carelon Rx

Drug and biologic pipeline update Q2 2023

Q2 2023

1051548MUEENCRX 03/23

CarelonRx's quarterly Drug and biologic pipeline update

Our Q2 2023 edition provides details on three agents with the potential to reach the market this year: lotilaner for Demodex blepharitis, obeticholic acid for nonalcoholic steatohepatitis (NASH), and nedosiran for primary hyperoxaluria. Other select drugs and biologics in the pipeline, including gene therapies and biosimilars, are highlighted. Also profiled is a summary of Food and Drug Administration (FDA) 2022 approvals, the respiratory syncytial virus (RSV) therapy pipeline, and an update on beta-amyloid agents for Alzheimer's disease.

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

3 Top emerging new therapies

7 Other significant product approvals

10 Humira® biosimilar pipeline update

12 Gene therapies in the pipeline

15 Analysis: 2022 year in review for new drug approvals

16 Market trends

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 April 14, 2023.

Top emerging new therapies

Lotilaner

Condition:
Blepharitis is an eye disease characterized by inflammation, redness, and irritation. Demodex blepharitis is caused by an infestation of Demodex mites around hair follicles or sebaceous glands at the edge of the eyelids. It accounts for greater than two-thirds of all blepharitis cases, with recent estimates of 25 million people in the U.S. being affected.

Role in treatment:
There are currently no FDA-approved therapies for Demodex blepharitis. Management consists of off-label use of tea tree oil and eyelid wipes, neither of which have been proven effective.

Efficacy:
The FDA submission was supported by results from the phase 2 SATURN-1 and SATURN-2 trials. Both met the primary outcome of collarette cure at Day 43.[1] Collarettes contain mite waste products and eggs and are seen at the base of the upper eyelashes. They signal mite infestation.[2] Secondary outcomes of mite eradication and cure based on a composite score (collarette score and redness cure) were also met.[1]

Safety:
Adverse events in clinical trials were mild or moderate. The most common adverse event was instillation site pain, burning, or stinging.[1]

Financial impact:
It is unclear how common Demodex blepharitis may be because it is thought to be underdiagnosed. Future financial impact of lotilaner will depend on the cost and whether screening for Demodex blepharitis will increase if an FDA-approved treatment option is available.

CarelonRx view:
Lotilaner would be the first FDA-approved treatment for Demodex blepharitis. Current use of off-label therapies has not been shown to be effective. Lotilaner is also being studied in Meibomian gland disease in people with Demodex mites.

Product:
Lotilaner

Indication:
Demodex blepharitis

Estimated FDA approval:
August 2023

Therapeutic class:
Gamma-aminobutyric acid chloride (GABA-Cl) channel inhibitor

Route of administration:
Ophthalmic

FDA designations:
Not applicable

Manufacturer:
Tarsus Pharmaceuticals

Obeticholic acid

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. The 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. behind hepatitis C.[3]

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 comorbid conditions, including weight loss, diet, and exercise.[3] If approved, obeticholic acid (OCA) would be the first agent FDA-approved for the treatment of NASH. OCA 5 mg and 10 mg doses are FDA-approved under the brand name Ocaliva® for the treatment of adults with primary biliary cholangitis (PBC), a different liver disease.

Efficacy:
Over 2,400 adults with biopsy-proven NASH and fibrosis stages 2 or 3 were randomized to treatment with placebo, OCA 10 mg, or OCA 25 mg once daily in the pivotal REGENERATE trial. In an interim 18-month analysis including 931 adults, only the higher OCA dose met statistical significance for only one of the two primary efficacy measures compared to the placebo. No significant difference was found between groups in the percentage of people with the resolution of NASH with no worsening of liver fibrosis. Statistically, significantly more people receiving OCA 25 mg did experience at least one stage of fibrosis improvement with no worsening of NASH compared to the placebo, 22% versus 10%, respectively. We await the end-of-study analysis, which will help evaluate OCA's potential effect on liver-related clinical outcomes and mortality. In a separate phase 3 trial, OCA is being studied in people with compensated cirrhosis due to NASH.

Safety:
The most common adverse event, and the most frequent reason for study discontinuation, was itching, which occurred in 55% of people taking OCA 25 mg, 33% taking OCA 10 mg, and 24% taking placebo. Serious biliary adverse events occurred in more people taking OCA 25 mg compared to other groups, with an incidence of less than 3%. The OCA 25 mg group also had a higher rate of hepatic safety events. Hepatic safety events are of special interest with OCA for NASH because hepatic decompensation and liver failure have been reported in people taking Ocaliva for PBC. These events with Ocaliva resulted in the addition of a boxed warning due to the risk of liver failure. It is unclear if OCA for NASH will carry a similar boxed warning.

Product:
Obeticholic acid

Indication:
Fibrosis due to nonalcoholic steatohepatitis (NASH)

Estimated FDA approval:
June 2023

Therapeutic class:
Farnesoid X receptor (FXR) agonist

Route of administration:
Oral

FDA designations:
Breakthrough Therapy

Manufacturer:
Intercept Pharmaceuticals

Obeticholic acid

Continued

Financial impact:
While the wholesale acquisition cost of Ocaliva is approximately $97,000 annually per person treated for PBC, the price for OCA for the treatment of fibrosis due to NASH remains unknown.[4] Intercept filed a separate new drug application (NDA) for OCA for its NASH indication, meaning that, if approved, OCA for NASH will likely have a different brand name and price. Analysts anticipate that the entire group of NASH therapies in development (obeticholic acid and others) could grow to more than $4 billion in sales by the end of 2030.[5]

CarelonRx view:
In 2020, Intercept failed its first attempt to receive approval for OCA for the treatment of fibrosis due to NASH. In its rejection, the FDA noted the benefits of treatment using the surrogate endpoint, improvement in fibrosis, did not outweigh the risks and, as a result, did not support accelerated approval. However, Intercept refiled its NDA, again seeking accelerated approval using the endpoint improvement in fibrosis. Since being rejected, Intercept completed a new interim analysis using a consensus panel approach to reading histology results, compared to individual reviewers used the first time. Interestingly, results from these interim analyses were similar. An FDA advisory committee will be convened in May to discuss OCA and its potential role in NASH.

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. Competition for OCA could come as early as 2024 with several other pipeline agents in development for NASH.

Product:
Obeticholic acid

Indication:
Fibrosis due to nonalcoholic steatohepatitis (NASH)

Estimated FDA approval:
June 2023

Therapeutic class:
Farnesoid X receptor (FXR) agonist

Route of administration:
Oral

FDA designations:
Breakthrough Therapy

Manufacturer:
Intercept Pharmaceuticals

Nedosiran

Condition:
Primary hyperoxaluria is a group of rare genetic disorders characterized by the accumulation of oxalate in the kidneys due to an enzyme deficiency. There are three main types, 1, 2, and 3, depending on which enzyme is lacking. Oxalate binds with calcium in the kidneys to form calcium oxalate which is the main component of urinary and kidney stones. Chronic stone formation and accumulation of calcium oxalate in kidney tissue may lead to kidney disease or failure. Eventually, oxalate may begin to accumulate in other organs.[6]

Type 1 is the most severe and most common type of hyperoxaluria, affecting less than 5,000 people in the United States. Types 2 and 3 each affect less than 1,000 people in the U.S.

Role in treatment:
There is currently one FDA-approved product for hyperoxaluria type 1 called Oxlumo® (lumasiran subcutaneous injection). There are no approved products for types 2 and 3. Therefore, nedosiran may be an option for a broader range of people diagnosed with hyperoxaluria.

Efficacy:
The FDA submission was supported by results from the PHYOX clinical trial program. Nedosiran showed statistically significant sustained reduction in the primary endpoint of percent change from baseline in 24-hour urinary oxalate excretion assessed from day 90 to day 180 in one trial that included type 1 and 2 subjects. An extension trial included all types and demonstrated normalization or near-normalization of urinary oxalate by day 180.

Safety:
Nedosiran was generally well tolerated in clinical trials. The most common adverse events were mild injection site reactions that resolved on their own.

Financial impact:
Nedosiran, if approved, will be indicated for use in all types of primary hyperoxaluria. It may be an option for people who do not respond to Oxlumo in type 1, and it will be the only FDA-approved option in types 2 and 3. Revenues for nedosiran are estimated to reach $171 million in 2025.[7]

CarelonRx view:
The available data for nedosiran suggests long-term potential for slowing disease progression. An ongoing trial is evaluating kidney function and stone formation. The anticipated initial approval for nedosiran would be in people age 6 years and older. Additional development is ongoing in people under age 5 years and in those with severe renal impairment with or without dialysis.

Product:
Nedosiran

Indication:
Primary hyperoxaluria types 1, 2, and 3

Estimated FDA approval:
September 2023

Therapeutic class:
Lactate dehydrogenase A (LDHA) enzyme inhibitor

Route of administration:
Subcutaneous injection

FDA designations:
Breakthrough; Orphan

Manufacturer:
Novo Nordisk

Other significant product approvals

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

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Momelotinib Sierra Oncology	Myelofibrosis/oral	**Addition to class:** targets similar population to Vonjo®	6/16/2023	
Obeticholic acid Intercept Pharmaceuticals	Non-alcoholic steatohepatitis/oral	**First in class:** will be first FDA-approved treatment for this indication	6/22/2023	
NovaTears (perfluoroh-exyloctane) Bausch Health	Dry eyes/ ophthalmic	**First in class:** preservative-free eye lubricant and tear film stabilizer	6/28/2023	
Ritlecitinib Pfizer	Alopecia/oral	**Addition to class:** will compete with Olumiant®; also seeking approval in adolescents	6/30/2023	
Zilucoplan UCB	Myasthenia gravis, anti-acetylcholine receptor antibody positive/SC	**First in class:** will complete with Soliris® and Vyvgart™; self-administration	Between August and September 2023	
Rozanolixizumab UCB	Myasthenia gravis, including muscle-specific tyrosine kinase antibody positive/SC	**First in class:** will complete with Soliris® and Vyvgart™; includes MuSK antibody positive disease	Between August and September 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

MuSK: muscle-specific tyrosine kinase

PPD: postpartum depression

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)

Zuranolone Sage Therapeutics	Major depressive disorder/postpartum depression (PPD)/oral	**Addition to class:** rapid onset of action; first oral option for PPD	8/5/2023	
Zimura® (avacincaptad pegol) Iveric Bio	Geographic atrophy secondary to age-related macular degeneration/ intravitreal	**Addition to class:** will be second FDA-approved product for this indication	8/5/2023	
Pozelimab Regeneron	CHAPLE disease/IV; SC	**Addition to class:** will be first FDA-approved treatment for this indication	8/19/2023	
Lotilaner Tarsus Pharmaceuticals	Demodex blepharitis/ ophthalmic	**Addition to class:** will be first FDA-approved treatment for this indication	8/20/2023	
Nedosiran Novo Nordisk	Primary hyperoxaluria/SC	**First in class:** ability to treat a broader range of disease	8/25/2023	
Concizumab Novo Nordisk	Hemophilia A and B/SC	**First in class:** once-daily prophylactic treatment in hemophilia A and B with inhibitors	September 2023	

Other significant product approvals (continued)

Lebrikizumab Eli Lilly	Atopic dermatitis/SC	**Addition to class:** same mechanism of action as Dupixent® and Adbry™	September 2023	
Nirsevimab AstraZeneca	Respiratory syncytial virus treatment/IM	**Addition to class:** use in broad population of infants for prevention of RSV lower respiratory tract disease	September 2023	
Vamorolone Santhera Pharmaceuticals	Duchenne muscular dystrophy/oral	**Addition to class:** will compete with Emflaza® and prednisone	10/26/2023	
Reproxalap Aldeyra Therapeutics	Dry eyes/ophthalmic	**First in class:** new mechanism of action for dry eye	11/23/2023	
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®	Second half of 2023	

*As of April 11, 2023

Humira (adalimumab) was approved in 2002 by the FDA and has become a top selling biologic in the United States. AbbVie reported $18.619 million in net revenues in the U.S. for 2022.

There are currently eight FDA-approved biosimilars to Humira, and Amjevita™ is the only biosimilar that has launched. Of the eight approved biosimilars, currently only Cyltezo® has received interchangeability status. However, there are several other FDA-approved biosimilars that are seeking interchangeability. Cyltezo was granted interchangeability status in October 2021, making it the first non-insulin biosimilar to be interchangeable with its reference product.

There are some differences between Humira and the FDA-approved biosimilars regarding the FDA-approved indications. Only Humira is approved for Hidradenitis suppurativa (HS), uveitis, and pediatric ulcerative colitis.

Humira biosimilar pipeline update

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

Type of benefit	Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval*	Launched
Pharmacy	Humira 50 mg/mL	AbbVie	Abrilada™*	Pfizer	11/15/19 Seeking interchangeability	No
Pharmacy	Humira 50 mg/mL	AbbVie	Amjevita™*	Amgen	9/23/16 Seeking interchangeability	Yes
Pharmacy	Humira 50 mg/mL	AbbVie	Cyltezo®*	Boehringer Ingelheim P	8/25/17 Interchangeability granted 10/15/21	No
Pharmacy	Humira 50 mg/mL	AbbVie	Hadlima™	Samsung Bioepis Organon	7/23/19	No
Pharmacy	Humira 100 mg/mL	AbbVie	Hadlima HC™*	Samsung Bioepis Organon	8/15/22 Seeking interchangeability	No
Pharmacy	Humira 50 mg/mL	AbbVie	Hulio®*	Fujifilm, Mylan	7/6/20	No
Pharmacy	Humira 50 mg/mL	AbbVie	Hyrimoz™	Sandoz	10/30/18	No

Biosimilar products awaiting launch (continued)

Type of benefit	Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval †	Launched
Pharmacy	Humira 100 mg/mL	AbbVie	Hyrimoz HCF™*	Sandoz	3/20/23	No
Pharmacy	Humira 50 mg/mL	AbbVie	Yusimry™*	Coherus	12/17/21	No
Pharmacy	Humira 50 mg/mL	AbbVie	Idacio®*	Fresenius Kabi	12/13/22	No
Pharmacy	Humira 100 mg/mL	AbbVie	AVT02*	Alvotech	Pending	No
Pharmacy	Humira 100 mg/mL	AbbVie	Yuflyma™* (CT-P17)	Celltrion	Pending	No

*Manufacturer states this is a citrate-free formulation.

† As of April 11, 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 three recent approvals in the past year: Hemgenix® in November, Skysona® in September, and Zynteglo® in August. All FDA-approved gene therapies currently use viral-based therapy, where the infectious parts of viruses are replaced with a gene that can be used to help treat or modify a disease.

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

Gene therapy/ Gene-based therapy	Indication/route**	Expected use	Place in therapy**	Estimated approval date
Beremagene geperpavec (B-VEC) Krystal Biotech	Epidermolysis bullosa (EB)/topical gel	Once weekly application to wound(s)	First localized gene-based wound therapeutic for people age 1 year or older with EB	5/17/2023
Delandistrogene moxeparvovec (SRP-9001) Sarepta and Roche	Duchenne muscular dystrophy/IV	One-time dose	First gene therapy for this indication; will compete with Exondys 51, Vyondys 53, and Emflaza®	5/29/2023
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®	6/30/2023 (three-month delay)
Exagamglogene autotemcel (exa-cel; formerly CTX001) Vertex and CRISPR Therapeutics	Beta-thalassemia anemia/IV Sickle cell anemia/IV	One-time dose; potentially curative	Second gene therapy for this indication; will compete with Zynteglo First gene therapy for this indication; will compete with HCT and chronic RBC transfusions	2023/2024

** 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 April 11, 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
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	2023 to 2024 (plans to file 2023)
OTL-200 Orchard Therapeutics	Metachromatic leukodystrophy/IV	One-time dose; potentially curative	First gene therapy for this indication; will compete with HCT	2023 to 2024 (plans to file early 2023)
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	2023 to 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	2023 to 2024 (plans to file 1H23)
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	2023+
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	2023+
ABO-101 Abeona Therapeutics	Mucopolysaccharidosis IIIA (Sanfilippo Type B)/IV	One-time dose; potentially curative	First gene therapy for this indication; will compete with HCT	2023+

* As of April 11, 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
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	2023+
OTL-201 Orchard	Mucopolysaccharidosis IIIA (Sanfilippo Type A)/IV	One-time dose; potentially curative	Competing to be first gene therapy for this indication; will compete with HCT	2023+
Engensis (donaperminogene seltoplasmid) Helixmith	Diabetic foot ulcers/ intramuscular Diabetic peripheral neuropathy/intramuscular	Multiple injections	First gene-based therapeutic for these indications	2023+
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	2023+
TAVO (tavokinogene telseplasmid) OncoSec Medical	Advanced melanoma/ intratumoral	Administered on days 1, 5, and 8 every six weeks	First gene-based therapeutic for this indication; used in combination with Keytruda®	2023+ (potential to file with accelerated pathway)
RP-L102 Rocket Pharmaceuticals	Fanconi anemia (FA)/IV	One-time dose; potentially curative	First gene therapy for this indication	2024 (plans to file 4Q23)

* As of April 11, 2023

Analysis: 2022 year in review for novel drug approvals

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

Approval highlights from the 2022 report (2021 numbers in parentheses) include: [8,9]

- **37** (50) therapies approved in total
- **20** (27) first in class therapies (unique mechanisms of action)
- **20** (26) therapies approved for orphan diseases (affect < 200,000 people in U.S.)
- **12** (18) therapies approved with Fast Track status
- **13** (14) therapies approved as Breakthrough Therapies
- **21** (34) therapies approved with Priority Review status (six-month review versus 10-month for standard review)
- **6** (14) therapies approved under Accelerated Approval (confirmatory trials must be conducted)
- **24** (37) of the **37** (50) approvals used one or more expedited programs (Fast Track Designation, Breakthrough Therapy Designation, Priority Review, and/or Accelerated Approval)
- **36** (49) of the **37** (50) approvals came on or before the Prescription Drug User Fee Act (PDUFA) goal date

Market Trends

Respiratory syncytial virus (RSV) pipeline

Respiratory syncytial virus (RSV) is a common infection that causes cold-like symptoms, such as runny nose, fever, and coughing. Most people experience mild symptoms which resolve in a few weeks without any treatment. For people at higher risk such as older adults with chronic medical conditions and infants, severe RSV infection can cause pneumonia requiring hospitalization and, for some, lead to death.

RSV infections generally follow a seasonal pattern with circulation starting in the fall and peaking in the winter. On average, in the United States, annual RSV infections require hospitalization for approximately 69,000 people younger than 5 years of age, and 110,000 older adults at higher risk of severe disease. Importantly, about 8,000 of hospitalized older adults die from RSV each year.

There are no FDA-approved RSV vaccines. As outlined in the table, there are a handful of RSV vaccines in late-stage development, with two potential candidates competing for FDA approval in May. Each of these vaccines are administered as a single intramuscular (IM) injection. In late February and early March, the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) reviewed the Pfizer and GlaxoSmithKline (GSK) RSV vaccines for use in older adults. While decisions were not all unanimous, both Pfizer and GSK vaccines received an overall vote in favor of potential FDA approval for the older adult population based on the efficacy and safety data presented to the committee. Questions remain, including vaccine safety and the duration of vaccine effectiveness after a single dose is administered.

Infants under 6 months of age, including premature infants, represent another population vulnerable to RSV. There were 3.7 million births in the United States in 2019. Different approaches are being explored to help protect infants from RSV. Unlike vaccines in development which rely on active immunity, requiring a person's immune system to build its own protection after vaccination, monoclonal antibodies can provide passive immunity, or immediate protection from RSV. Active immunity takes several weeks to develop after vaccination and is typically long-lasting, while passive immunity is transient. Pfizer is evaluating active immunization of pregnant women and AstraZeneca is evaluating passive immunity through the use of monoclonal antibodies.

Currently, Synagis® is the only FDA-approved monoclonal antibody indicated to prevent serious disease due to RSV. Synagis is only indicated for a subgroup of high-risk children younger than age 2 years and requires monthly IM injections administered during the RSV season to provide passive immunity.

AstraZeneca is developing a longer-acting RSV monoclonal antibody, nirsevimab, administered as a single-dose IM injection. Nirsevimab is seeking FDA approval for use in all infants to prevent serious disease due to RSV during their first RSV season, and for select higher risk one-year-olds during their second RSV season.

RSV prevention products in late-stage development

Vaccine/biologic Manufacturer	Indication**	FDA status**	Estimated approval date
RSV vaccines			
Arexvy (GSK3844766A) GlaxoSmithKline	Prevention of lower respiratory tract disease (LRTD) caused by RSV in adults age 60 years and older	BLA	5/3/2023
	RSV prevention in adults age 50-59 years with underlying comorbidities	Phase 3	2024
Abrysvo (PF-06928316) Pfizer	Prevention of acute respiratory disease and LRTD caused by RSV in adults age 60 years and older	BLA	5/31/2023
	Prevention of LRTD and severe lower respiratory tract disease caused by RSV in infants from birth up to six months of age by active immunization of pregnant people	BLA	August 2023
mRNA-1345 Moderna	Prevention of RSV-associated LRTD in adults age 60 years or older	Phase 3	2024
MVA-BN RSV Bavarian Nordic	Prevention of LRTD caused by RSV in adults age 60 years and older	Phase 3	2024
RSV monoclonal antibody			
Nirsevimab AstraZeneca	Prevention of RSV lower respiratory tract disease in newborns and infants entering or during their first RSV season, and for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season	BLA	Third quarter of 2023

** Key

BLA: biologics license application

RSV: respiratory syncytial virus

LRTD: lower respiratory tract disease

Update: Anti-beta-amyloid antibodies for early Alzheimer's disease

Aduhelm® (aducanumab intravenous infusion) was approved in June 2021 for the treatment of early Alzheimer's disease with the presence of beta-amyloid plaques. It was approved under the FDA accelerated approval pathway using results of surrogate endpoints measuring beta-amyloid plaque reduction in the brain. Surrogate endpoints are markers such as laboratory measurements or radiographic images that may predict clinical benefit. There were reports of amyloid-related imaging abnormalities (ARIA), including cerebral edema and microhemorrhages that may lead to death.[10]

In January 2023, a second anti-beta-amyloid antibody was approved for early Alzheimer's disease. Like Aduhelm, Leqembi™ (lecanemab intravenous infusion) was granted accelerated approval based on plaque measurements in the brain which may predict clinical improvement. Also like Aduhelm, there is a risk of ARIA. Shortly after accelerated approval was granted, a request for traditional FDA approval was submitted by the manufacturer based on phase 3 clinical trial data in which subjects treated with Leqembi demonstrated a numerical difference in slowing cognitive decline compared to placebo. This was measured using the clinical dementia rating sum of boxes (CDR-SB), a direct measure of clinical benefit. The difference in cognitive decline measured by CDR-SB was 0.45.[11] A difference of one point is considered a minimum clinically meaningful change.[12] Safety concerns, including deaths, were reported in the phase 3 extension data. The FDA will make a final decision by July 6, 2023, following a planned Advisory Committee meeting that remains unscheduled.

The FDA decision on Leqembi is being closely watched. Currently, both Aduhelm and Leqembi are only covered by the Centers for Medicare and Medicaid Services (CMS) in the setting of a clinical trial conducted under an investigational new drug application as outlined in the CMS Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. However, if Leqembi gains full approval, CMS may broaden coverage.

There are many other beta-amyloid antibodies in the pipeline for Alzheimer's disease. Donanemab is the only one near potential approval. The FDA denied accelerated approval in January 2023, but the manufacturer is expected to submit data for a traditional approval by mid-2023.

Finding treatments for Alzheimer's disease that are successful in slowing clinical decline is important. In the United States, an estimated 5.8 million people have dementia due to Alzheimer's disease. This number is expected to grow to 13.8 million by 2050.[13]

Analysts predict that major market sales for Leqembi and donanemab will grow to almost $28 billion in 2031.[5] Adoption of these agents depends on many factors, including future confirmatory trials focused on clinically significant endpoints, additional information on severity and frequency of safety events, and Medicare coverage determinations.

References

1 GlobalNewsWire. *Tarsus Submits New Drug Application to the FDA for TP-03 for the Treatment of Demodex Blepharitis* (accessed December 1, 2022): globalnewswire.com.

2 Yahoo Finance. *Tarsus Pharmaceuticals' TP-03 Hits Primary, Secondary Endpoints In Demodex Blepharitis Study* (accessed December 12, 2022): finance.yahoo.com.

3 Cusi K, Isaacs S, Barb D, et al. *American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases* (AASLD). Endocr Pract 2022 May;28(5):528-562. doi: 10.1016/j.eprac.2022.03.010.

4 IBM Micromedex® DRUGDEX® (accessed February 2023, registration required): micromedexsolutions.com.

5 Clarivate (accessed March 2023, registration required): Clarivate.com.

6 National Organization for Rare Disorders (NORD). *Primary Hyperoxaluria* (accessed February 3, 2023): rarediseases.org.

7 Pharmaceutical Technology. *Dicerna's best hope for nedosiran use likely in non-responders to Alnylam's Oxlumo in primary hyperoxaluria type 1* (accessed February 8, 2023): pharmacology-technology.com.

8 Center for Drug Evaluation and Research. *New Drug Therapy Approvals 2021* (Accessed February 2023): fda.gov.

9 Center for Drug Evaluation and Research. *New Drug Therapy Approvals 2022* (Accessed February 2023): fda.gov.

10 MedPage Today. *Alzheimer's Drugs Race to FDA* (accessed March 8, 2023): medpagetoday.com.

11 Van Dyck CH, Swanson CJ, Aisen P, et al. *Lecanemab in Early Alzheimer's Disease* (accessed March 8, 2023): nejm.org.

12 Andrews JS, Desai U, Kirson NY, et al. *Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials* (accessed March 8, 2023): alz-journals.onlinelibrary.wiley.com.

13 Hampel, H., Hardy, J., Blennow, K. et al. *The Amyloid Pathway in Alzheimer's Disease*. (accessed March 8, 2023): nature.com.

©2023 CarelonRx, Inc. All Rights Reserved. The CarelonRx name and CarelonRx logo are registered trademarks. No portion of this publication may be reproduced in any format, print, electronic, or otherwise, without the express written permission of CarelonRx.

Information contained within this document is compiled from various sources and is provided for informational purposes only. 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.