carelon Rx

Drug and biologic pipeline update Q3 2024

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CarelonRx's quarterly Drug and biologic pipeline update

Our Q3 2024 update features three agents of interest with anticipated approvals this year: garadacimab for hereditary angioedema, obecabtagene autoleucel for acute lymphoblastic leukemia (ALL), and eladocagene exuparvovec for aromatic L-amino acid decarboxylase (AADC) deficiency. Other select drugs and biologics in the pipeline, including gene therapies and biosimilars, are also highlighted. An update on the outcomes of Food and Drug Administration (FDA) Accelerated Approvals will be provided. Other topics this quarter include a nonopioid acute pain drug in the late-stage pipeline and recently updated nonalcoholic steatohepatitis (NASH) guidelines, including what is expected in the pipeline following the first FDA approval for this disease earlier this year.

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.

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Top emerging new therapies

Garadacimab

Condition:
Hereditary angioedema (HAE) is a rare genetic condition that affects an estimated 1 in 50,000 individuals. There are three different types of HAE; types I (deficiency of C1 esterase inhibitor (C1-INH)) and II (dysfunction of C1-INH) are the most prevalent. C1-INH helps regulate the plasma bradykinin-forming cascade and the kallikrein-kinin pathway. HAE attacks result from the excessive production of bradykinin that causes edema, affecting the skin, gastrointestinal system, or upper respiratory tract. Individuals may experience swelling and pain that can significantly impact their daily activity, lead to physical changes, and can, in serious cases (e.g., involving swelling of the throat), be fatal.

Role in treatment:
There is no cure for HAE. Management focuses on trigger avoidance, treatment of acute attacks, and prevention of further attacks. Common triggers include dental and medical procedures, stress, menstruation, pregnancy, and infection. All individuals with HAE should have access to on-demand therapy for acute attacks. First-line therapy options include C1-INH concentrates Berinert® and Ruconest®, a bradykinin antagonist icatibant, and a kallikrein inhibitor Kalbitor.

Individuals who experience frequent or severe HAE attacks may be considered for long-term prophylaxis. First-line options include C1-INH concentrates (intravenous Cinryze® and subcutaneous Haegarda®) and kallikrein inhibitors (subcutaneous Takhzyro® and oral Orladeyo®). Cinryze and Haegarda are administered twice weekly. Takhzyro is administered every 2 weeks; Orladeyo requires daily administration.

Garadacimab is a monoclonal antibody with a unique mechanism of action that targets activated FXIIa, a protein that initiates the kallikrein-kinin cascade. It is administered via subcutaneous injection once monthly and will be available as an autoinjector.

Efficacy:
The New Drug Application (NDA) submitted to the FDA was supported by data from the VANGARD phase 3 clinical trial. Individuals receiving garadacimab experienced a reduction in monthly HAE attack rate and a reduction in the number of HAE attacks requiring on-demand rescue medication compared with individuals receiving placebo.

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

Financial impact:
If approved, garadacimab will be a first-in-class subcutaneous injection for long-term prophylaxis of HAE. Due to its once-monthly dosing, garadacimab could be priced at a premium compared to available products. Garadacimab is also being studied for use in idiopathic pulmonary fibrosis.

CarelonRx view:
The availability of a new drug class for preventing HAE attacks is promising, but clinical data is limited. Direct comparisons to current first-line prophylactic therapies (with which it would compete) are not available, but indirect comparison suggests similar safety and efficacy. Garadacimab's once-monthly dosing may provide an advantage over Haegarda and Takhzyro, which require more frequent administration.

Product:
Garadacimab

Indication:
Hereditary angioedema (HAE) prophylaxis

Estimated FDA approval:
Fourth quarter 2024

Therapeutic class:
Factor XIIa-inhibitory monoclonal antibody (anti-FXIIa mAb)

Route of administration:
Subcutaneous injection

FDA designations:
Fast track; Orphan drug

Manufacturer:
CSL Behring

Obecabtagene autoleucel

Condition:

Acute lymphoblastic leukemia (ALL), also known as acute lymphocytic leukemia, is a kind of cancer that occurs when immature lymphocytes, a type of white blood cell formed in the bone marrow, begin to grow out of control and overtake the blood. Without treatment, ALL can spread to the lymph nodes, spleen, liver, brain and spinal cord, and testicles in males. While there are two types of lymphocytes, B cells are responsible for making antibodies which attach to germs and initiate the immune response towards attacking them. Symptoms of ALL are typically due to decreased normal blood cells and include fatigue, weakness, dizziness, shortness of breath, pale skin, frequent or untreatable infections, bleeding and bruising, unexplained weight loss, fever, night sweats, and loss of appetite.[1]

Risk factors for developing ALL include radiation or chemical exposure, history of specific viral infections, certain genetic syndromes, and being male or white. The risk is highest in children younger than 5 years of age but then declines until age 50 when it rises again. The American Cancer Society estimates there will be about 6,550 new cases of ALL diagnosed in the United States in 2024 and about 1,330 deaths from ALL. While only approximately 4 of every 10 cases of ALL are in adults, death is more likely to occur in this population.[2]

ALL is diagnosed from a combination of physical exam, blood tests and bone marrow biopsy. Additional tests are needed to assess the extent and spread of the disease.[1]

Role in treatment:

Treatment for ALL generally consists of three phases of chemotherapy. The induction and consolidation phases are very intense, while the maintenance phase is less intense but usually lasts for about two years. The goal of the induction phase is to get the cancer into remission, which occurs when bone marrow biopsy and blood tests show eradication of all detectable leukemia cells and other blood counts return to normal. Consolidation chemotherapy is necessary to eradicate any undetectable leukemia cells — in specific cases, hematopoietic cell transplantation (HCT) from a donor may also be considered. The latter is effective but comes with high treatment-related toxicities, thus the benefits and risks must be weighed. Maintenance therapy is continued only for those who received consolidation chemo.

While approximately 80% to 90% of individuals achieve complete remission, about half of those will relapse. For disease refractory to initial treatment, other chemotherapies may be tried, immunotherapy with monoclonal antibodies or chimeric antigen receptor (CAR) T-cell therapy may be used, or HCT from a donor may be considered if at least a partial response is achieved with initial treatment. Treatment of relapsed disease depends on the duration of remission, with longer durations having the possibility of repeating the original or similar treatment. Shorter durations of remission will require moving on to the subsequent lines outlined for refractory disease.[3]

Obecabtagene autoleucel (obe-cel) is a CAR T-cell therapy for one-time intravenous administration. It is designed to minimize the adverse effects seen with other CAR T-cell therapies, including Tecartus® (brexucabtagene autoleucel, injection; Kite Pharma), the only CAR T-cell therapy approved by the FDA for ALL. The fast target binding off-rate, not seen in other therapies, decreases toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) as well as improves durability.

Product:
Obecabtagene autoleucel

Indication:
B-cell acute lymphoblastic leukemia in adults, relapsed or refractory

Estimated FDA approval:
November 2024

Therapeutic class:
CD19 chimeric antigen receptor (CAR) T cell therapy

Route of administration:
Intravenous infusion

FDA designations:
Orphan Drug; Regenerative Medicine Advanced Therapy

Manufacturer:
Autolus Therapeutics

Obecabtagene autoleucel

Efficacy:
The biologics license application (BLA) for obe-cel was supported by findings from the phase 2 FELIX trial, which showed that 78% of adults with a median two prior lines of therapy (range 1-5) who received obe-cel had an objective response (complete response or complete response with incomplete blood count recovery). At a median follow up of 21 months, 40% of individuals were still in ongoing remission without HCT or other treatment. The median event free and overall survivals were 11.9 months and 23.8 months, respectively.

Safety:
Any grade CRS or ICANS occurred in 63% and 23% respectively, with grade 3 or higher reported in 3% and 8%. Grade 3 or higher febrile neutropenia and anemia were the other common adverse events.

Financial impact:
If approved, obe-cel provides another option for the treatment of relapsed or refractory ALL. This is a relatively rare cancer with expanded future use in pediatrics. The anticipated cost of obe-cel is unknown but expected to be high, similar to what has been seen with other CAR T-cell therapies. Peak year sales are estimated at up to $50 million for obe-cell in ALL.[4]

CarelonRx view:
As relapse occurs in approximately half of individuals who achieve remission in ALL, an additional treatment option is encouraging. While there are no direct studies comparing obe-cel to other therapy, decreased toxicity may make this a more beneficial choice given the increased risk of mortality, burden, and cost associated with CRS and ICANS.

Product:
Obecabtagene autoleucel

Indication:
B-cell acute lymphoblastic leukemia in adults, relapsed or refractory

Estimated FDA approval:
November 2024

Therapeutic class:
CD19 chimeric antigen receptor (CAR) T cell therapy

Route of administration:
Intravenous infusion

FDA designations:
Orphan Drug; Regenerative Medicine Advanced Therapy

Manufacturer:
Autolus Therapeutics

Eladocagene exuparvovec

Condition:
Aromatic L-amino acid decarboxylase (AADC) deficiency is a fatal disorder caused by a mutation in the DDC gene. The AADC enzyme is responsible for making several key neurotransmitters, including dopamine and serotonin. Without these neurotransmitters people with AADC deficiency present with a myriad of complex symptoms, such as motor dysfunction and behavioral concerns, usually starting in infancy. There are fewer than 1,000 people living with AADC deficiency in the U.S.

Role in treatment:
Current standard of care for people with AADC deficiency includes supportive care and pharmaceutical treatments directed at increasing dopamine and serotonin levels. While there is no cure for AADC, eladocagene exuparvovec gene therapy was approved in the European Union (EU) under the brand name Upstaza™ for the treatment of individuals aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of AADC deficiency with a severe phenotype (i.e., individuals who cannot sit, stand, or walk). If eladocagene receives approval in the U.S., it would become the first disease-modifying treatment for AADC deficiency.

Efficacy:
Three early-stage trials evaluating 28 children with severe AADC deficiency found 70% were able to control head movement and 65% were able to sit unassisted two years after a single treatment with eladocagene administered as an intraputaminal infusion.[5] Historical data suggest untreated children would not achieve these same milestones. With up to 5 years of sustained efficacy follow-up data available for a handful of treated individuals, eladocagene has demonstrated the potential for durability after a single treatment.

Safety:
The most common adverse reaction after treatment with eladocagene is uncontrollable movements, or dyskinesia.[5]

Financial impact:
While the price for eladocagene is unknown, it will likely garner a similar price as other gene therapies for rare diseases — between $3 and $4 million per person for a one-time treatment.[6]

CarelonRx view:
There are currently no disease-modifying therapies for AADC deficiency, which is a fatal diagnosis. If approved, eladocagene would introduce a treatment option for children with severe disease, with the potential to improve symptoms of the condition associated with dopamine deficiency, specifically the ability to coordinate movements. Eladocagene is given as a single infusion, administered directly into the putamen, as part of a brain surgery. Administration is performed by a neurosurgeon in a specialized center, using a minimally invasive, stereotactic neurosurgical procedure. It is designed to restore dopamine production but has yet to show the ability to improve serotonin deficiency. Even with 10 years of follow-up data for a subgroup of eladocagene-treated individuals, the question about long-term durability remains.

Product:
Eladocagene exuparvovec

Indication:
Treatment of aromatic L–amino acid decarboxylase (AADC) deficiency

Estimated FDA approval:
November 2024

Therapeutic class:
Gene therapy

Route of administration:
Intraputaminal infusion (i.e., infusion administered through a surgical procedure into the brain)

FDA designations:
Orphan; Priority Review

Manufacturer:
PTC Therapeutics

Other significant product approvals

We expect these products to reach the market in 2024/early 2025:*

Drug or biologic (Manufacturer)	Indication/route**	Place in therapy	Estimated approval date*	Impact on overall drug or medical spend
Tradipitant Vanda	Gastroparesis symptoms/oral	**Addition to class:** would compete with metoclopramide	09/18/2024	
Arimoclomol Orphazyme	Niemann-Pick Disease type C/oral	**First in class:** competing to be first FDA-approved treatment for this indication	09/21/2024	
Acetylleucine IntraBio	Niemann-Pick Disease type C/oral	**First in class:** competing to be first FDA-approved treatment for this indication	09/24/2024	
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 prophylactic treatment	Between October and November 2024	
Lazertinib Genosco	Non-small cell lung cancer, locally advanced or metastatic with epidermal growth factor receptor (EGFR) exon 19 deletions or L858R substitution mutations/oral	**Addition to class:** would be used in combination with Rybrevant®	10/21/2024	
Marstacimab Pfizer	Hemophilia A and B/SC	**First in class:** would compete with Hemlibra®	Fourth quarter 2024	

*As of July 15, 2024

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

** Key

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
Eladocagene exuparvovec PTC Therapeutics	Aromatic L-amino acid decarboxylase (AADC) deficiency/ intracerebral	**First in class:** would be first FDA-approved treatment for this indication	11/13/2024	
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	
Acoramidis BridgeBio	Transthyretin amyloid cardiomyopathy/ oral	**Addition to class:** would compete with Vyndamax®/Vyndaqel®	11/29/2024	
Zanidatamab Zymeworks	Biliary tract cancer/ IV	**Addition to class:** first targeted therapy for overexpression of human epidermal growth factor receptor 2 (HER2) in biliary tract cancer	12/02/2024	
Glepaglutide Zealand Pharma	Short bowel syndrome/SC	**Addition to class:** would compete with Gattex®	12/22/2024	
Revumenib Syndax Pharmaceuticals	Acute myelogenous leukemia (AML)/oral	**First in class:** effective against menin-mixed lineage leukemia (MLL)-rearranged and nucleophosmin (NPM) 1-mutant leukemia	12/26/2024	
Ensartinib Xcovery	Non-small cell lung cancer (NSCLC), first-line treatment/ oral	**Addition to class:** for anaplastic lymphoma kinase (ALK)-positive NSCLC; will compete with Xalkori®, Alecensa®, Alunbrig®, and Lorbrena®	12/28/2024	

*As of July 15, 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
Vicagrel Jiangsu Vcare PharmaTech	Thrombotic cardiovascular and cerebrovascular diseases, including acute coronary syndrome, ischemic stroke, and peripheral arterial disease/oral	**Addition to class:** potential for improved safety profile compared with clopidogrel	12/28/2024	
Govorestat Applied Therapeutics	Classic galactosemia/oral	**First in class:** would be first FDA-approved treatment for this indication	12/31/2024	
Suzetrigine Vertex	Acute pain/oral	**First in class:** nonopioid pain medication	01/30/2025	
Etripamil Milestone Pharmaceuticals	Supraventricular tachycardia/intranasal	**Addition to class:** rapid-response therapy that is self-administered	03/28/2025	

*As of July 15, 2024

*As of July 15, 2024

Currently* fifty-three biosimilar products are FDA approved in the United States, including eight approved in 2024: Bkemv™ (eculizumab-aeeb), Hercessi™ (trastuzumab-strf), Jubbonti® and Wyost® (denosumab-bbdz), Opuviz™ (aflibercept-yszy), Selarsdi™ (ustekinumab-aekn), Simlandi® (adalimumab-ryvk), Tyenne® (tocilizumab-aazg), and Yesafili™ (aflibercept-jbvf).

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's 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. The following biosimilar products have been granted interchangeability status, with more seeking interchangeability:

- Opuviz and Yesafili, biosimilars to Eylea® (aflibercept).
- Abrilada™, Cyltezo®, Hyrimoz®, and Simlandi, biosimilars to Humira® (adalimumab).
- Rezvoglar™ and Semglee®, biosimilars to Lantus Solostar® (insulin glargine).
- Byooviz™ and Cimerli™, biosimilars to Lucentis® (ranibizumab).
- Jubbonti and Wyost, biosimilars to Prolia® and Xgeva® (denosumab).
- Wezlana™, a biosimilar to Stelara® (ustekinumab).

Biosimilar pipeline update

Biosimilar products awaiting launch and/or approval*

Brand name	Brand manufactuer	Biosimilar name	Biosimilar manufacturer	FDA approval*
Actemra® IV/SubQ	Genentech; Roche	CT-P47	Celltrion	Pending
Actemra SubQ		Tyenne	Fresenius Kabi	3/5/2024
Avastin®	Genentech; Roche	Avzivi®	Bio-Thera Solutions; Sandoz	4/25/2019
		FKB238	Centus Biotherapeutics; AstraZeneca; Fujifilm	8/30/2016
Enbrel®	Amgen; Immunex	Eticovo™	Samsung Bioepis	4/25/2019
		Erelzi™	Sandoz	8/30/2016
Eylea	Regeneron	Opuviz	Samsung Bioepis; Biogen	5/20/2024
		Yesafili	Momenta; Mylan; Johnson & Johnson (Janssen); Biocon; Viatris	5/20/2024
		CT-P42	Celltrion	Pending
		FYB203	Formycon; Santo Holding; Klinge Pharma	Pending
		ABP 938	Amgen	Pending
Herceptin®	Roche; Genentech	Hercessi	Henlius; Accord; Intas	4/25/2024
Humalog®, Humalog Pen, Humalog U-100 KwikPen	Eli Lilly	GL-LIS	Gan & Lee; Sandoz	Pending

*As of June 21, 2024

Biosimilar products awaiting launch and/or approval* (continued)

Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval*
Humira (100 mg/mL)	AbbVie	Adalimumab AbbVie	AbbVie	11/3/2023
Lantus Solostar	Sanofi	GL-GLA	Gan & Lee; Sandoz	Pending
Neulasta®	Amgen	Lapelga	Apotex; Accord; Intas	Pending
Neupogen®	Amgen	TX01	Tanvex	Pending
		Grastofil	Apotex; Accord; Intas	Pending
Novolog® (10 mL vial), Novolog FlexPen, Novolog FlexTouch, Novolog PenFill	Novo Nordisk	GL-ASP	Gan & Lee; Sandoz	Pending
		AMP-004	Amphastar	Pending
Prolia	Amgen	Jubbonti	Sandoz	3/5/2024
		FKS518	Fresenius Kabi	Pending
		CT-P41	Celltrion	Pending
Soliris®	Alexion; AstraZeneca	Bkemv	Amgen	5/28/2024
		SB12	Samsung Bioepis	Pending
Stelara IV/ SubQ	Johnson & Johnson (Janssen)	Wezlana	Amgen	10/31/2023
		CT-P43	Celltrion	Pending
		FYB202	Formycon; Fresenius Kabi	Pending
		DMB-3115	Dong-A Pharmaceutical; Intas; Meiji Seika; Accord	Pending
		Bmab1200	Biocon	Pending
		SB17	Samsung Bioepis; Sandoz	Pending

*As of June 21, 2024

Biosimilar products awaiting launch and/or approval* (continued)

Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval*
Stelara SubQ	Johnson & Johnson (Janssen)	Selarsdi	Alvotech; Teva; Alvogen	4/16/2024
Tysabri® IV	Biogen; Royalty Pharma	Tyruko™	Polpharma; Sandoz	8/24/2023
Xgeva	Amgen	Wyost	Sandoz	3/5/2024
		FKS518	Fresenius Kabi	Pending
		CT-P41	Celltrion	Pending
Xolair®	Roche; Genentech; Novartis	CT-P39	Celltrion	Pending

*As of June 21, 2024

Gene therapies in the pipeline

Gene therapy is a novel approach to treatment that introduces genetic material into an individual's body to help fight various diseases. To differentiate gene therapy products, we break them into two broad categories: gene therapy and gene-based therapeutics. The main difference is that gene therapies are usually one-time treatments that aim to treat or cure a genetic disease, while gene-based therapeutics require multiple treatments.

The following gene therapies and gene-based therapeutics are scheduled to receive an FDA decision in the next 12 months, or we expect they could file a biologics license application (BLA) with the FDA in 2024/2025. The price of gene therapies has traditionally been announced after FDA-approval, making prediction of pipeline therapy pricing a particular challenge. We anticipate the majority of future gene therapy approvals will fall within the $2 - $4 million range of costs associated with current FDA-approved gene therapies.[6]

Gene and gene-based therapies with submitted applications for potential FDA-approval in 2024/2025*

Gene therapy/ gene-based therapy	Indication/route**	Expected use	Place in therapy**	Estimated approval date
Elevidys (delandistrogene moxeparvovec-rokl) Sarepta Therapeutics	Duchenne muscular dystrophy (DMD)/IV	One-time dose	First gene therapy for DMD approved for individuals 4 years and older regardless of ambulation status.	APPROVED 06/20/2024
Marnetegragene autotemcel (RP-L201) Rocket Pharmaceuticals	Leukocyte adhesion deficiency-I/IV	One-time dose	First gene therapy for this indication. Uses viral vector (lentivirus).	FDA-denied (plans to refile)
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).	11/13/2024

*As of July 15, 2024

**Key

BLA: biologics license application

DNA: deoxyribonucleic acid

EB: epidermolysis bullosa

FVIII: factor 8

HCT: hematopoietic cell transplantation

IV: intravenous

Gene and gene-based therapies with submitted applications for potential FDA-approval in 2024/2025* (continued)

Gene therapy/ gene-based therapy	Indication/route**	Expected use	Place in therapy**	Estimated approval date
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).	FDA-denied (plans to refile 3Q24)

*As of July 15, 2024

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
RP-L102 Rocket Pharmaceuticals	Fanconi anemia (FA)/IV	One-time dose	First gene therapy for this indication. Uses viral vector (lentivirus).	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
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).	2024-2025
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

*As of July 15, 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
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).	2024-2025
OTL-201 Orchard	Mucopolysaccharidosis IIIA (Sanfilippo Type A)/IV	One-time dose	Competing with ABO-102 to be first gene therapy for this indication; will compete with HCT. Uses viral vector (lentivirus).	2024-2025
RP-A501 Rocket Pharmaceuticals	Danon disease/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2024-2025
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).	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).	2025

*As of July 15, 2024

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

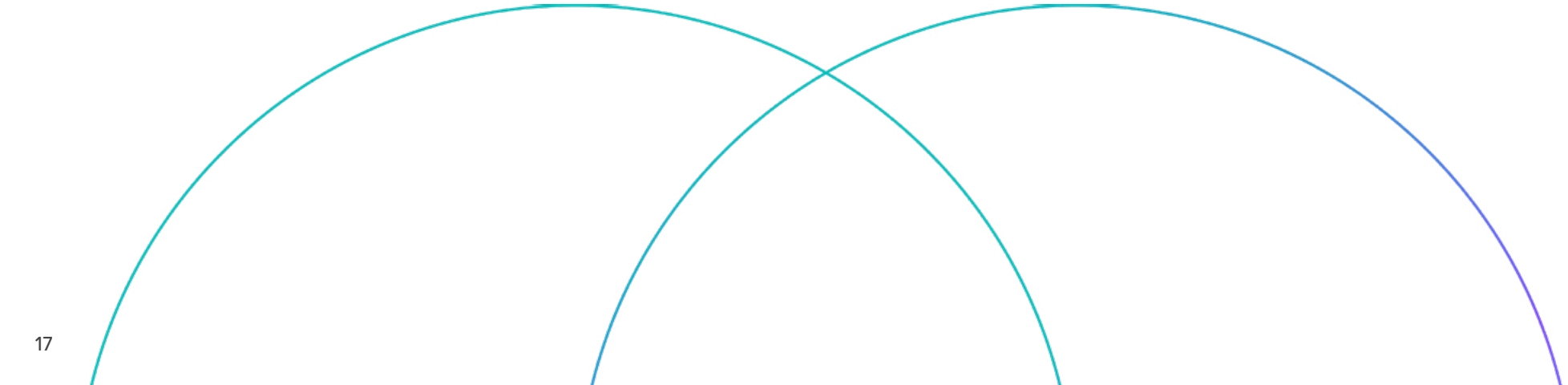
Gene therapy/ gene-based therapy	Indication/route**	Expected use	Place in therapy**	Estimated approval date
Giroctocogene fitelparvovec (PF-07055480; SB-525) Pfizer and Sangamo Therapeutics	Hemophilia A/IV	One-time dose	Competing with dirloctogene to be second gene therapy for hemophilia A; will compete with FVIII products, Hemlibra, and Roctavian. Uses viral vector (adeno-associated virus).	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).	2025
Sonpiretigene isteparvovec (MCO-010) Nanoscope Therapeutics	Retinitis Pigmentosa (RP)/IV	One-time dose	First mutation-agnostic gene therapy for RP. Uses viral vector (adeno-associated virus).	2025
UX111 (ABO-102) Abeona Therapeutics	Mucopolysaccharidosis IIIA (Sanfilippo Type A)/IV	One-time dose	Competing with OTL-201 to be first gene therapy for this indication; will compete with HCT. Uses viral vector (adeno-associated virus).	2025
DTX301 Ultragenyx Pharmaceutical	Ornithine transcarbamylase (OTC) deficiency/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2025-2026
Generx® (alferminogene tadenovec) Gene Biotherapeutics	Angina/intracoronary infusion	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2025-2026
TAVO (tavokinogene telseplasmid) OncoSec Medical	Metastatic melanoma/intratumoral injections	Intratumoral injections (multiple doses)	First gene therapy for this indication. Uses non-viral vector (plasmid DNA).	2025-2026

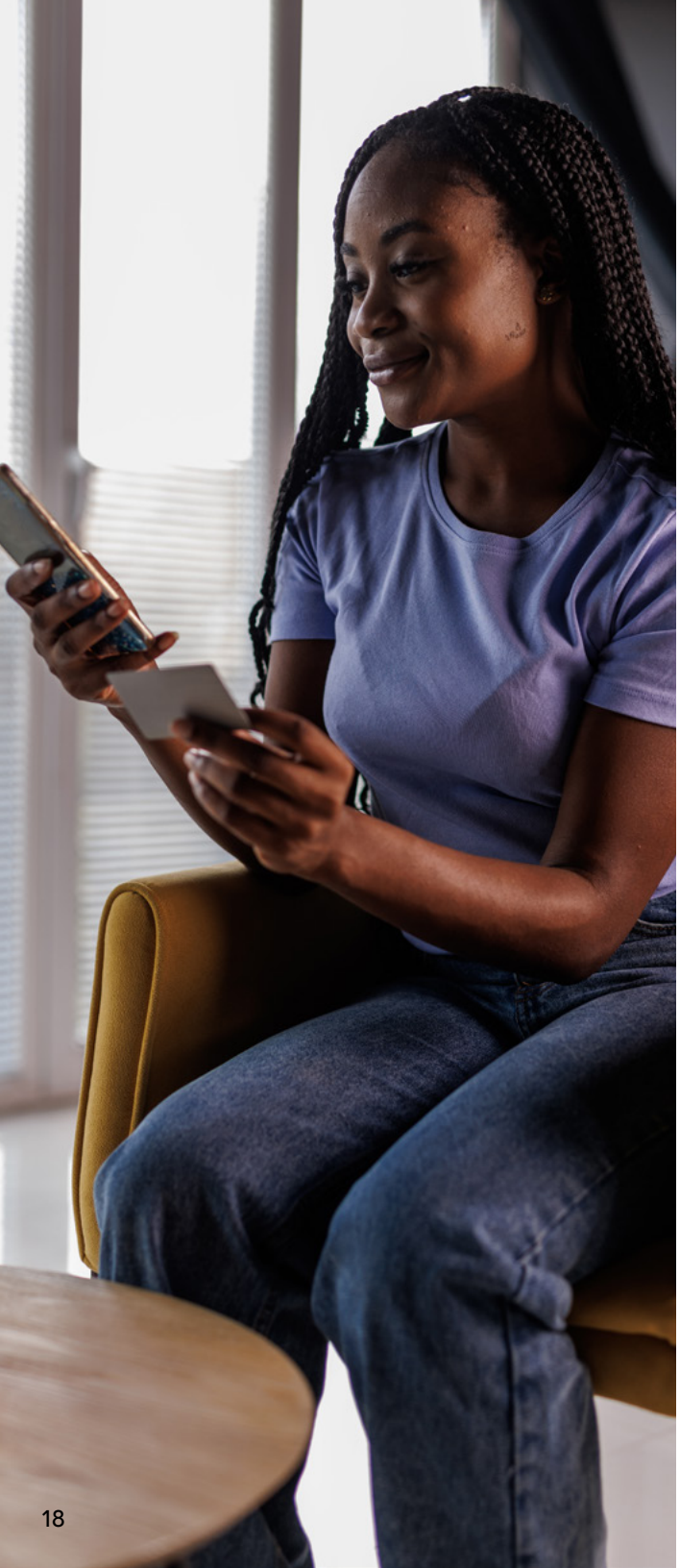
*As of July 15, 2024

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
UX701 Ultragenyx	Wilson disease/IV	One-time dose	First gene therapy for this indication. 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
Vyjuvek (beremagene geperpavec-svdt) Krystal Biotech	Dystrophic epidermolysis bullosa (DEB)/ophthalmic	Multiple dosing	Potential to expand approval to include an ophthalmic formulation of Vyjuvek to treat ocular complications secondary to DEB. Uses viral vector (herpes simplex virus).	2026

*As of July 15, 2024





FDA Accelerated Approval pathway updates

The FDA implemented the Accelerated Approval pathway in 1992 to more quickly bring drugs and biologics to market for serious diseases or conditions with an unmet medical need. While the traditional pathway requires a well-conducted randomized controlled trial (RCT) showing positive clinical outcomes (for example, decrease in rates of death or disease exacerbations), the accelerated pathway allows use of surrogate endpoints (for example, laboratory measures, radiographic images, physical signs, etc.) that are hypothesized to predict clinical benefit.

Key limitations of using surrogate endpoints for approval are not knowing the true benefit of the medication or any long-term consequences, since the advantage of this approach is a shorter study duration.

Use of the accelerated pathway often requires the manufacturer to conduct a confirmatory post-marketing study to prove a clinical benefit exists. If the benefit is not proven, or it is not as clinically meaningful as anticipated, the FDA can withdraw or modify the approved indication.

Historically, most drugs and biologics approved using the Accelerated Approval pathway have had oncologic indications. However, in recent years there have been more approvals for infectious disease, neurologic, and hematologic indications. To ensure consistent and appropriate use of the pathway, the FDA has created the Accelerated Approval Coordinating Council (AACC), which consists of the directors of the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Oncology Center for Excellence.

CBER has recently expressed an even greater push for the use of biomarkers and the Accelerated Approval pathway for rare diseases, especially in pediatrics and for the approval of gene therapies. They recognize the critical need for accuracy and precision of biomarker measurements through validated assays to ensure people are not left out of potentially beneficial therapies.[7] While there are differences to consider between a small molecule drug and a large biologic, such as gene therapy, the AACC is working to find more standardization in how biomarkers are used in the approval process to prevent a surrogate marker from being approved in one instance and denied in another without transparent explanation.

Additionally, the AACC has created a draft guidance of recommendations to sponsors of anti-cancer drugs on considerations for designing trials intended to support Accelerated Approval. Although not finalized, the guidance recommends two separate RCTs be conducted, one assessing an early endpoint such as response rate, and a second powered for a longer-term clinical endpoint such as progression-free or overall survival. If only one RCT is conducted, it should be adequately powered to detect clinically meaningful and statistically significant differences in both endpoints for Accelerated Approval and verification of clinical benefit. Regardless of study design chosen, the guidance also states the FDA may require, as appropriate, that confirmatory studies be underway at the time of approval to minimize the duration of clinical uncertainty.

While there are significantly more drugs with confirmed benefit, the table below provides a summary of drugs or indications withdrawn by the FDA after failure of confirmatory trials. It may take several years before withdrawal due to delays in confirmatory clinical trial completion.

Drug manufacturer	Accelerated Approval indication**	Accelerated Approval date	Withdrawal date
	Oncology		
Withdrawn agent			
Truseltiq® (infigratinib) BridgeBio	Previously treated unresectable locally advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangement	5/28/2021	5/16/2024
Aliqopa® (copanlisib) Bayer	Relapsed follicular lymphoma after 2 or more lines of therapy	9/14/2017	3/18/2024
Pepaxto® (melphalan flufenamide) Oncopeptides AB	R/R MM in combination with dexamethasone after 4 or more lines of therapy	2/26/2021	2/23/2024
Blenrep® (belantamab vedotin-blmf) GlaxoSmithKline	R/R MM after 4 or more lines of therapy	8/5/2020	2/6/2023
Ukoniq® (umbralisib) TG Therapeutics	R/R marginal zone lymphoma after 1 or more anti-CD20-based regimens	2/5/2021	5/31/2022
Ukoniq® (umbralisib) TG Therapeutics	R/R follicular lymphoma after 3 or more lines of therapy	2/5/2021	5/31/2022
Marqibo (vincristine sulfate [liposomal]) Talon	Ph-chromosome negative ALL in second or greater relapse or after 2 or more lines of therapy	8/9/2012	5/2/2022

**Key

ALL: acute lymphoblastic leukemia

AML: acute myeloid leukemia

Chemo: chemotherapy

CLL: chronic lymphocytic leukemia

GEJ: gastroesophageal junction

HER2: human epidermal growth factor receptor 2

LH: luteinizing hormone

MM: multiple myeloma

NHL: non-Hodgkin's lymphoma

NSCLC: non-small cell lung cancer

R/R: relapsed or refractory

SCLC: small cell lung cancer

TNBC: triple negative breast cancer

Success and failure with Accelerated Approval program

- Withdrawn cancer Accelerated Approvals = 29
- Cancer Accelerated Approvals with verified clinical benefit = 103
- Ongoing cancer Accelerated Approvals = 62
- Average time from Accelerated Approval to withdrawal = 5.5 years (range: 1.3 to 12.6 years)
- Average time from Accelerated Approval to verified clinical benefit = 3.9 years (range: 0.46 to 18.1 years)

Drug manufacturer	Accelerated Approval indication**	Accelerated Approval date	Withdrawal date
	Oncology		
Withdrawn agent			
Farydak® (panobinostat) Secura Bio	R/R MM in combination with bortezomib and dexamethasone after 2 or more lines of therapy	2/23/2015	3/24/2022
Lartruvo® (olaratumab) Eli Lilly	Soft tissue sarcoma in combination with doxorubicin	10/19/2016	2/25/2020
Bexxar® (tositumomab and iodine I 131 tositumomab) GlaxoSmithKline	R/R low-grade follicular lymphoma or CD20+ NHL not treated with rituximab	12/22/2004	10/23/2013
Iressa® (gefitinib)* AstraZeneca	Locally advanced or metastatic NSCLC after failure of platinum-based and docetaxel chemo	5/5/2003	4/25/2012
Oforta® (fludarabine phosphate) Sanofi Aventis	R/R B-cell CLL after 1 or more lines of therapy containing alkylating agent	12/18/2008	12/31/2011
Mylotarg® (gemtuzumab ozogamicin)* Wyeth	First relapse of CD33+ AML in those 60 or older and ineligible for cytotoxic chemo	5/17/2000	11/28/2011

*New application submitted for separate indication and approved at a later date

Drug manufacturer	Accelerated Approval indication**	Accelerated Approval date	Withdrawal date
	Oncology		
Withdrawn indication (product still on market)			
Lynparza® (olaparib) Genentech	Deleterious or suspected deleterious germline BRCA mutated advance ovarian cancer after 3 or more lines of therapy	12/19/2014	3/26/2024
Gavreto® (pralsetinib) Blueprint Medicines	Advanced or metastatic RET-mutant medullary thyroid cancer in those 12 years and older who require systemic therapy	12/1/2020	7/20/2023
Imbruvica® (ibrutinib) Pharmacyclics	Mantle cell lymphoma after 1 or more lines of therapy	2/16/2018	5/18/2023
Imbruvica® (ibrutinib) Pharmacyclics	Marginal zone lymphoma after 1 or more lines of therapy	2/16/2018	5/18/2023
Tecentriq® (atezolizumab) Genentech	Locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemo, have disease progression during or after platinum-based chemo or within 12 months of neoadjuvant or adjuvant platinum-containing chemo	4/17/2017	12/2/2022
Keytruda® (pembrolizumab) Merck	Recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 after 2 or more lines of therapy	9/22/2017	2/4/2022
Zydelig® (idelalisib) Gilead Sciences	Relapsed follicular lymphoma after 2 or more lines of therapy Relapsed small lymphocytic lymphoma after 2 or more lines of therapy	7/23/2014	2/18/2022
Copiktra® (duvelisib) Secura Bio	R/R follicular lymphoma after 2 or more lines of therapy	9/24/2018	12/17/2021

Drug manufacturer	Accelerated Approval indication**	Accelerated Approval date	Withdrawal date
	Oncology		
Withdrawn indication (product still on market)			
Romidepsin Teva	Peripheral T-cell lymphoma after 1 or more lines of therapy	3/13/2020	12/8/2021
Tecentriq® **(atezolizumab)** Genentech	Unresectable, locally advanced or metastatic TNBC	3/8/2019	10/6/2021
Istodax® **(romidepsin)** Celgene	Peripheral T-cell lymphoma after 1 or more lines of therapy	6/16/2011	7/30/2021
Opdivo® **(nivolumab)** Bristol Myers Squibb	Hepatocellular carcinoma previously treated with sorafenib	9/22/2017	7/23/2021
Tecentriq® **(atezolizumab)** Genentech	R/R locally advanced or metastatic urothelial carcinoma after platinum-containing chemo or within 12 months of neoadjuvant or adjuvant platinum-containing chemo	5/18/2016	4/13/2021
Keytruda® **(pembrolizumab)** Merck	R/R metastatic SCLC after platinum-based chemo and 1 or more lines of therapy	6/17/2019	3/30/2021
Imfinzi® **(durvalumab)** AstraZeneca	R/R locally advanced or metastatic urothelial carcinoma after platinum-containing chemo or within 12 months of neoadjuvant or adjuvant platinum-containing chemo	5/1/2017	2/19/2021
Opdivo® **(nivolumab)** Bristol Myers Squibb	R/R metastatic SCLC after platinum-based chemo and 1 or more line of therapy	8/16/2018	12/29/2020

Drug manufacturer	Accelerated Approval indication**	Accelerated Approval date	Withdrawal date
	Oncology		
Withdrawn indication (product still on market)			
Celebrex® (celecoxib) Searle	Reduce number of adenomatous colorectal polyps in familial adenomatous polyposis	12/23/1999	6/8/2012
Avastin® (bevacizumab) Genentech	Chemo-naïve metastatic HER2 negative breast cancer in combination with paclitaxel	2/22/2008	11/18/2011
Ethyol® (amifostine) Clinigen	Reduce cumulative renal toxicity from cisplatin administration in NSCLC	3/15/1996	3/28/2006
	Non-oncology		
Withdrawn agent			
Makena® (hydroxyprogesterone caproate) Covis Pharma	Reduce risk of preterm birth in women with singleton pregnancy with history of singleton spontaneous preterm birth	2/3/2011	4/6/2023
Sulfamylon® (mafenide acetate) Mylan	Adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings and over meshed autografts on excised burn wounds	6/5/1998	11/30/2022
Luveris® (lutropin alpha) EMD Serono	Stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency	10/8/2004	4/12/2016
Withdrawn indication (product still on market)			
Synercid® (dalfopristin/quinupristin) King Pharmaceuticals	Vancomycin-resistant enterococcus faecium	9/21/1999	11/12/2010

Market trends

Nonopioid pain treatment late-stage pipeline

Opioids are substances that work by activating receptors on nerve cells to reduce pain intensity. They are prescribed for treating acute and chronic pain. Long-term use carries the risk of tolerance and addiction. Widespread misuse of prescription and illegal opioids led the U.S. Department of Health and Human Services to declare a public health emergency in 2017. A strategy was announced to address this crisis. However, opioid use disorder and addiction are still serious problems.

The Centers for Disease Control and Prevention (CDC) issued guidelines in 2022 that recommend nonopioid medication, both prescription and non-prescription (e.g. NSAIDs), for many types of acute pain because nonopioid therapies are considered at least as effective as opioids. The nonopioid pain market is expected to grow as pharmaceutical companies hope to address the opioid crisis. According to a recent report, the global market is anticipated to increase from $78.89 billion in 2024 to $140.56 billion by 2031.[8]

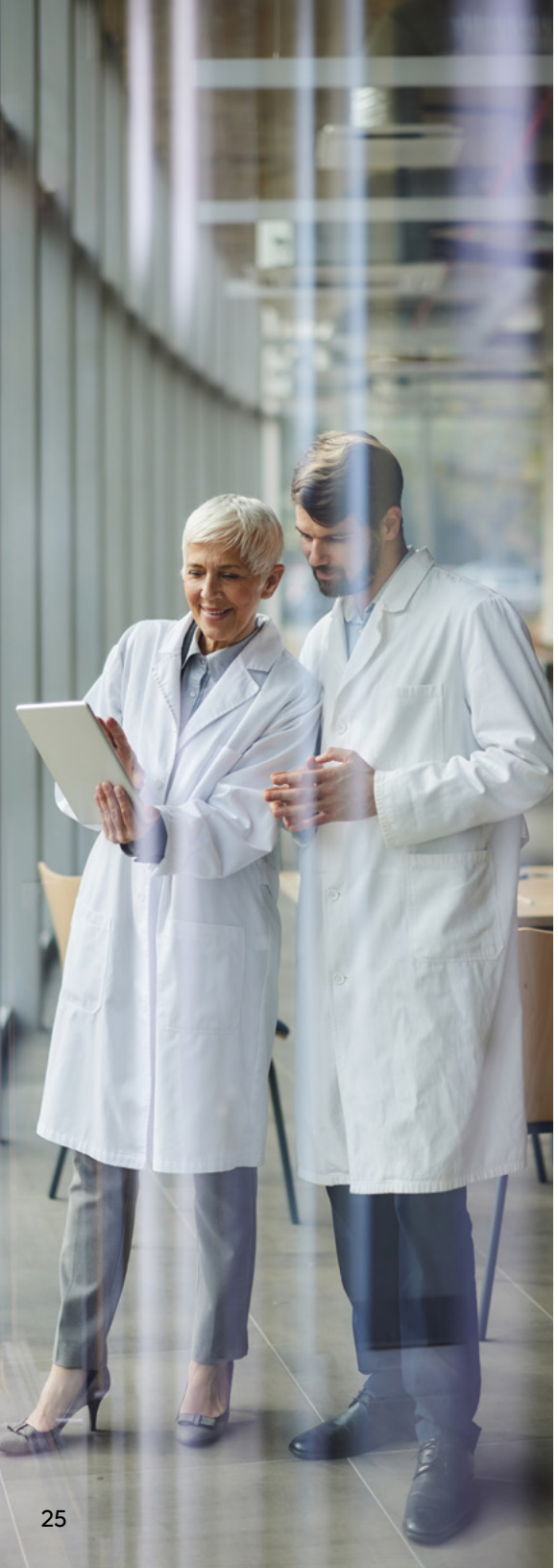
Researchers are looking for less-addictive and safer alternatives to help address the opioid crisis. Vertex Pharmaceuticals is a frontrunner with their novel, nonopioid product suzetrigine (formerly known as VX-548). It is an oral selective NaV1.8 pain signal inhibitor that aims to provide pain relief without the addictive potential of opioids.

Vertex recently announced positive phase 3 trial results. Suzetrigine achieved statistically significant improvements on pain primary endpoints compared to placebo in two phase 3 trials evaluating moderate-to-severe acute pain after surgery. These trials also looked at a secondary endpoint evaluating pain intensity to compare the efficacy of suzetrigine to Vicodin® (hydrocodone bitartrate/acetaminophen). Neither trial met this endpoint. The majority of adverse events were mild to moderate, and there were no serious adverse events related to the study drug. Suzetrigine has been evaluated in a separate single-arm trial across a wide range of surgical and non-surgical pain conditions with results suggesting safety and effectiveness in treating pain.

Vertex has submitted a New Drug Application (NDA) for suzetrigine for the treatment of moderate-to-severe acute pain, and a decision from the Food and Drug Administration (FDA) is expected in late 2024/early 2025. It is in phase 3 development for the treatment of pain associated with diabetic peripheral neuropathy (DPN), with a trial expected to begin in the second half of 2024. In addition, a phase 2 trial is enrolling in lumbosacral radiculopathy.

Vertex is working on additional oral and injectable drugs in the same class as suzetrigine as well as NaV1.7 pain signal inhibitors for use alone or in combination. Other companies are also attempting to develop nonopioid NaV1.7 and NaV1.8 options for acute and chronic pain treatment. These agents are in earlier development and may have advantages over suzetrigine including better selectivity leading to improved safety. In addition, some companies are working on improved nonsteroidal anti-inflammatory drugs (NSAIDs) with better safety and tolerability.[9]

Currently there are many opioid and anti-inflammatory options for the treatment of acute and chronic pain. While suzetrigine appears safe and effective compared to placebo, there is not enough evidence to determine how it compares to opioids. Early data versus Vicodin did not show comparable efficacy. The price has not been announced; however, it will likely cost more than generic opioid products. Interest in finding alternative pain treatments is high due to the need to address the opioid crisis.



Update on nonalcoholic steatohepatitis (NASH) guidelines and pipeline

Nonalcoholic steatohepatitis (NASH) is a subtype of nonalcoholic fatty liver disease (NAFLD) in which a person has not only a buildup of excess fat in the liver but also inflammation that causes damage. NALFD is estimated to affect 24% of U.S. adults; NASH is estimated to affect 1.5% to 6.5% of U.S. adults.

In our 2Q24 publication, we discussed the announcement of nomenclature updates for NAFLD and NASH. As a reminder, 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. NASH is now metabolic dysfunction-associated steatohepatitis (MASH) and will be used to describe a person with MASLD who also has inflammation that causes liver damage.[10] For this article, the terms will be used interchangeably.

Since our 2Q24 publication, the American Association for the Study of Liver Disease (AASLD) published new guidance to help providers identify people with fibrosis and steatosis using a combination of blood-based and imaging-based, non-invasive liver disease assessments (NILDA). These guidances provide detailed information, including the strengths and limitations, surrounding each NILDA. While the guidances help identify people with NAFLD and fibrosis, AASLD calls out NASH as an area that needs future research: "the diagnosis of NASH (not just fibrosis in NAFLD) represents a particular challenge for NILDA, and there is need for further study."[11,12] Differentiating NAFLD and NASH in clinical practice can be challenging and a definitive diagnosis of NASH requires a liver biopsy.

During the nomenclature update AASLD stated their previous treatment recommendations regarding NASH and NAFLD, included in the 2023 practice guidance for the management of NAFLD, can be applied to adults with MASH and MASLD, respectively.[10] The 2023 AASLD practice guidance for NAFLD recommends lifestyle interventions such as diet and exercise, and supports the management of comorbid conditions for all people with MASLD or MASH.[13] For people who are overweight, weight loss can improve liver fat, NASH, and liver fibrosis. The guidance predates the approval of Rezdiffra™ (resmetirom), the first and only FDA-approved treatment for NASH.

Rezdiffra is indicated in conjunction with diet and exercise for the treatment of adults with NASH with moderate to advanced liver fibrosis. While studies have not been completed, there is potential for combination therapy in clinical practice when more than one product receives FDA-approval for NASH in the future. Analysts anticipate the NASH market to exceed $21 billion in sales by the end of 2032, with semaglutide alone exceeding $5.5 billion.[4] With a handful of unique mechanisms of action CarelonRx is closely monitoring the pipeline, including the following late-stage products in development.

NASH pipeline: agents in late-stage development*

Drug or biologic Manufacturer	Route** (frequency)	Place in therapy	Estimated FDA approval date (stage of development)*
Semaglutide Novo Nordisk	SC (once weekly)	**First in class:** • Potential to be second FDA-approved agent, following Rezdiffra, for NASH. • First glucagon-like peptide-1 (GLP-1) for NASH. • Phase 3 ESSENCE trial initiated as single agent (monotherapy) with results expected in 2H24. • Unclear if Novo Nordisk will use a separate brand name for the NASH indication or if it will fall under an existing semaglutide brand (e.g., Wegovy®, Ozempic®). • In Phase 2 development, with Gilead, evaluating combination pipeline therapies that include semaglutide plus a non GLP-1 agent. • A GLP-1 competitor, tirzepatide, released Phase 2 data in 2024 and is also pursuing a NASH indication.	2025 (Phase 3)
Lanifibranor inventiva	Oral (once daily)	• First peroxisome proliferator-activated receptor (PPAR) agonist designed to target PPAR alpha, delta, and partial activation of gamma (i.e. pan-PPAR agonist). • Phase 3 NATiV3 trial initiated; results expected first half of 2026.	2026-2027 (Phase 3)
Efruxifermin Akero Therapeutics	SC (once weekly)	• Competing to become first fibroblast growth factor 21 (FGF21) agonist for NASH. • Phase 3 SYNCHRONY trials initiated in late 2023 as monotherapy.	2027+ (Phase 3)
Pegozafermin 89bio	SC (once weekly or once every 2 weeks)	• Competing to become first fibroblast growth factor 21 (FGF21) agonist for NASH. • Phase 3 ENLIGHTEN-Fibrosis trial initiated in early 2024 as monotherapy. • Also in phase 3 development for severe hypertriglyceridemia (SHTG).	2027+ (Phase 3)

*As of July 15, 2024

**Key

NASH: nonalcoholic steatohepatitis

SC: subcutaneous injection

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