carelon Rx

Drug and biologic pipeline update Q3 2023

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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 within 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 Q3 2023 edition includes details on three agents of interest with potential to reach the market this year or early next year: tirzepatide for weight loss, resmetirom for nonalcoholic steatohepatitis (NASH), and lifileucel for melanoma. Other select drugs and biologics in the pipeline, including gene therapies and biosimilars, are highlighted. The pipeline landscape for dry eye disease will also be spotlighted. Finally, summaries of psychedelic agents in development for treatment of diseases such as depression and post-traumatic stress disorder (PTSD) and the emerging area of digital therapeutics will be provided.

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 July 12, 2023.

Top emerging new therapies

Tirzepatide

Condition:

Many causes of obesity are preventable and reversible.[1] Losing or maintaining weight involves a lifestyle of healthy eating and regular physical activity that reduces or balances calories consumed with calories used by the body for energy. Obesity guidelines recommend lifestyle interventions (i.e., diet and exercise) as first-line management followed by the addition of drug therapy for those who have had an inadequate response to lifestyle interventions alone.[2] Healthy eating emphasizes fruits, vegetables, and whole grains, includes a variety of proteins, and limits added sugars, sodium, and certain fats. In general, adults should engage in 150 minutes of physical activity weekly, while children need 60 minutes daily to maintain a healthy weight.

Obesity affects 42% of adults and 20% of children in the United States. Obesity is associated with other health conditions, such as type 2 diabetes, heart disease, certain types of cancer, and mental illness. Body weight greater than what is considered healthy for a given height is described as overweight or obese. Factors contributing to excess weight gain include eating and physical activity patterns, insufficient sleep, social drivers of health, genetics, and certain illnesses and medications.

Role in treatment:

Tirzepatide was first approved by the Food and Drug Administration (FDA) in May 2022 for the treatment of type 2 diabetes (Mounjaro®, injection; Eli Lilly). Tirzepatide is under review by the FDA for people with obesity or who are overweight with weight-related conditions. If approved, tirzepatide will join Wegovy® (semaglutide, injection; Novo Nordisk) and Saxenda® (liraglutide, injection; Novo Nordisk) as the third injectable anti-obesity medication targeting the GLP-1 receptor. Novo Nordisk has an oral formulation of semaglutide in phase 3 development for obesity with plans to file for approval this year. These agents should be used in combination with diet and exercise, and only started in those with an inadequate response to diet and exercise alone.

Both GLP-1 and GIP receptors are found in areas of the brain involved in appetite regulation. Tirzepatide is unique in that it also targets the GIP receptor. GIP may complement the effects of GLP-1 receptor agonists, potentially resulting in greater weight loss. Like Wegovy, tirzepatide is injected weekly, while Saxenda requires daily injection.

Efficacy:

The FDA rolling submission was supported by data from two phase 3 studies in adults with obesity or who were overweight with or without type 2 diabetes. Both studies met the co-primary endpoints compared to placebo. After 72 weeks, participants without diabetes lost up to 22.5% (52 pounds) of baseline body weight (SURMOUNT-1) while those with diabetes lost up to 15.7% (34.4 pounds) of baseline body weight (SURMOUNT-2).

Product:
Tirzepatide

Indication:
Obesity

Estimated FDA approval:
Late 2023/early 2024

Therapeutic class:
Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) co-agonist

Route of administration:
Subcutaneous injection

FDA designations:
Fast track

Manufacturer:
Eli Lilly and Company

Tirzepatide

Continued

Safety:
Adverse events were similar to other anti-obesity drugs targeting the GLP-1 receptor. The most common adverse events for tirzepatide were gastrointestinal-related (e.g., nausea, diarrhea, vomiting, and constipation) and these occurred more frequently than placebo. Gastrointestinal adverse events were generally mild to moderate in severity and usually occurred during dose escalation. Discontinuations due to adverse events in the two studies ranged from 4% to 7% for those treated with tirzepatide. If approved, FDA labeling will potentially include safety warnings similar to Mounjaro, Wegovy, and Saxenda, such as risk of thyroid C-cell tumors (black box warning), acute pancreatitis, acute gallbladder disease, severe gastrointestinal disease, acute kidney injury, and hypersensitivity reactions.

Financial impact:
Because phase 3 studies show tirzepatide to have the greatest weight loss efficacy on indirect comparison, shifts from Wegovy and Saxenda to tirzepatide are expected. Cost of tirzepatide, entry of liraglutide generics, launch of pipeline competitor CagriSema (cagrilintide-semaglutide, injection; Novo Nordisk), and off-label use of medicines for weight loss may impede uptake of tirzepatide; however, demand will remain high with sales expected to exceed $1 billion by 2031 for the indication of weight loss.[3]

CarelonRx view:
Key areas where information is lacking include long-term cardiovascular benefits, safety risks, and maintenance of weight loss.

A study of tirzepatide evaluating the reduction of morbidity and mortality in people with obesity or who are overweight and with established cardiovascular disease, peripheral arterial disease, or multiple cardiovascular risk factors is ongoing with an estimated completion date of October 2027. If cardiovascular results are positive, use of tirzepatide may increase. Tirzepatide is also being studied for potential treatment in those with obesity and/or who are overweight with heart failure with preserved ejection fraction, non-alcoholic steatohepatitis, and obstructive sleep apnea.

Increased demand for weight loss drugs, including off-label use, have led to ongoing drug shortages for the GLP-1 class.[4] Several major pharmaceutical companies are increasingly investing in research and development for obesity treatments. Although the late-stage obesity pipeline is limited, the early-phase obesity pipeline is large, with approximately 100 drugs in active clinical development.[3]

Product:
Tirzepatide

Indication:
Obesity

Estimated FDA approval:
Late 2023/early 2024

Therapeutic class:
Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) co-agonist

Route of administration:
Subcutaneous injection

FDA designations:
Fast track

Manufacturer:
Eli Lilly and Company

Resmetirom

Condition:
Nonalcoholic fatty liver disease (NAFLD) occurs when there is a buildup of fat in the liver that cannot be attributed to another cause. NAFLD is the most common liver disease in the U.S. Nonalcoholic steatohepatitis (NASH) is a subtype of NAFLD when a person has a buildup of excess fat and inflammation causing damage to the liver. Many people with NAFLD and NASH are unaware of their disease because most do not experience symptoms and diagnosis of NASH requires a liver biopsy. NASH, likely underdiagnosed, is estimated to affect approximately 3% to 5% of the U.S. population and can progress to fibrosis, cirrhosis, or liver cancer. NASH is the second most common indication for a liver transplant in the U.S. after hepatitis C.[5]

Role in treatment:
NAFLD is often accompanied by other diseases, including obesity, type 2 diabetes, and high cholesterol. Currently, there are no FDA-approved treatments for NAFLD or NASH. Disease management is guided by and focused on managing co-morbid conditions, including weight loss, diet, and exercise.[5] Until late June 2023, resmetirom was competing with obeticholic acid (OCA) in a race to become the first agent FDA-approved for the treatment of NASH. OCA, a farnesoid X receptor (FXR) agonist, works differently than resmetirom. In late June 2023, OCA received its second denial from the FDA and Intercept Pharmaceuticals announced that it will no longer continue development.

Efficacy:
Madrigal Pharmaceuticals is seeking accelerated approval based on histological response to resmetirom treatment. Clinical outcomes such as progression to cirrhosis and hepatic decompensation events are being evaluated in ongoing studies.

The pivotal trial evaluating people with biopsy-confirmed NASH, with fibrosis stages 1 through 3 (F1-F3), given resmetirom once daily versus placebo met both its co-primary efficacy endpoints with statistical significance. One year after treatment, 26% of people given resmetirom 80 mg, 30% given resmetirom 100 mg, and 10% of placebo-treated people achieved NASH resolution with ≥2-point reduction in NAS (NAFLD Activity Score) with no worsening of fibrosis. The second co-primary endpoint, a 1-point decrease in fibrosis with no worsening of NASH after one year of treatment, was achieved in 24%, 26%, and 14% of people treated with resmetirom 80 mg, 100 mg, and placebo, respectively. Secondary endpoints also met statistical significance, including an improvement in lipids and liver enzymes with both resmetirom doses compared to placebo.

Safety:
The most common adverse events reported in the biopsy-confirmed NASH and NAFLD studies with higher incidence with resmetirom compared to placebo were diarrhea and nausea. These side effects were described as mild and transient for most people.

Financial impact:
The price of resmetirom is unknown. However, analysts anticipate that the entire group of NASH therapies in development could grow to more than $4 billion in sales by the end of 2030.[3]

CarelonRx view:
Madrigal began a rolling submission for accelerated approval in the second quarter of 2023.

While the current standard to diagnose NASH requires a liver biopsy, many noninvasive methods are being evaluated. If accepted into practice, noninvasive diagnostics could increase the number of people diagnosed with and potentially treated for NASH.

Product:
Resmetirom

Indication:
Fibrosis due to nonalcoholic steatohepatitis (NASH)

Estimated FDA approval:
2024

Therapeutic class:
Thyroid hormone receptor (THR) beta-selective agonist

Route of administration:
Oral

FDA designations:
Breakthrough Therapy; Fast track

Manufacturer:
Madrigal Pharmaceuticals

Lifileucel

Condition:
Melanoma is a type of skin cancer. It develops in melanocytes, which are the cells that give skin its color. It's less common than other types of skin cancers, but it is also more likely to spread to other parts of the body. Melanomas can develop on any part of the skin but are most common on the chest and back in men and on the legs in women. Other common sites are the neck and face.[6]

Although only accounting for approximately 1% of skin cancers, melanoma causes the majority of skin cancer deaths. An estimated 97,610 new diagnoses of melanoma will be made this year and approximately 7,990 people will die. The majority of deaths occur in disease that has spread to other parts of the body.[7]

Role in treatment:
Lifileucel is for people with advanced melanoma who have progressed after failing first-line therapies such as programmed death receptor-1 (PD-1) blocking antibodies. There are no FDA-approved therapies for this population. Lifileucel would be the first one-time cell therapy for a solid tumor cancer. TILs are isolated from the tumor, expanded, and infused back into the person to fight against the tumor.

Efficacy:

The FDA submission was supported by data from a phase 2 clinical trial. The primary endpoint of objective response rate (ORR) was met. The ORR (percentage of people whose tumor shrinks or disappears after treatment) was 31%. The accelerated approval pathway was used for submission and approval would be based on a surrogate endpoint, a measure that may correlate with clinical benefit. A confirmatory trial with a clinical outcome endpoint (e.g., survival) would be needed for continued approval. The phase 3 confirmatory trial has been announced. This trial will support full approval for lifileucel as monotherapy in advanced melanoma after prior treatment. Additionally, it will support a second indication of first-line treatment in combination with Keytruda® (pembrolizumab injection; Merck), a PD-1 inhibitor.

Safety:
Adverse events were consistent with the underlying disease and with conditioning treatment given prior to lifileucel infusion and interleukin-2 (IL-2) therapy given after infusion. The incidence of adverse events decreased rapidly during the first two weeks after infusion of lifileucel.

Financial impact:
Lifileucel is expected to be the first cell therapy approved for solid tumors. Lifileucel has a complex administration process that could limit uptake. It will be used mostly as a later line of therapy after failure of first line treatment. Peak year sales for lifileucel are expected to reach $500 million to $750 million.[3]

CarelonRx view:

Initial approval of lifileucel will be after failure of first-line therapies. Expanded use as first-line treatment in combination therapy may come later. In addition, there are ongoing studies in other types of solid tumors.

Product:
Lifileucel

Indication:
Melanoma

Estimated FDA approval:
November 2023

Therapeutic class:
Tumor-infiltrating lymphocyte (TIL) cell therapy

Route of administration:
Intravenous infusion

FDA designations:
Fast track; Orphan; Regenerative medicine advanced therapy

Manufacturer:
Iovance Biotherapeutics

Other significant product approvals

We expect these products to reach the market in late 2023/early 2024:*

Drug or biologic manufacturer	Indication/route**	Place in therapy	Estimated approval date	Impact on overall drug or medical spend**
Nedosiran Novo Nordisk	Primary hyperoxaluria/SC	**First in class:** ability to treat a broader range of disease	September 2023	
Lebrikizumab Eli Lilly	Atopic dermatitis/SC	**Addition to class:** same mechanism of action as DUPIXENT® and ADBRY®	September 2023	
Nirsevimab AstraZeneca	Respiratory syncytial virus prevention/IM	**Addition to class:** use in broad population of infants for prevention of RSV, lower respiratory tract disease	Third quarter 2023	
Elranatamab Pfizer	Multiple myeloma, relapsed or refractory/SC	**Addition to class:** would compete directly with TECVAYLI™	10/22/2023	
Vamorolone Santhera Pharmaceuticals	Duchenne muscular dystrophy/oral	**Addition to class:** will compete with EMFLAZA® and prednisone	10/26/2023	
Reproxalap Aldeyra Therapeutics	Dry eye disease/ophthalmic	**First in class:** new mechanism of action for dry eye	11/23/2023	

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

PD-1: programmed cell death protein 1

SC: subcutaneous

TIL: tumor-infiltrating lymphocyte

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**
Lifileucel Iovance	Melanoma/IV	**First in class:** ready-to-infuse autologous cell therapy product containing TILs	11/24/2023	
Etrasimod Pfizer	Ulcerative colitis/oral	**Addition to class:** will compete with Zeposia® or biologics	Second half of 2023	
CTX001 (exa-cel) Vertex/CRISPR Therapeutics	Sickle cell disease/IV	**First in class:** first gene therapy for sickle cell disease; also under review for beta-thalassemia where it would compete with ZYNTEGLO®	12/8/23	
Talquetamab Johnson & Johnson	Multiple myeloma/SC	**First in class:** off-the-shelf (ready to use), investigational bispecific T-cell engager antibody	12/11/2023	
ARQ-154 (roflumilast) Arcutis Biotherapeutics	Seborrheic dermatitis in people age 9 years and older/topical	**Addition to class:** foam formulation of roflumilast for dermatitis of the scalp	12/16/2023	
Aprocitentan Johnson & Johnson	Hypertension, resistant/oral	**First in class:** would be first FDA-approved product specifically for resistant hypertension	12/20/2023	

Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy	Estimated approval date	Impact on overall drug or medical spend **
Lovo-cel; Lovotibeglogene autotemcel (formerly LentiGlobin) bluebird bio	Sickle cell disease/IV	**Addition to class:** would likely be second gene therapy for sickle cell disease	12/20/2023	⊗
iDose TR (travoprost implant) Glaukos Corporation	Glaucoma; Ocular hypertension/ ophthalmic implant	**Addition to class:** novel formulation of travoprost designed to continuously release therapeutic levels for at least one year. Will compete with DURYSTA®, another bimatroprost implant	12/22/2023	⊗
Eplontersen Ionis	Familial amyloid polyneuropathy/SC	**Addition to class:** second generation ligand-conjugated antisense (LICA) agent targeting transthyretin	12/22/2023	⊗
Cosibelimab Checkpoint Therapeutics	Metastatic cutaneous squamous cell carcinoma/IV	**Addition to class:** would compete with other PD-1 inhibitors	1/3/2024	⊗
Roluperidone Minerva Neurosciences	Schizophrenia/oral	**First in class:** would be first FDA-approved treatment for negative symptoms of schizophrenia	2/26/2024	⊗

*As of July 12, 2023

Currently, 41 biosimilar products are FDA-approved in the United States, including one approved in 2023: Yuflyma®, a biosimilar to HUMIRA® (adalimumab).

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 can be approved for all or some of the reference product indications due to patent exclusivity. Prescriptions for biosimilar products should be written for the biosimilar by name.

Interchangeable biosimilar products are allowed to be substituted at the pharmacy level without the intervention of the prescriber. However, the ability to substitute at the pharmacy is dependent on individual state laws. Currently, four biosimilar products have been granted interchangeability status with more seeking interchangeability.

- SEMGLEE®, a biosimilar to LANTUS® (insulin glargine)
- REZVOGLAR™, a biosimilar to Lantus
- CIMERLI™, a biosimilar to LUCENTIS® (ranibizumab)
- CYLTEZO®, a biosimilar to Humira (adalimumab)

Biosimilar pipeline update

Biosimilar products awaiting launch

Reference drug name	Reference drug companies	Biosimilar name	Biosimilar companies	FDA approval †
ACTEMRA® IV/SC	Genentech	BAT1806	Bio-Thera Solutions; Biogen	Pending
Actemra IV/SC	Genentech	MSB11456	Fresenius	Pending
Avastin®	Genentech	BAT1706	Bio-Thera Solutions; Sandoz	Pending
Avastin	Genentech	FKB238	Centus Biotherapeutics; AstraZeneca; Fujifilm	Pending
Avastin	Genentech	SB8	Samsung Bioepis; Organon	Pending
ENBREL®	Amgen; Immunex	ERELZI®	Sandoz	8/30/2016
Enbrel	Amgen; Immunex	ETICOVO™	Samsung Bioepis	4/25/2019
EYLEA®	Regeneron	MYL-1701P	Momenta; Mylan; Viatris, multiple	Pending
HERCEPTIN®	Genentech	HLX02	Henlius; Accord	Pending
Humira (100 mg/mL)	AbbVie	HYRIMOZ® HCF	Sandoz	3/20/2023
Humira (100 mg/mL)	AbbVie	HADLIMA™ HC	Samsung Bioepis; Organon	8/15/2022
Humira (100 mg/mL)	AbbVie	AVT02	Alvotech; Teva; Alvogen	Pending
Humira (100 mg/mL)	AbbVie	Yuflyma®	Celltrion	5/23/2023

Biosimilar products awaiting launch (continued)

Reference drug name	Reference drug companies	Biosimilar name	Biosimilar companies	FDA approval †
Humira (50 mg/mL)	AbbVie	YUSIMRY™	Coherus BioSciences	12/17/2021
Humira (50 mg/mL)	AbbVie	CYLTEZO®	Boehringer Ingelheim	8/25/2017
Humira (50 mg/mL)	AbbVie	HULIO®	Fujifilm Kyowa Kirin; Viatris; Mylan; Biocon	7/6/2020
Humira (50 mg/mL)	AbbVie	ABRILADA™	Pfizer	11/15/2019
Humira (50 mg/mL)	AbbVie	HYRIMOZ®	Sandoz	10/30/2018
Humira (50 mg/mL)	AbbVie	IDACIO®	Fresenius	12/13/2022
Humira (50 mg/mL)	AbbVie	HADLIMA™	Samsung Bioepis; Organon; Biogen	7/23/2019
Lantus Solostar®	Sanofi Aventis US	Rezvoglar	Eli Lilly	12/17/2021
Lucentis	Genentech	Xlucane™	Xbrane; Bausch Health; Bausch + Lomb; Stada	Pending
Neulasta®	Amgen	Lupifil-P®	Lupin	Pending
Neulasta	Amgen	Lapelga™	Apotex; Accord; Intas	Pending
Neulasta® Onpro®	Amgen; Insulet	UDENYCA® OBI	Coherus BioSciences	Pending
NEUPOGEN®	Amgen	TX01	Tanvex	Pending
Neupogen	Amgen	Grastofil®	Apotex; Accord; Intas	Pending
Prolia®	Amgen	GP2411	Sandoz; Hexal	Pending

*Manufacturer states this is a citrate-free formulation.

Biosimilar products awaiting launch (continued)

Reference drug name	Reference drug companies	Biosimilar name	Biosimilar companies	FDA approval †
REMICADE®	Janssen	IXIFI™	Pfizer	12/13/2017
SOLIRIS®	Alexion Pharmaceuticals	ABP 959	Amgen	Pending
STELARA® IV/SC	Janssen	ABP 654	Amgen	Pending
STELARA IV/SC	Janssen	AVT04	Alvotech; Teva; Alvogen	Pending
Tysabri IV	Biogen	Tyruko™	Polpharma; Sandoz	Pending
XGEVA®	Amgen	GP2411	Sandoz; Hexal	Pending

**Excludes biosimilar products that have launched.

† As of July 12, 2023

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 now approved a handful of gene therapies including five recent approvals in the past year: Elevidys in June, VYJUVEK™ in May, HEMGENIX® in November, SKYSONA® in September, and ZYNTEGLO® in August 2022. With the exception of Vyjuvek, these 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.

In May 2023, the FDA approved the first herpes simplex virus type 1 (HSV-1) vector-based, redosable gene-based therapeutic, VYJUVEK™ (beremagene geperpavec, topical gel; Krystal Biotech, Inc.) for the treatment of wounds in people age 6 months and older with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene. VYJUVEK is a live, non-replicating, gene-based therapeutic designed to express the COL7 protein when applied topically, directly to DEB wounds. It is the first FDA-approved treatment for people living with DEB. Two additional localized gene-based therapeutics for epidermolysis bullosa are in phase 3 development.

In June 2023, the FDA approved the first gene therapy for boys age 4 and 5 years with Duchenne muscular dystrophy (DMD). Elevidys (delandistrogene moxeparvovec, infusion; Sarepta) is administered as a single intravenous infusion and is dispensed as a customized kit based on weight. The one-time treatment, each individual kit, has a wholesale acquisition cost of $3.2 million. It will compete with exon-skipping agents like Exondys 51 and steroids like EMFLAZA®. While the initial indication is limited to ambulatory boys 4 and 5 years of age with DMD, Sarepta plans to file for an expanded approval to include a broader population of DMD in early 2024.

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
Roctavian (valoctogene roxaparvovec) BioMarin	Hemophilia A/IV	One-time dose; potentially curative; however, in ongoing studies, factor levels have declined over time introducing doubt in durability of effect	First gene therapy for this indication; will compete with FVIII products and HEMLIBRA®	Approved 6/29/2023

** Key

BLA: biologics license application

EB: epidermolysis bullosa

FVIII: factor 8

FIX: factor 9

HCT: hematopoietic cell transplantation

IV: intravenous

RBC: red blood cell

* As of July 12, 2023

Gene therapies in the pipeline (continued)

Gene therapy/ Gene-based therapy	Indication/route**	Expected use	Place in therapy	Estimated approval date
Exagamglogene autotemcel (exa-cel; formerly CTX001) Vertex/CRISPR Therapeutics	Beta-thalassemia anemia/IV	One-time dose; potentially curative	Second gene therapy for this indication; will compete with ZYNTEGLO	3/30/2024 (standard review)
	Sickle cell anemia/IV		First gene therapy for this indication; will compete with HCT and chronic RBC transfusions	12/8/2023 (priority review)
Lovotibeglogene autotemcel; lovo-cel (formerly LentiGlobin) bluebird bio	Sickle cell anemia/IV	One-time dose; potentially curative	Second gene therapy for this indication; will compete with HCT, chronic RBC transfusions, and, if FDA-approved, exa-cel gene therapy	12/20/2023
OTL-200 Orchard Therapeutics	Metachromatic leukodystrophy/IV	One-time dose; potentially curative	First gene therapy for this indication; will compete with HCT	2024 (plans to complete rolling BLA in mid-2023; requesting priority review)

* As of July 12, 2023

Gene and gene-based therapies of significant interest with potential FDA submissions in 2023*

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; potentially curative	First gene therapy for this indication	2024 (plans to file 1H23)
RP-L201 Rocket Pharmaceuticals	Leukocyte adhesion deficiency-I/IV	One-time dose; potentially curative	First gene therapy for this indication	2024 (plans to file 2Q23)
D-Fi (FCX-007; dabocemagene autoficel) Castle Creek Biosciences	Epidermolysis bullosa/autologous, gene-modified skin grafts	Multiple intradermal treatments to wound(s)	Competing to be second localized gene-based wound therapeutic for people age 2 years or older with EB	2024+
EB-101 Abeona Therapeutics	Epidermolysis bullosa/autologous, gene-modified skin grafts	One-time surgically placed skin graft to wound(s)	Competing to be second localized gene-based wound therapeutic for people age 6 years or older with EB	2024 (plans to file in 3Q23)
ABO-102 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	2024+
OTL-201 Orchard Therapeutics	Mucopolysaccharidosis IIIA (Sanfilippo Type A)/IV	One-time dose; potentially curative	Competing to be first gene therapy for this indication; will compete with HCT	2024+

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

Gene therapy/ Gene-based therapy	Indication/route**	Expected use	Place in therapy**	Estimated approval date
Engensis (donaperminogene seltoplasmid) Helixmith	Diabetic foot ulcers/ intramuscular Diabetic peripheral neuropathy/ intramuscular	Multiple injections	First gene-based therapeutic for these indications	2024+
Fidanacogene elaparvovec (PF-06838435) Pfizer	Hemophilia B/IV	One-time dose; potentially curative	Second gene therapy for this indication; will compete with Hemgenix and with FIX products	2024 (has now submitted)
RP-L102 Rocket Pharmaceuticals	Fanconi anemia (FA)/ IV	One-time dose; potentially curative	First gene therapy for this indication	2024 (plans to file 4Q23)
Fordadistrogene movaparvovec Pfizer	Duchenne muscular dystrophy/IV	One-time dose; potentially curative	Second gene therapy for this indication	2024 (potential to file by end of 2023)

*As of July 12, 2023

Dry eye disease landscape and pipeline

Dry eye disease (DED), often a chronic condition, occurs when either a reduced quantity or lower quality of tears are produced. Prevalence estimates vary ranging from 16 million to 39 million people living with DED in the U.S. Most people do not have sight-threatening disease, but rather experience bothersome symptoms such as dry, red, itchy, or irritated eyes.

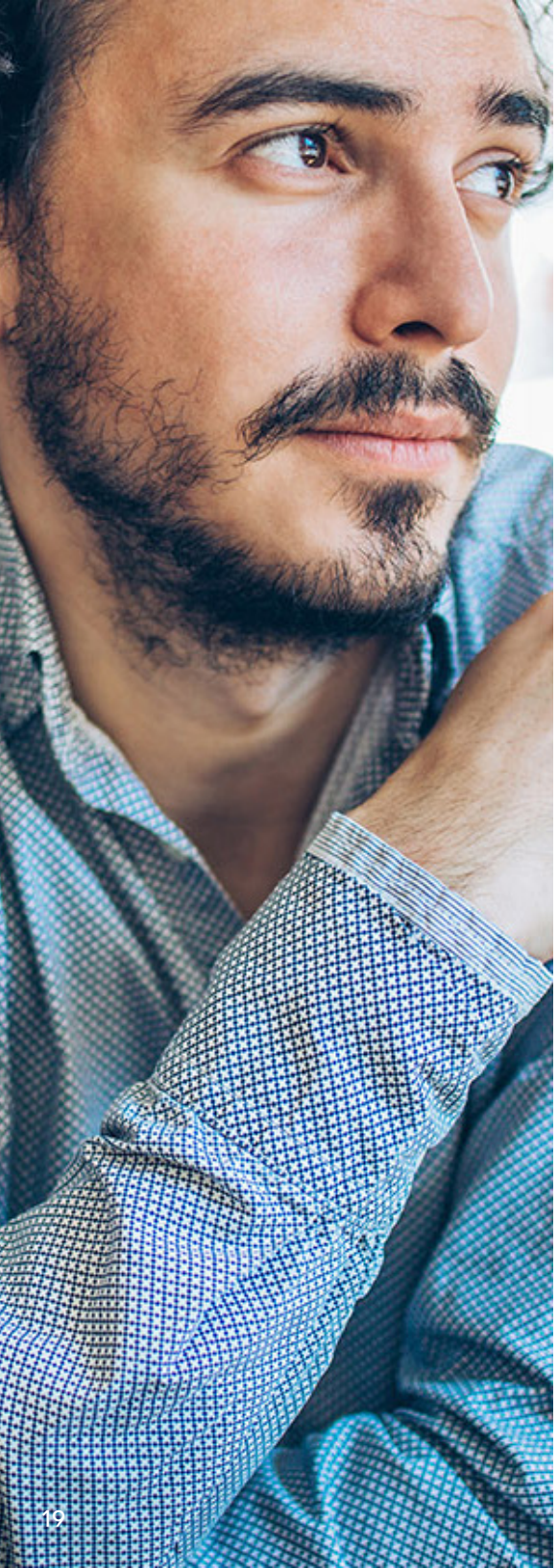
Current pharmacologic treatment options are over-the-counter artificial tears and prescription therapies. Many different mechanisms of action are available, each aiming to improve the signs and symptoms of DED. Topical anti-inflammatory drugs include CEQUA™ (cyclosporine ophthalmic; Sun Pharma), EYSUVIS® (loteprednol ophthalmic; Kala), generically available RESTASIS® (cyclosporine ophthalmic; Allergan), and Xiidra® (lifitegrast ophthalmic; Novartis).
For people who fail to achieve relief with artificial tears, LACRISERT® (hydroxypropyl cellulose ophthalmic; Aton Pharma), an ophthalmic insert, is available and acts to lubricate and protect the eye. In 2021, the first nasal spray, Tyrvaya® (varenicline nasal spray; Oyster Point Pharma), was approved, offering people a non-ophthalmic treatment option for DED. While most prescription therapies have not been studied for combination use, it is likely combination therapy is occurring.

Even with so many agents already on the market for DED, the late-stage drug development pipeline is robust. The following topical ophthalmic drugs have either recently received or have submitted a new drug application for potential FDA approval this year.

- In May, **MIEBO**™ (perfluorohexyloctane ophthalmic; Bausch + Lomb) was FDA-approved as a water-free and preservative-free solution to treat the signs and symptoms of DED. While the exact mechanism of action of Miebo is unknown, it is thought to reduce tear evaporation. Miebo joins a crowded market but is the first perfluorohexyloctane-containing product.
    - Analysts predict Miebo will have peak-year sales exceeding $1 billion.[3]
- In June, **VEVYE**™ (cyclosporine 0.1% solution, Novaliq) became the third cyclosporine ophthalmic FDA-approved for DED. Vevye is a water-free, preservative-free, ophthalmic formulation and will likely compete most closely with other twice daily cyclosporine products which differ slightly in strength and formulation, including Cequa (0.09% solution) and generically available Restasis (0.05% emulsion).
    - Analysts predict Vevye will have peak-year sales of $250 million to $500 million.[3]

- **Reproxalap**, a 0.25% solution, developed by Aldeyra, is a first-in-class reactive aldehyde species (RASP) inhibitor seeking approval for the treatment of signs and symptoms of DED. In trials, it was administered twice daily after initial loading doses for DED. Reproxalap will likely compete most closely with anti-inflammatory drugs, including generic Restasis.
    - The FDA decision date is November 2023.
    - Analysts predict Reproxalap will have peak-year sales exceeding $1 billion.[3]
    - Reproxalap is also in phase 3 development as a once daily treatment for allergic conjunctivitis.

Overall, Clarivate analysts predict the global DED prescription drug market to grow from $3.9 billion in 2019 to approximately $7.3 billion in 2029.[3] Much of this growth is attributed to the U.S. market, with expansion projected to originate mostly from newly approved agents, with a smaller amount due to increased disease awareness leading to more DED diagnoses over the forecast period. With the recent FDA approval of Miebo and Vevye, a third new drug slated for approval in 2023, and over 10 additional phase 3 drugs in development, DED will likely continue to be of great interest.



Market trends

Psychedelic drugs in the pipeline

Psychedelic therapy is the use of plant compounds that can induce hallucinations to treat mental health disorders such as depression and post-traumatic stress disorder (PTSD). It is unclear how these compounds work, but some theories include neurotransmitter changes that affect mood, increased suggestibility making people more responsive to therapy, and intense experiences that may affect a person's mindset. Because adverse events may be serious, use is only intended for people who are resistant to all other therapy. Examples of psychedelics being studied include psilocybin (mushrooms), lysergic acid diethylamide (LSD) found in several plants, 3,4-methylenedioxy-methamphetamine (MDMA) found in the sassafras tree and commonly called ecstasy, and mescaline found in some cacti. Psychedelics may be used alongside traditional treatments or in guided therapy.[8]

The U.S. Drug Enforcement Administration (DEA) currently has these agents classified as Schedule I Controlled Substances, which are defined as drugs with no accepted medical use and high potential for abuse. It is unclear at this time how the DEA would handle approval of a psychedelic drug for therapeutic use. Funding for research in this area is limited, but as evidence for use grows, discussions concerning the legal obstacles are increasing.[9]

Clinical development of psychedelics for therapeutic use is still in the early stages. The two most advanced products are highlighted in the table below. However, there are numerous other products in earlier development.

Compound type	Drug name	Manufacturer	Therapeutic use	Phase of development
Psilocybin	COMP360	Compass Pathways	Major depressive disorder	Phase 3
3,4-methylenedioxy-methamphetamine (MDMA)	Midomafetamine	Multidisciplinary Association for Psychedelic Studies	Post-traumatic stress disorder	Phase 3 Expected to submit in the third quarter 2023

The FDA announced a draft guidance, Psychedelic Drugs: Considerations for Clinical Investigations, to provide considerations in developing psychedelic drugs for the treatment of medical conditions. This guidance applies to clinical trials that will be conducted under an investigational new drug application.

Digital health technology

The FDA recently issued a Digital Health Technology (DHT) framework document designed to help guide the use of DHT-derived information in regulatory decision-making for drugs and biologics. DHTs are defined as systems that use computing platforms, connectivity, software, and/or sensors for healthcare and related uses. They include technologies that may be used as a medical product, in a medical product, or along with other medical products. Examples of DHTs include software applications or technologies, such as wearable, implantable, ingestible, and environmental sensors. Some DHTs may support drug and biologic development and review.

Advances in technology have enabled DHTs to support traditional site-based clinical trials and allow for decentralized clinical trials (DCTs) in which some or all activity occurs remotely. DHT software can also be used with a prescription drug.

Advantages of using DHTs include maintenance of blinding or masking, increased trial recruitment, longer participation time, increased subject diversity, use in subjects who are unable to report experiences due to age or cognitive impairment, and ability to continue trials during a pandemic. Potential disadvantages of DHTs include determining clinical significance of the measurements and privacy or confidentiality concerns.

This FDA guidance details considerations when using DHTs for clinical trials. This includes programs to support DHT-related activities internally within the FDA and to engage industry in developing and using DHTs. Internal FDA programs include a steering committee, technical training, consistency of evaluations, statistical analysis considerations, and information technology capabilities. External FDA programs include engagement activities with stakeholders, such as public meetings, demonstrations, and publishing guidance on using DHTs to support drug and biologic development.

DHTs and DHT-derived data may promote more efficient drug and biologic development. The Framework for the Use of Digital Health Technologies in Drug and Biological Product Development outlines how the FDA plans to implement DHT.

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