
Side effects from trials were similar with each of these PPAR agonists. Compared to placebo, more people taking PPAR agonists experienced abdominal pain, headache, and gastrointestinal side effects such as nausea, vomiting, and diarrhea. Ocaliva carries a boxed warning ("black box warning") due to the risk of liver failure and is contraindicated for use in people with advanced liver disease or cirrhosis. It is unclear if PPAR agonists will carry this same safety concern.

Financial impact:
The prices of elafibranor and seladelpar are unknown. However, it will likely be priced similarly to Ocaliva which carries a wholesale acquisition cost of approximately $100,000 per person per year.[2] Some analysts have estimated the PBC market to reach $1.5B by 2030.

CarelonRx view:
The addition of two new agents that offer a new mechanism of action will increase competition for PBC second-line treatments. It is unclear if PPAR agonists will carry a similar contraindication like Ocaliva for use in people with cirrhosis. Elafibranor is a PPAR alpha/delta agonist while seladelpar is only a PPAR delta agonist. The clinical impact of these slightly different PPAR receptor targets remains unknown.

Chronic itch can be a major issue for people living with PBC. In clinical practice when selecting a second-line treatment for PBC, an important consideration may be its side-effect profile. In trials each PPAR agonist decreased itch in people compared to placebo. By indirect comparison, in Ocaliva trials people using Ocaliva experienced more itch compared to placebo. Itching may be an important distinction that could drive utilization towards PPAR agonists versus Ocaliva as initial second-line treatments.

Product:
Seladelpar

Indication:
Treatment of adults with primary biliary cholangitis (PBC) either in combination with ursodeoxycholic acid (UDCA; ursodiol) with an inadequate response to ursodiol, or as monotherapy in those unable to tolerate ursodiol.

Estimated FDA approval:
August 2024

Therapeutic class:
Selective peroxisome proliferator-activated receptor delta (PPARδ) agonist.

Route of administration:
Oral

FDA designations:
Breakthrough Therapy; Orphan; Priority Review

Manufacturer:
CymaBay

Midomafetamine (MDMA)

Condition:
Post-Traumatic Stress Disorder (PTSD) is a mental health condition that can develop after an individual experiences or witnesses a traumatic event such as physical or sexual assault, the unexpected death of a loved one, or military combat. Approximately 13 million Americans are affected by PTSD each year. Women and marginalized groups are more likely to be affected by PTSD. Military personnel also have a greater prevalence of PTSD than the general population. However, the largest cause of PTSD is non-combat-related trauma. PTSD symptoms of fall into four categories:

- Re-experiencing (e.g., flashbacks or dreams)
- Avoidance (e.g., avoiding places or thoughts related to the trauma)
- Arousal and reactivity (e.g., being easily startled, feeling on edge, sleep difficulties, and engaging in risky behaviors)
- Cognition and mood (e.g., forgetting key features of the trauma, ongoing negative emotions, lost interest in enjoyable activities, and feelings of social isolation)

PTSD symptoms can greatly impact one's quality of life. Individuals with PTSD often have other mental health disorders that may include anxiety, substance use disorder, depression, and suicidal thoughts.

Role in treatment:
First-line treatment for PTSD is psychotherapy (talk therapy) which can be used alone or in combination with medication. Talk therapy can target PTSD symptoms or focus on social, family, or work-related issues; this therapy usually lasts 6–12 weeks but can last longer. Key components of talk therapy involve learning skills to identify triggers and manage symptoms.

Two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, have FDA-approved indications for PTSD. Other medications may be used off-label. If MDMA is FDA-approved, it would be the first psychedelic-assisted therapy and the first new drug approved for PTSD in over two decades.

MDMA (also known as "Ecstasy" or "Molly") is an entactogen, which increases self-awareness, introspection, and personal reflection. MDMA was historically used in the 1970s and early 1980s in combination with talk therapy to help individuals access, process, and communicate difficult experiences and emotions. Under the Controlled Substances Act, MDMA is currently a Schedule I drug; this prevents it from being used recreationally or medically. If FDA-approved, the Drug Enforcement Administration (DEA) would be required to reschedule MDMA so that it is available for prescription medical use.

Product:
MDMA

Indication:
In combination with psychological intervention for post-traumatic stress disorder (PTSD)

Estimated FDA approval:
August 2024

Therapeutic class:
Psychedelic (entactogen)

Route of administration:
Oral

FDA designations:
Breakthrough Therapy

Manufacturer:
Lykos Therapeutics

Midomafetamine (MDMA)

(continued)

Efficacy:
The New Drug Application submitted to the FDA was supported by data from two phase 3 clinical trials, MAPP1 and MAPP2, which respectively included adults with severe and moderate-to-severe PTSD. In both trials, participants received three 90-minute preparation sessions with a two-person therapy team prior to receiving experimental treatment. Experimental sessions consisted of three 8-hour dosing sessions of MDMA or placebo, both in conjunction with therapy conducted by trained personnel. Following each experimental session, participants received three 90-minute integration sessions for support in processing and understanding their experience. MDMA demonstrated improvements in PTSD symptom severity and functional impairment compared to placebo over 18 weeks.

Safety:
Adverse events that occurred most frequently with MDMA included muscle tightness, nausea, decreased appetite, and excessive sweating. There were no serious adverse events reported for MDMA in either phase 3 study.

Financial impact:
The cost of MDMA upon approval has not yet been determined. One cost-effectiveness analysis found the cost of MDMA-assisted therapy as conducted in phase 3 trials is approximately $11,500 per individual, of which more than 90% is attributed to therapists' compensation.[3] MDMA is also being studied for use in other indications, which may further expand use.

CarelonRx view:
Although new treatment options for PTSD are greatly needed, questions remain about how MDMA may fit best in clinical practice, including which population may benefit most, along with long-term safety and response to treatment. MDMA will likely be used only by trained healthcare professionals and only after first-line treatment options have been unsuccessful. MDMA is currently a Schedule I controlled substance which means it has a high abuse potential and no accepted medical uses. If approved, it would require DEA rescheduling in order to allow for prescribing. MDMA will likely be part of the medical benefit since it is administered during in-person sessions with a trained therapist. There are many other psychedelic therapies in development for diagnoses that include depression, anxiety, eating disorders, and substance use disorders.

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
Elafibranor Genfit	Primary biliary cholangitis/oral	**Addition to class:** would compete with Ocaliva	06/10/2024	
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	
Arimoclomol Orphazyme	Niemann-Pick disease type C/oral	**First in class:** would be first FDA-approved treatment for this indication	06/21/2024	
Ensifentrine Verona Pharma	Chronic obstructive pulmonary disease (COPD)/nebulization	**First in class:** moderate to severe COPD; bronchodilator and anti-inflammatory properties	06/26/2024	
Patritumab deruxtecan Amgen	Non-small cell lung cancer, locally advanced or metastatic epidermal growth factor receptor (EGFR)-mutated/IV	**First in class:** human epidermal growth factor receptor 3 (HER3) — directed DXd antibody drug conjugate for disease previously treated with two or more systemic therapies	06/26/2024	
Dupixent® (dupilumab) Sanofi	Chronic obstructive pulmonary disease (COPD)/SC	**New Indication:** would be first biologic approved for use in people with COPD with type 2 inflammation	06/27/2024	

*As of April 16, 2024

In addition to treatments listed previously, these important drugs and biologics are scheduled to receive FDA approval within the next 12 months. Several new indications for existing products are also included.

Key

IM: intramuscular

IV: intravenous

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
Deuruxolitinib Sun Pharmaceuticals	Alopecia areata in adults, moderate to severe disease/oral	**Addition to class:** would compete with Olumiant® and Litfulo®	July 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	⊗
Midomafetamine Lykos Therapeutics	Post-traumatic stress disorder (PTSD)/oral	**First in class:** given during an in-person session with a trained therapist; would be first psychedelic agent approved for therapeutic use	08/14/2024	⊗
Seladelpar CymaBay Therapeutics	Primary biliary cholangitis/oral	**Addition to class:** would compete with Ocaliva	08/15/2024	📈
Tradipitant Vanda	Gastroparesis symptoms/oral	**Addition to class:** would compete with metoclopramide	09/18/2024	⊗
KarXT (xanomeline tartrate/ trospium chloride) Karuna Therapeutics	Schizophrenia/oral	**Addition to class:** works on both positive and negative symptoms of schizophrenia	09/28/2024	⊗
Garadacimab CSL Limited	Hereditary angioedema, prevention of attacks/SC	**First in class:** novel mechanism of action; once-monthly	Between October and November 2024	⊗

*As of April 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
Marstacimab Pfizer	Hemophilia A and B/SC	**First in class:** would compete with Hemlibra	Fourth quarter 2024	
Obecabtagene autoleucel Autolus Therapeutics	Acute lymphoblastic leukemia/IV	**Addition to class:** next chimeric antigen receptor T-cells (CAR-T) therapy; potential for better safety	11/16/2024	
Govorestat Applied Therapeutics	Classic galactosemia/oral	**First in class:** would be first FDA-approved treatment for this indication	11/28/2024	
Acoramidis BridgeBio	Transthyretin amyloid cardiomyopathy/oral	**Addition to class:** would compete with Vyndamax®/Vyndaqel®	11/29/2024	
Wegovy® (semaglutide) Novo Nordisk	Heart failure with preserved ejection fraction (HFpEF)/SC	**New Indication:** phase III trial showed reductions in heart failure-related symptoms and physical limitations, improvements in exercise function, and resulted in greater weight loss in adults with HFpEF and obesity	11/30/2024	

*As of April 16, 2024

Humira (adalimumab) was approved in 2002 by the FDA and became a top-selling biologic in the United States. Biosimilar competition entered the market in July 2023 and impacted AbbVie's financial performance. The company reported $12,160 million in net revenue for Humira in the U.S. for 2023, a 35% decline from 2022.

Unbranded adalimumab products are marketed under a manufacturer's approved Biologics License Applications (BLA) without its brand name on label. The FDA considers it to be equivalent to its brand-name biological product.

There are currently ten FDA-approved biosimilars to Humira, with nine having launched in 2023. The most recent approval, in February 2024, was Simlandi®. It is the first high-concentration, citrate-free interchangeable biosimilar to Humira. The majority of Humira use is for the high-concentration formulation. Abrilada and Cyltezo are low-concentration biosimilars to Humira with interchangeability status, and additional FDA-approved Humira biosimilars are seeking interchangeability with anticipated decisions in 2024.

There are some differences between Humira and the FDA-approved biosimilars with regard to FDA-approved indications. Only Humira has pediatric approval for the following indications: hidradenitis suppurativa, uveitis, and ulcerative colitis. Other differences between the reference and biosimilar products that may affect selection include concentration (e.g., 50 mg/mL or 100 mg/mL); device availability (e.g., prefilled syringe or pen device); and inactive ingredients (e.g., latex and citrate).

Humira® biosimilar pipeline update

Humira biosimilar products in the near-term pipeline, pending launch, or on the market

Biosimilar name	Biosimilar manufacturer	Concentration	FDA approval	Interchangeable	Launched	Unbranded product available
Abrilada™	Pfizer	50 mg/mL	11/15/19	Yes	Yes	No
Amjevita™	Amgen	50 mg/mL	9/23/16	No	Yes	No
Amjevita HCF™		100 mg/mL	8/14/23	No	Yes	No
Cyltezo®	Boehringer Ingelheim	50 mg/mL	8/25/17	Yes	Yes	Yes
Hadlima™	Organon	50 mg/mL	7/23/19	Pending	Yes	No
Hadlima HC™		100 mg/mL	8/15/22	Pending	Yes	No
Hulio®	Mylan	50 mg/mL	7/6/20	No	Yes	Yes
Humira reference product	AbbVie	50 mg/mL	12/31/02	Not applicable	Yes	No
		100 mg/mL	9/10/15		Yes	Yes, not available
Hyrimoz™	Sandoz	50 mg/mL	10/30/18	No	No	No
Hyrimoz HCF™		100 mg/mL	3/21/23	No	Yes	Yes
Idacio®	Fresenius Kabi	50 mg/mL	12/13/22	No	Yes	Yes
Simlandi	Alvotech	100 mg/mL	2/23/24	Yes	No	No
Yuflyma™	Celltrion	100 mg/mL	5/23/23	Pending	Yes	Yes, not available
Yusimry™	Coherus	50 mg/mL	12/17/21	No	Yes	No

Gene therapies in the pipeline

Gene therapy is a novel approach to treatment. It introduces genetic material into an individual's body to help fight various diseases. To differentiate gene therapy products, we divide them into two broad categories: gene therapy and gene-based therapeutics. Gene therapies are typically 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 FDA decisions in the next 12 months, or we expect they could file a BLA with the FDA in 2024/2025.

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

Gene therapy/ gene-based therapy	Indication/route	Expected use	Place in therapy	Estimated approval date
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 (approved)
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).	04/26/2024 (approved)
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 6 and older with DEB; will compete with Vyjuvek™. Uses viral vector (adeno-associated virus).	05/25/2024 (FDA denied at this time; will resubmit later in 2024)
Elevidys (delandistrogene moxeparvovec-rokl) Sarepta Therapeutics	Duchenne muscular dystrophy (DMD)/IV	One-time dose	Submitted supplemental BLA to expand approval to people with DMD without restriction to age or ambulatory status.	06/21/2024 (priority review)
Marnetegragene autotemcel (RP-L201) Rocket Pharmaceuticals	Leukocyte adhesion deficiency-I/IV	One-time dose	First gene therapy for this indication. Uses viral vector (lentivirus).	06/30/2024 (priority review)

*As of April 16, 2024

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 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).	03/19/2025 (submitted)
RP-L102 Rocket Pharmaceuticals	Fanconi anemia/IV	One-time dose	First gene therapy for this indication. Uses viral vector (lentivirus).	2024
Fordadistrogene movaparvovec Pfizer	Duchenne muscular dystrophy/IV	One-time dose	Second gene therapy for this indication. Uses viral vector (adeno-associated virus).	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
RGX-121 Regenxbio	Mucopolysaccharidosis II (MPS II; Hunter syndrome)/intracisternal or intracerebroventricular injection	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025
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
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

*As of April 16, 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
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
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
RP-A501 Rocket Pharmaceuticals	Danon disease/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025
UX701 Ultragenyx	Wilson disease/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025
ABO-102 Abeona Therapeutics	Mucopolysaccha-ridosis 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 2 and older with DEB; will compete with Vyjuvek. Uses viral vector (lentivirus).	2024+
Engensis; donaperminogene 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	Mucopolysaccha-ridosis 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+

*As of April 16, 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
TAVO (tavokinogene telseplasmid) OncoSec Medical	Metastatic melanoma/intra-tumoral injections	Intratumoral injections (multiple doses)	First gene therapy for this indication. Uses non-viral vector (plasmid DNA).	2024+
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
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
Generx® (alferminogene tadenovec) Gene Biotherapeutics	Angina/intra-coronary infusion	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2025-2026
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
Zolgensma® (onasemnogene abeparvovec) Novartis	Spinal muscular atrophy (SMA) type 2/intrathecal infusion	One-time dose	Potential expanded indication for Zolgensma to include children 2 to < 18 years of age with SMA type 2; will compete with Spinraza® and Evrysdi®. Uses viral vector (adeno-associated virus).	2025-2026
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

*As of April 17, 2024

Analysis: 2023 year in review for novel drug approvals

The FDA's Center for Drug Evaluation and Research releases an annual report entitled "Advancing Health Through Innovation: New Drug Therapy Approvals." The report summarizes notable approvals for the prior year.

Below are approval highlights from the 2023 report (2022 numbers in parentheses):[4,5]

- 55 (37) therapies approved in total
- 20 (20) first-in-class therapies (unique mechanisms of action)
- 28 (20) therapies approved for orphan diseases (those that affect < 200,000 people in the U.S.)
- 25 (12) therapies approved with Fast Track status
- 9 (13) therapies approved as Breakthrough Therapies
- 31 (21) therapies approved with Priority Review status (6-month review versus 10-month for standard review)
- 9 (6) therapies approved under Accelerated Approval (confirmatory trials must be conducted)
- 36 (24) of the 55 (37) approvals used one or more expedited programs (Fast Track Designation, Breakthrough Therapy Designation, Priority Review, and/or Accelerated Approval)
- 49 (36) of the 55 (37) approvals came on or before the Prescription Drug User Fee Act goal date

Market trends

New nomenclature for NASH and NAFLD

Nonalcoholic steatohepatitis (NASH) is a subtype of nonalcoholic fatty liver disease (NAFLD) where a person has a buildup of excess fat in the liver along with inflammation that causes damage. Differentiating NAFLD and NASH in clinical practice can be challenging. A new factor to consider is the recent announcement of nomenclature updates for NAFLD and NASH.

In 2023, a multisociety NAFLD consensus group agreed to change the names for NASH and NAFLD.[6] NAFLD is now called metabolic dysfunction-associated steatotic liver disease (MASLD) and will be used to describe a person with fatty liver who also has at least one of five specific cardiometabolic risk factors.[7] NASH is now metabolic dysfunction-associated steatohepatitis (MASH) and will be used to describe a person with MASLD who also has inflammation causing liver damage.

Nomenclature changes are not expected to greatly affect the drug development pipeline for MASH. The Food and Drug Administration (FDA) recently approved the first treatment for MASH, Rezdiffra™ (resmetirom oral). Competition is on its heels with four additional drugs in phase 3 development creating the potential for additional MASH treatments to enter the market in 2024 and 2025.

Market trends (continued)

Update on atopic dermatitis guidelines and pipeline

Atopic dermatitis (AD), the most common type of eczema, is an inflammatory skin disease that causes red, itchy, and sometimes painful rashes. Beginning as early as infancy for some, AD affects approximately 10% to 20% of children and 5% to 10% of adults. Disease severity ranges from mild, isolated flare-ups to severe, widespread disease that can significantly affect quality of life — including ability to sleep.

Guideline updates:

The American Academy of Dermatology (AAD) recently updated both their topical and systemic guidelines for the treatment of adults with AD. Updated recommendations now include statements for all of the current FDA-approved treatments.

Topical steroids and emollients are the backbone of AD treatment. For mild disease, these agents are often used in combination with other topicals. Topical treatment guidelines provide strong recommendations for the use of steroids, calcineurin inhibitors, the phosphodiesterase-4 (PDE-4) inhibitor Eucrisa®, and the Janus kinase (JAK) inhibitor Opzelura™.[8] While first-line treatment often begins with topical steroids, guidelines do not provide clear advice regarding second-line topical treatments.

When topicals are inappropriate or do not adequately control symptoms, phototherapy and systemic treatments may be added. The updated AAD phototherapy and systemic treatment guidelines provide strong recommendations for the use of all four current FDA-approved therapies.[9] The injectable biologics Adbry® and Dupixent are recommended for adults with moderate to severe AD, while oral JAK inhibitors Cibinqo® and Rinvoq® are reserved for adults with moderate to severe AD who have failed other systemic therapies including biologics, or when those therapies are not advisable.

AD pipeline:

There is significant activity in the biopharma industry in the development of treatments for AD. Analysts anticipate continued growth in AD over the next several years with major markets set to exceed $36 billion by 2032.[1] Looking ahead into 2024 and beyond, CarelonRx is closely monitoring the pipeline, including the following late-stage products in development (table begins on next page):

Key

AD: atopic dermatitis

BLA: Biologics License Application

CRL: complete response letter from FDA

JAK: Janus kinase

IL: interleukin

SC: subcutaneous injection

sNDA: supplemental new drug application

Atopic dermatitis (AD) pipeline: agents in late-stage development

Drug or biologic (Manufacturer)	**Route (Target)**	**Place in therapy**	**Estimated FDA approval date (stage of development)**
Topical competitors			
Zoryve® (roflumilast 0.15% and 0.05%) cream Arcutis Biotherapeutics	Topical (PDE-4 inhibitor)	**Addition to class:** • Joins Eucrisa as a once-daily next generation PDE-4 inhibitor for AD. • Zoryve 0.15% cream has filed for approval in people 6 years of age and older with AD. • Zoryve 0.05% cream is in development for people 2 to 5 years of age with AD. • Zoryve is currently FDA-approved as a 0.3% cream for the treatment of people 6 years of age and older with plaque psoriasis.	07/07/2024 (0.15% cream; submitted sNDA) 2024-2025 (0.05% cream; phase 3)
Vtama® (tapinarof) cream Dermavant Sciences	Topical (aryl hydrocarbon receptor agonist)	**First in class:** • First aryl hydrocarbon receptor agonist for AD; has filed for approval of a second indication as a once-daily treatment for people 2 years of age and older with AD. • Vtama 1% cream is FDA-approved for the treatment of adults with plaque psoriasis.	08/14/2024 (submitted sNDA)
Opzelura (ruxolitinib) cream Incyte	Topical (JAK inhibitor)	**Expanded indication:** • Once daily; seeking potential age expansion for people 6 to 12 years of age with AD. • Opzelura is FDA-approved as non-continuous treatment of people 12 years of age and older with AD whose disease is not adequately controlled with topical prescription therapies or when those are not advisable.	2025 (phase 3)
MH004 cream Minghui Pharmaceutical	Topical (pan-JAK inhibitor)	**Addition to class:** • Would join Opzelura as the second JAK inhibitor for AD.	2025+ (phase 3)
Difamilast Medimetriks Pharmaceuticals	Topical (PDE-4 inhibitor)	**Addition to class:** • Would join Eucrisa as another PDE-4 inhibitor for AD.	2025+ (phase 3)

Atopic dermatitis (AD) pipeline: agents in late-stage development (continued)

Systemic competitors

Nemolizumab Galderma	SC (IL-31 inhibitor)	**First in class:** • Would be first IL-31 inhibitor; seeking approval in people 12 and older with moderate to severe AD. • Administered every 4 weeks. • Also submitted a BLA for prurigo nodularis with a priority review FDA decision date of 08/14/2024.	12/14/2024 (submitted BLA)
Lebrikizumab Eli Lilly	SC (IL-13 inhibitor)	**Addition to class:** • Would join Adbry as a second selective IL-13 inhibitor; seeking approval in people 12 and older. • Administered every 2 weeks with potential every 4 week maintenance dosing. • Received a CRL in October 2023 citing manufacturing inspection issues. Unclear refiling timeline.	Unclear (CRL issued)
Amlitelimab Sanofi	SC (OX40-ligand inhibitor)	**First in class:** • Competing to be first anti-OX40-ligand monoclonal antibody; pivotal studies in adults with moderate-to-severe AD whose disease cannot be adequately controlled with topicals. • Administered every 4 weeks with potential maintenance dosing every 12 weeks or longer.[10]	2025-2026 (phase 3)
Rocatinlimab Amgen	SC (OX40 inhibitor)	**First in class:** • Competing to be first anti-OX40 monoclonal antibody; pivotal studies in adults with moderate-to-severe AD whose disease cannot be adequately controlled with topicals. • Administered every 4 weeks	2025-2026 (phase 3)
Velsipity™ (etrasimod) Pfizer	Oral (sphingosine 1-phosphate [S1P] receptor modulator)	**First in class:** • Velsipity is FDA-approved for ulcerative colitis. • Would be first SP1-receptor modulator for AD; seeking approval in adults with moderate-to-severe AD who have failed other systemic therapies.	2026+ (phase 2/3)

References

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9 Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, et al.: Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies (February 2024): pubmed.ncbi.nlm.nih.gov/37943240/.

10 FirstWord PHARMA: AAD Daily: Atopic dermatitis agents move towards less-frequent dosing, oral JAK inhibitor shows rapid action in PN...and more (accessed April 2024): firstwordpharma.com

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