carelon Rx

Drug and biologic pipeline update Q4 2024

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CarelonRx's quarterly Drug and biologic pipeline update

Our Q4 2024 update provides summaries of three agents of interest with anticipated approvals in 2024 or 2025: vanzacaftor/tezacaftor/deutivacaftor for cystic fibrosis, crinecerfont for congenital adrenal hyperplasia, and cretostimogene grenadenorepvec for bladder cancer. Other select drugs and biologics in the pipeline, including gene therapies and biosimilars, are also highlighted. An update on Alzheimer's disease will be featured. Other topics this quarter include updates on recent respiratory syncytial virus (RSV) and coronavirus disease (COVID-19) vaccine recommendations from the Centers for Disease Control and Prevention (CDC) and an overview of two Food and Drug Administration (FDA) programs: the Support for Clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program and the Rare Disease Innovation Hub.

CarelonRx continues to closely monitor the drug and biologic pipeline and to 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.

Top emerging new therapies

Vanzacaftor/tezacaftor/deutivacaftor

Condition:

Cystic fibrosis (CF) is a condition caused by mutations in the *CFTR* gene that lead to dysfunctional CFTR protein. Approximately 40,000 individuals are living with CF in the U.S., and most are diagnosed with CF by the age of 2. Without a functional CFTR protein, mucus becomes thick and sticky, leading to blockages, damage, and infections in affected organs such as the lungs and digestive system. Disease severity varies depending on the type of mutations present, but common symptoms include chronic lung and sinus infections, malnutrition, poor growth, pancreatitis, and chronic diarrhea or constipation.

Role in treatment:

There is no cure for CF. Management focuses on treating symptoms, delaying end-organ damage, and includes CFTR modulator treatments that aim to improve the production, intracellular processing, and function of the CFTR protein. Selection of therapy depends on an individual's age and genetic mutations. Approximately 90% of the CF population carries a mutation responsive to modulator therapy, most commonly the *F508del* mutation.[1]

Food and Drug Administration (FDA)-approved CFTR modulators are each administered by mouth and can be broken down into two groups, "potentiators," which help open the CFTR protein channel to increase chloride transport, and "correctors," which help the defective CFTR protein fold properly. Kalydeco® (ivacaftor) is a potentiator available as a monotherapy or in combination with correctors in the dual- and triple-combination therapies, Symdeko® (tezacaftor/ivacaftor), Orkambi® (lumacaftor/ivacaftor), and Trikafta® (elexacaftor/tezacaftor/ivacaftor). If an individual has a genotype that is eligible for more than one CFTR modulator, triple therapy is preferred over dual therapy and monotherapy.

Vanzacaftor/tezacaftor/deutivacaftor ("vanza triple") will be the second oral triple therapy for individuals with CF, composed of a potentiator and two correctors, like Trikafta. While treatment with Trikafta involves twice-daily dosing, vanza triple will allow for once-daily dosing.

Efficacy:

The New Drug Application submitted to the FDA was supported by data from the Phase 3 SKYLINE 102 and SKYLINE 103 trials, as well as the open-label RIDGELINE 105 study. The SKYLINE trials evaluated the efficacy of vanza triple compared to Trikafta in individuals 12 years of age and older with CF and at least one responsive mutation. In both trials, vanza-triple therapy was noninferior to Trikafta in improving the percent predicted forced expiratory volume in one second, a measure of lung function. Although the main goal of the Phase 3 RIDGELINE 105 study was to support the safety of vanza triple in children 6 to 11 years of age previously receiving Trikafta, results indicate maintenance of baseline lung function and a decrease in sweat chloride concentration from baseline. Sweat chloride concentration is a measure of CFTR protein dysfunction, so lower levels indicate vanza triple restored CFTR function in these individuals.

Safety:

Vanza-triple therapy was well tolerated in all three studies. Safety was similar between vanza triple and Trikafta in SKYLINE 102 and SKYLINE 103.

Financial impact:

The cost of vanza triple is currently unknown but may be more than Trikafta due to the potential dosing advantage. Since both products are from Vertex, their marketing may focus on the new market entry. Analysts estimate peak sales of $9.9 billion for vanza triple.[2]

CarelonRx view:

The availability of another CFTR modulator triple therapy for CF is promising, and data suggest similar efficacy and safety to Trikafta. The once-daily dosing of vanza triple may provide an advantage over Trikafta, which requires twice-daily dosing, and could provide a new treatment option for individuals who have failed Trikafta therapy.

Product:
Vanzacaftor/tezacaftor/deutivacaftor

Indication:
Cystic fibrosis (CF) in individuals 6 years and older with at least one F508del mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

Estimated FDA approval:
January 2025

Therapeutic class:
CFTR modulator

Route of administration:
Oral

FDA designations:
Fast track; Orphan drug; Priority

Manufacturer:
Vertex Pharmaceuticals

Crinecerfont

Condition:

Congenital adrenal hyperplasia (CAH) is a rare genetic disorder characterized by an enzyme deficiency that affects the production of adrenal hormones. A majority of CAH cases are due to a mutation that leads to deficiency of the enzyme 21-hydroxylase (21-OHD). If the deficiency is severe, the adrenal glands stop cortisol production, and in about 75% of these cases, aldosterone production is also affected. Cortisol helps the body respond to injury or illness. Aldosterone helps regulate blood pressure and salt levels. If cortisol is absent, the adrenal glands overcompensate and produce too many androgens. There are two types of CAH: nonclassic and classic. Nonclassic is milder and more common. Severe or classic CAH is typically diagnosed at birth and affects approximately 30,000 people in the US. Classic CAH may lead to adrenal crisis and possibly death without treatment.

Role in treatment:

The primary goal for treatment of classic CAH is replacement of deficient hormones and reduction of excess androgen. Currently, the only Food and Drug Administration (FDA)-approved treatments for CAH are glucocorticoids. High doses are sometimes needed and can lead to long-term adverse events such as weight gain, cardiovascular disease, diabetes, and abnormal growth in children. Crinecerfont is a novel treatment with the advantage of being a nonglucocorticoid option without the risk of complications seen with high doses of glucocorticoids. It has the potential to reduce the total daily dose of glucocorticoid needed to manage symptoms.

Efficacy:

The New Drug Application submitted to the FDA was supported by data from the CAHtalyst adult and pediatric Phase 3 trials. Both trials met the primary endpoints related to androgen reduction and glucocorticoid dose reduction while maintaining androgen control. Applications were submitted for two dosage forms, a capsule and an oral solution.

Safety:

In the adult trials, crinecerfont was generally well tolerated, with the most common adverse events being fatigue and headache. In the pediatric trials, the most common adverse events were headache, fever, vomiting, upper respiratory tract infection, and nasopharyngitis.

Financial impact:

If approved, crinecerfont will be a new first-in-class treatment option for adults and pediatric individuals with classic CAH. The cost of crinecerfont is unknown at this time but is expected to be more costly than traditional glucocorticoid therapy.

CarelonRx view:

The availability of a nonglucocorticoid treatment option for CAH may help reduce the risk of high-dose, long-term steroid complications. The open-label treatment portions of both crinecerfont clinical trials are ongoing and may be able to further assess safety, which is important, as crinecerfont will be chronic daily therapy.

Product:
Crinecerfont

Indication:
Congenital adrenal hyperplasia

Estimated FDA approval:
December 2024

Therapeutic class:
Corticotropin releasing factor receptor antagonist

Route of administration:
Oral

FDA designations:
Breakthrough; Orphan drug; Priority review

Manufacturer:
Neurocrine Biosciences

Cretostimogene grenadenorepvec

Condition:

Bladder cancer occurs when cells of the bladder begin to grow out of control. Usually, the cancer begins in the urothelial cells that line the urinary tract, including the bladder. If the cancer spreads into the wall of the bladder, it is considered invasive and further classified into whether the cancer cells have grown into the muscle layer or not. The deeper the cancer has spread, the more difficult it is to treat. NMIBC makes up about 70% of urothelial bladder cancers and often can be cured with a five-year overall survival rate of approximately 96%. However, survival for those with high-risk disease drops to 70% to 85%.

According to the most recently available data from the United States (U.S.) Cancer Statistics Working Group, there were 75,450 new cases of bladder cancer reported in the U.S. in 2021, making it the sixth-highest cancer incidence. In 2022, 17,334 people died from bladder cancer.

Risk factors that increase the chance of developing bladder cancer include tobacco use, being male or white, having a family history of bladder cancer, genetic predisposition, exposure to certain toxins, and history of frequent or chronic urinary catheter use. Risk also increases as a person gets older. Symptoms may include frequent or painful urination, being unable to urinate, blood in the urine, pain in the lower back or abdomen, unintended weight loss, and loss of appetite.

Role in treatment:

NMIBC is treated according to the risk of disease recurrence and progression. In general, the tumors are surgically removed from the bladder, then chemotherapy is instilled in the bladder and held for one to two hours. Those with low-risk disease will receive a one-time infusion with gemcitabine intravesical, mitomycin intravesical, epirubicin intravesical, or pirarubicin intravesical. Intermediate-risk disease generally requires maintenance intravesical infusions into the bladder with the aforementioned drugs for up to one year. BCG intravesical may also be used for intermediate risk and is strongly recommended for up to three years in those with high risk of recurrence or progression.

Treatment options for individuals who do not respond to BCG are limited to surgical removal of part or all of the bladder, which is a highly invasive procedure known as a cystectomy. For those who are ineligible for or decline a radical cystectomy, bladder instillation of Adstiladrin® (nadofaragene firadenovec intravesical) or Anktiva® (nogapendekin alfa inbakicept intravesical) plus BCG is recommended over systemic chemotherapy.

Efficacy:

The efficacy of cretostimogene monotherapy was assessed in the Phase 3 BOND-003 study in which 105 individuals with high-risk NMIBC who did not respond to BCG therapy had a complete response (CR) rate of 75.2%. Duration of response had not been reached at time of reporting. Cystectomy was avoided in 92% of those treated; no one required a radical cystectomy or had disease progression to lymph nodes or other distant sites.

The CORE-001 Phase 2 trial assessed the use of cretostimogene plus Keytruda in 35 individuals with BCG-unresponsive NMIBC. The CR rate was 83%, and of the 20 people who had a CR at 12 months, 19 maintained a CR at 24 months.

Safety:

Treatment-related adverse events in the BOND-003 were mild, with the most common being bladder spasm, frequent or painful urination, and blood in the urine.

Treatment-related adverse events in the CORE-001 study were consistent with those reported with the individual agents and showed no synergistic toxicity.

Product:
Cretostimogene grenadenorepvec

Indication:
High-risk Bacillus Calmette Guerin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS; cancer that has not spread to nearby tissues) as a single agent or in combination with Keytruda® (pembrolizumab intravenous)

Estimated FDA approval:
2025

Therapeutic class:
Oncolytic immunotherapy; gene-based therapeutic, adenovirus

Route of administration:
Instillation into the bladder via a urinary catheter (intravesical)

FDA designations:
Fast track; Breakthrough therapy

Manufacturer:
CG Oncology

Cretostimogene grenadenorepvec

Financial impact:

If approved, cretostimogene will be the second gene-based therapeutic approved for NMIBC, competing with Adstiladrin. Cretostimogene induction consists of six weekly intravesical instillations, followed by three weekly maintenance doses at months 3, 6, 9, 12, and 18. Moderate uptake is anticipated due to the competitive market in this disease state. However, due to expected high cost, these gene-based therapies will have an estimated $900 million in peak sales in 2033 in the U.S.[3]

CarelonRx view:

Given the invasive nature of completely removing the bladder and its risk of complications, cretostimogene may prove to be a considerable option given its high efficacy rate and minimal side effect profile. Longer-term data is needed to know its true place in therapy.

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Cretostimogene grenadenorepvec

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Estimated FDA approval:
2025

Therapeutic class:
Oncolytic immunotherapy; gene-based therapeutic, adenovirus

Route of administration:
Instillation into the bladder via a urinary catheter (intravesical)

FDA designations:
Fast track; Breakthrough therapy

Manufacturer:
CG Oncology

Other products expected to reach the market in the next 12 months.*

Drug or biologic manufacturer	Indication/route**	Place in therapy	Estimated approval date	Impact on overall drug or medical spend
Olezarsen Akcea	Familial chylomicronemia syndrome (FCS)/SC	**First in class:** would be first FDA-approved treatment for this indication	12/19/2024	
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	
Cosibelimab Checkpoint Therapeutics	Metastatic cutaneous squamous cell carcinoma/IV	**Addition to class:** would compete with other programmed cell death protein 1 (PD-1) inhibitors	12/28/2024	
Vicagrel Jiangsu Vcare PharmaTech	Thrombotic cardiovascular and cerebrovascular diseases, including acute coronary syndrome, ischaemic stroke, and peripheral arterial disease/oral	**Addition to class:** potential for improved safety profile compared with clopidogrel	12/28/2024	
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	

** 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

* As of November 7, 2024

Other products expected to reach the market in the next 12 months.* (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy	Estimated approval date	Impact on overall drug or medical spend
Crinecerfont Neurocrine Biosciences	Congenital adrenal hyperplasia (CAH)/oral	**First in class:** would compete with glucocorticoids	12/29/2024	
Vanzacaftor/ tezacaftor/ deutivacaftor Vertex	Cystic fibrosis/oral	**Addition to class:** next-generation triple therapy for cystic fibrosis; would compete with Trikafta®	01/02/2025	
Zenocutuzumab Merus	Non-small cell lung cancer and pancreatic cancer in individuals with neuregulin 1 fusion (NRG1+) disease/IV	**First in class:** would be first approved targeted therapy for NRG1+ cancer	01/06/2025	
Tabelecleucel Atara Biotherapeutics	Treatment of adult and pediatric individuals 2 years of age and older with Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD)/IV	**First in class:** in individuals who have received at least one prior therapy	01/15/2025	
Elamipretide Stealth BioTherapeutics	Barth syndrome/SC	**First in class:** would be first FDA-approved agent for this indication	01/29/2025	
Suzetrigine Vertex	Acute pain/oral	**First in class:** nonopioid pain medication	01/30/2025	

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Other products expected to reach the market in the next 12 months.* (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy	Estimated approval date	Impact on overall drug or medical spend
Mirdametinib SpringWorks Therapeutics	Neurofibromatosis type 1-associated plexiform neurofibromas (NF1-PN), pediatrics and adults/oral	**Addition to class:** would complete with Koselugo®	02/28/2025	⊗
Etripamil Milestone Pharmaceuticals	Supraventricular tachycardia/intranasal	**Addition to class:** rapid-response therapy that is self-administered	03/28/2025	⊗
Fitusiran Alnylam	Hemophilia A or B/SC	**Addition to class:** for individuals with or without inhibitors	03/28/2025	⊗
Atrasentan AbbVie	Immunoglobulin A (IgA) nephropathy/oral	**Addition to class:** would compete with Filspari® and Fabhalta®	Between May and June 2025	⊗
Sebetralstat KalVista Pharmaceuticals	Hereditary angioedema, on-demand treatment/ oral	**Addition to class:** would be the first oral option for on-demand treatment	06/18/2025	⊗
Sepiapterin PTC Therapeutics	Phenylketonuria/oral	**Addition to class:** would compete with Kuvan® and its generics	07/30/2025	⊗
Elinzanetant Bayer	Menopause, vasomotor symptoms/oral	**Addition to class:** nonhormonal therapy; would compete with Veozah®	08/01/2025	⊗

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The Food and Drug Administration (FDA) requires all approved biologic products, including reference, biosimilar, and interchangeable products, be evaluated for safety and efficacy to determine whether the benefits outweigh any known potential risks.

Reference biologics undergo several phases of clinical studies to establish safety and effectiveness before they are FDA approved. Clinical trials begin with early, small-scale, Phase 1 studies and move toward late-stage, large-scale, Phase 3 studies. After the biologic has entered the market, post-marketing monitoring continues to assess the safety, efficacy, and clinical benefit in a larger population.

Biosimilar products are highly similar to their reference product in terms of structure and function and lack clinically meaningful differences in terms of safety and efficacy. Biosimilar products may be approved for all or some of the reference product indications due to patent exclusivity. Prescriptions for biosimilar products typically need to be written for the biosimilar by name, depending on state laws. Biosimilar products that are granted interchangeability are allowed to be substituted for their reference biologic without the intervention of the prescriber. This is similar to how generic drugs may be substituted for brand-name drugs.

Unlike reference biologics, biosimilar products are not required to submit evidence to establish safety and efficacy. However, a biosimilar manufacturer must submit clinical trial data that establishes biosimilarity with the reference product.

The table to the right presents key biologic products that have biosimilar competition in Phase 3 clinical trials. Some of these reference biologic products have existing FDA approval and launched biosimilar competition. FDA approval of additional biosimilars in Phase 3 clinical trials would allow for more options.

Biosimilar pipeline update

Biologic products with biosimilars in Phase 3 clinical trials*

Reference biologic	Therapeutic use	Existing FDA-approved biosimilar	Launched biosimilar
Actemra®	Inflammatory conditions	Yes	Yes
Avastin®	Cancer	Yes	Yes
Cosentyx®	Inflammatory conditions	No	No
Enbrel®	Inflammatory conditions	Yes	No
Entyvio®	Inflammatory conditions	No	No
Epogen®/Procrit®	Erythropoiesis-stimulating agent (ESA)	Yes	Yes
Eylea®	Eye conditions	Yes	No
Herceptin®	Cancer	Yes	Yes
Humira®	Inflammatory conditions	Yes	Yes
Keytruda®	Cancer	No	No
Lucentis®	Eye conditions	Yes	Yes
Novolog® products	Insulin	Yes	Yes
Ocrevus®	Multiple sclerosis	No	No
Opdivo®	Cancer	No	No
Perjeta®	Cancer	No	No

* As of November 7, 2024

Biologic products with biosimilars in Phase 3 clinical trials* (continued)

Reference biologic	Therapeutic use	Existing FDA-approved biosimilar	Launched biosimilar
Prolia®/ Xgeva®	Bone conditions	Yes	No
Remicade®	Inflammatory conditions	Yes	Yes
Rituxan®	Cancer	Yes	Yes
Simponi®/ Simponi Aria®	Inflammatory conditions	No	No
Xolair®	Asthma	No	No

* As of November 7, 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 or 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 range of costs associated with the current FDA-approved gene therapies, between $2 million to $4 million.[4]

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
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
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).	04/29/2025
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)

** Key

BLA: biologics license application

DNA: deoxyribonucleic acid

EB: epidermolysis bullosa

FVIII: factor 8

HCT: hematopoietic cell transplantation

IV: intravenous

* As of November 7, 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
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).	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
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).	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).	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
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).	2025

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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
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).	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
RP-A501 Rocket Pharmaceuticals	Danon disease/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2025
RGX-202 Regenxbio	Duchenne muscular dystrophy (DMD)/ intravenous infusion	One-time dose	Second gene therapy for DMD; will compete with Elevidys. Uses viral vector (adeno-associated virus).	2025
RP-L102 Rocket Pharmaceuticals	Fanconi anemia (FA)/IV	One-time dose	First gene therapy for this indication. Uses viral vector (lentivirus).	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

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Gene and gene-based therapies of significant interest with potential FDA submissions in 2025/2026 (continued)

Gene therapy/ gene-based therapy	Indication/route**	Expected use	Place in therapy**	Estimated approval date
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
AMT-130 uniQure	Huntington's disease/stereotaxic surgery with infusion into the brain	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2025-2026
DTX301 Ultragenyx Pharmaceutical	Ornithine transcarbamylase (OTC) deficiency/IV	One-time dose	First gene therapy for this indication. Uses viral vector (adeno-associated virus).	2025-2026
Generx® (alferminogene tadenovec) Gene Biotherapeutics	Angina/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
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

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Gene and gene-based therapies of significant interest with potential FDA submissions in 2025/2026 (continued)

Gene therapy/ gene-based therapy	Indication/route**	Expected use	Place in therapy**	Estimated approval date
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
LX2006 Lexeo Therapeutics	Friedreich's Ataxia Cardiomyopathy/ intravenous infusion	One-time dose	First gene therapy for this indication. 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

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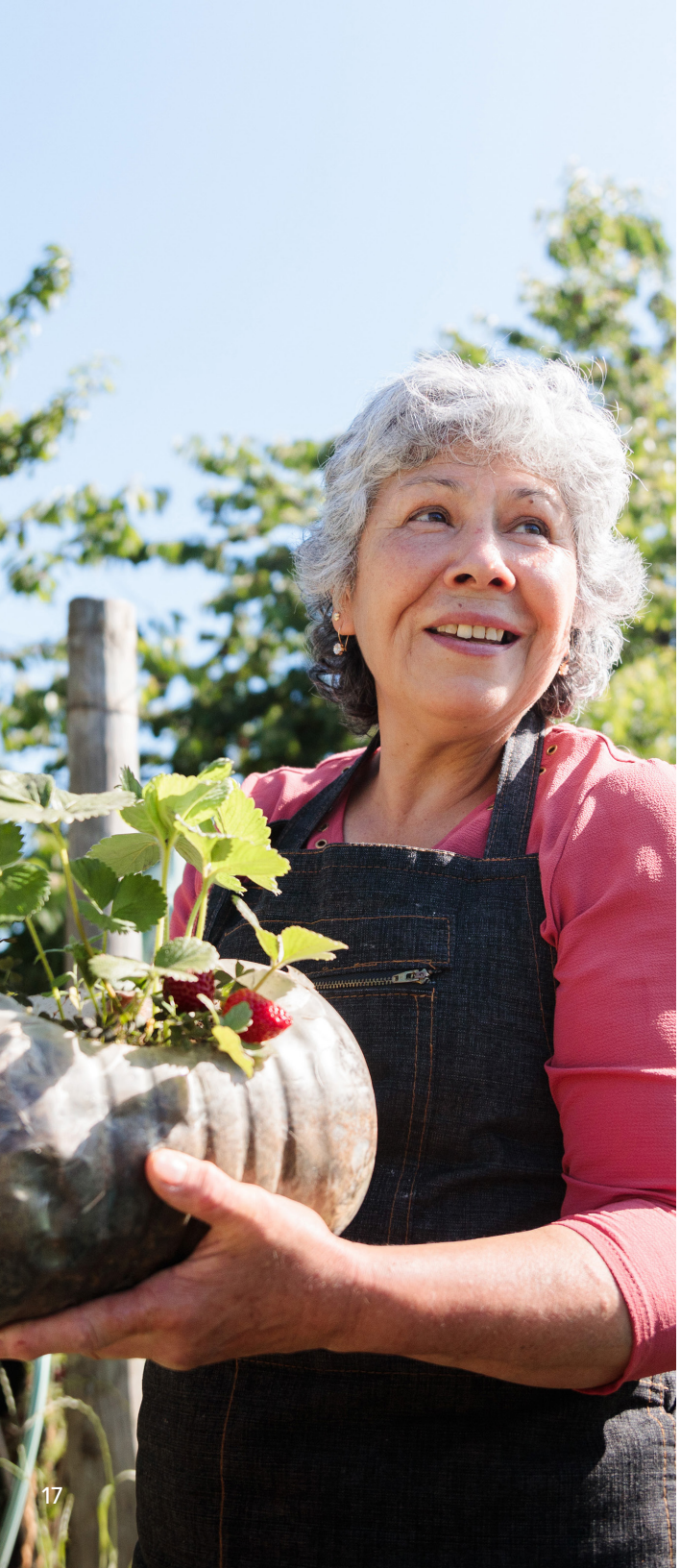
BLA: biologics license application • **DNA:** deoxyribonucleic acid • **EB:** epidermolysis bullosa • **FVIII:** factor 8 • **HCT:** hematopoietic cell transplantation • **IV:** intravenous

* As of November 7, 2024



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

Kisunla™ (donanemab-azbt intravenous (IV) infusion) was approved in July 2024 for the treatment of early Alzheimer's disease with the presence of beta-amyloid plaques. It joins Leqembi® (lecanemab-irmb IV infusion) as the only other available amyloid beta-directed antibody. Like Leqembi, there is a risk of amyloid-related imaging abnormalities (ARIA) resulting in swelling or bleeding of the brain and certain individuals may be at greater risk. Magnetic resonance imaging (MRI) is required before starting therapy and during treatment. Deaths related to Kisunla have been reported as part of the ongoing long-term extension phase of the Phase 3 clinical trial. Kisunla is administered as a 30-minute IV infusion every four weeks, and Leqembi is administered as a one-hour IV infusion every two weeks.

A similar product, Aduhelm® (aducanumab-avwa IV infusion), was discontinued in January 2024. Individuals can continue Aduhelm treatment through November 1, 2024, if their last infusion was on or before that date.[5]

Kisunla demonstrated a numerical difference in slowing cognitive decline compared to placebo in a Phase 3 clinical trial. Cognitive decline was measured by the integrated Alzheimer's disease rating scale (iADRS), which assesses cognition and daily function. The Food and Drug Administration (FDA) disagreed with the use of iADRS as the primary measure and recommended the clinical dementia rating sum of boxes (CDR-SB), which was used in trials with Leqembi. It is difficult to compare Kisunla to Leqembi as studies used different clinical endpoints, though neither demonstrated a clinically meaningful difference in slowing cognitive decline.

The actual (absolute) difference in cognitive decline for Kisunla-treated individuals was approximately 3 points on a 144-point scale (9.27 for placebo minus 6.02 for Kisunla).[6] This difference is not considered clinically meaningful. The minimum clinically important difference in iADRS is between 5 and 9 depending on level of cognitive impairment. Manufacturers commonly report results using relative risk reduction (35% reduction or 1 minus 6.02/9.27), which can be misleading.

Like Leqembi, Kisunla treated individuals also demonstrated a numerical difference in a surrogate endpoint (e.g., amyloid reduction in the brain) compared to placebo; this has not been correlated with clinical improvement.

The Kisunla Phase 3 study allowed for discontinuing dosing if brain amyloid levels reached a certain threshold, as measured by positron emission tomography (PET). At Weeks 24, 52, and 76, the proportion of participants in the Kisunla treatment arm who met dose-stopping criteria based on amyloid PET results was 17%, 42%, and 60%, respectively. The manufacturer is evaluating how long slowing will continue past the duration of the trial. Treatment duration is specific to each individual. It is not yet known whether or when treatment would need to be restarted.

Leqembi and Kisunla are covered by the Centers for Medicare and Medicaid Services (CMS) for Medicare enrollees diagnosed with mild cognitive impairment or mild Alzheimer's disease dementia, with documented evidence of amyloid beta plaque on the brain and under care of a physician who participates in a qualifying registry with an appropriate clinical team and follow-up care. Details are outlined in the CMS Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease.

There are many other beta-amyloid antibodies in the pipeline for Alzheimer's disease (AD). ALZ-801, an oral tablet given twice daily, is currently in Phase 3 trials for early AD with plans to submit for FDA approval later this year. A subcutaneous autoinjector formulation of Leqembi is under investigation for maintenance treatment of AD and may be self or caregiver administered with proper training. An FDA decision is expected mid-2025.

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.[7]

Analysts predict that U.S. sales for the entire anti-beta-amyloid class, including label expansions and new agents, will grow to an estimated $7.8B by 2032.[3] Adoption of these agents depends on many factors including additional information on severity and frequency of safety events and Medicare coverage determinations.

Market trends

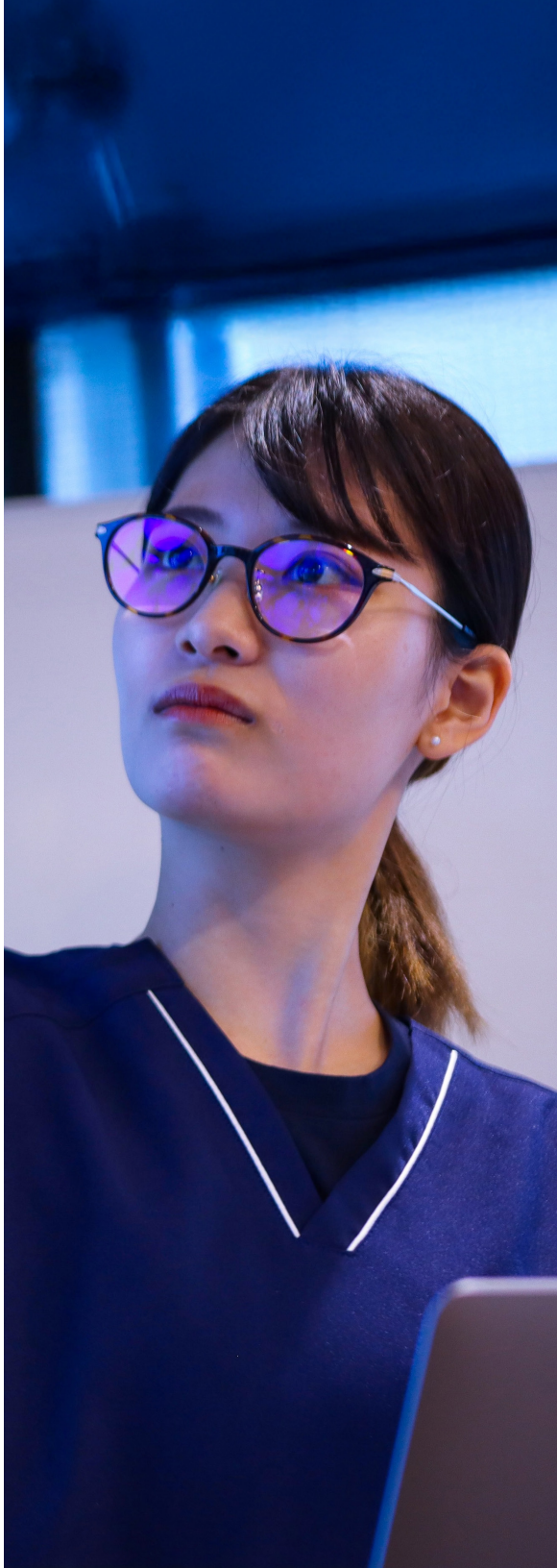
Updated vaccination recommendations for respiratory syncytial virus and coronavirus disease 2019

The Centers for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP) has approved updated recommendations for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) and coronavirus disease 2019 (COVID-19) vaccines.

RSV vaccine comparison

	Abrysvo®	Arexvy	mRESVIA®
Vaccine type	Viral vaccine (recombinant)	Viral vaccine (recombinant, adjuvant)	mRNA vaccine
Indication(s)	Active immunization for the prevention of LRTD caused by RSV in individuals ≥60 years Active immunization for the prevention of LRTD caused by RSV in individuals 18-59 years of age who are at increased risk Active immunization of pregnant individuals at 32 to 36 weeks' gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth to 6 months	Active immunization for the prevention of LRTD caused by RSV in individuals ≥60 years Active immunization for the prevention of LRTD caused by RSV in individuals 50–59 years of age who are at increased risk	Active immunization for the prevention of LRTD caused by RSV in individuals ≥60 years

In its updated guidance, ACIP strengthened its recommendation for RSV vaccination in older adults from the previous year. All adults ≥75 years are recommended to receive a single dose of an RSV vaccine. For adults aged 60 to 74 years who are at higher risk of severe RSV disease (i.e., individuals with lung disease, cardiovascular disease, moderate or severe immune compromise, diabetes mellitus with end-organ damage, severe obesity), a single dose is also recommended. No recommendation was provided for use in adults aged 50 to 59 years. At this time, RSV vaccination should be administered as a one-time lifetime dose, and individuals who have already been vaccinated are not recommended to receive an additional dose.



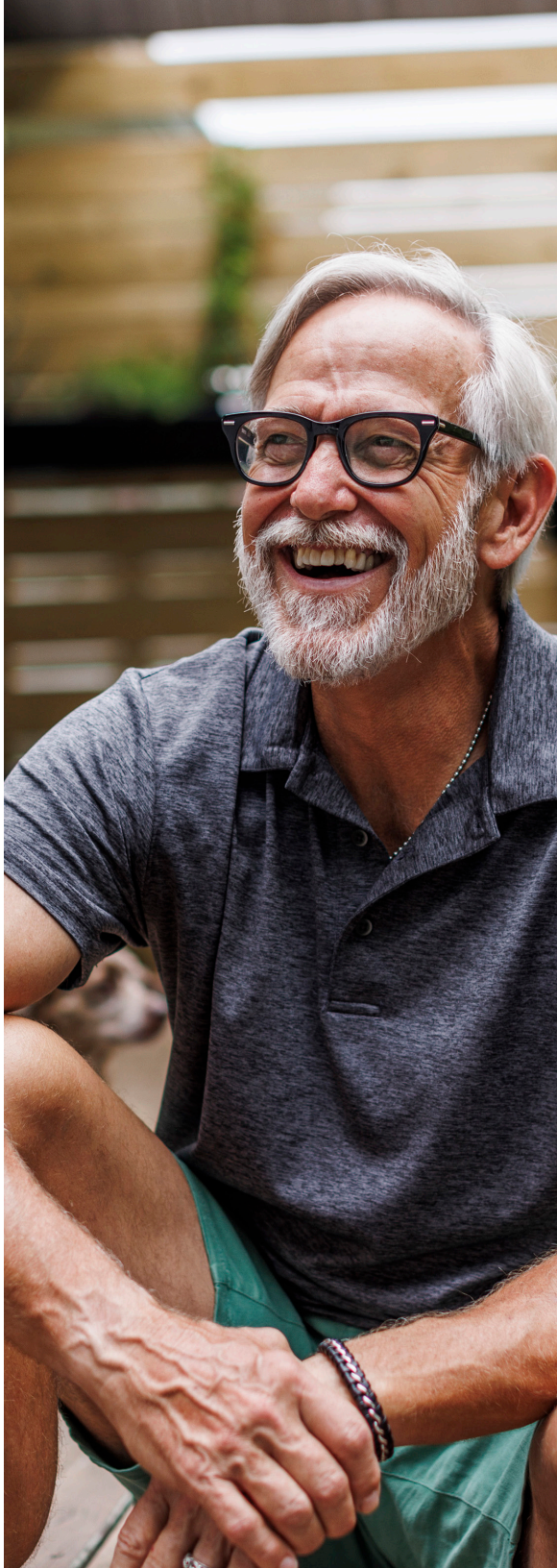
In addition, ACIP provided a recommendation for persons ≥6 months to receive a 2024-2025 COVID-19 vaccine. The updated vaccines are monovalent and target more recently circulating virus strains from the Omicron variant. After original guidance to manufacturers from the Food and Drug Administration (FDA) in early June 2024 to focus on the JN.1 strain, the recommendation was updated in late June 2024 to prefer KP.2, a descendant strain of JN.1 based on its increasing prevalence.

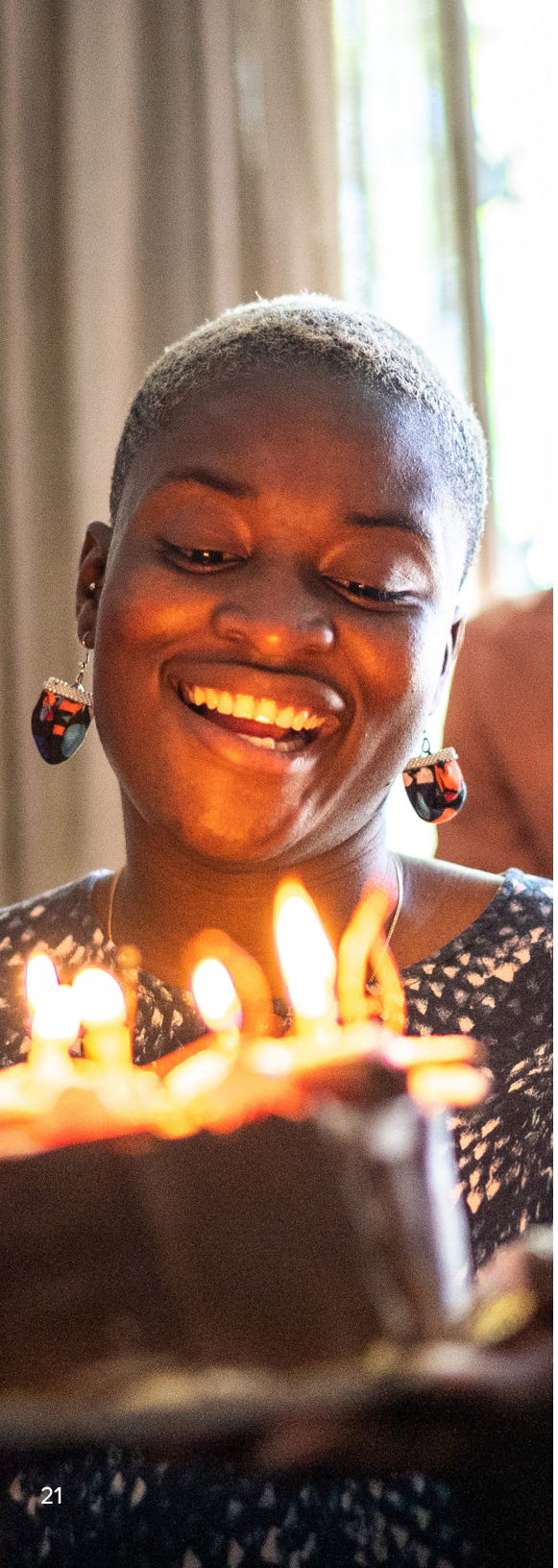
A second dose of 2024-2025 COVID-19 vaccine is recommended for adults ≥65 years and for individuals aged 6 months to 64 years who are moderately or severely immunocompromised. A 6-month interval is recommended between doses. Additional doses (i.e., 3 or more doses) may be considered in individuals who are moderately or severely immunocompromised based on discussions with an individual's health care provider.

COVID-19 vaccine comparison

Brand name (manufacturer)	**COMIRNATY®** (Pfizer-BioNTech)	**SPIKEVAX®** (Moderna)	**Nuvaxovid** (Novavax)
Vaccine type	mRNA vaccine		Protein subunit vaccine
Omicron target strain	KP.2		JN.1
FDA approval	Active immunization to prevent COVID-19 in individuals ≥12 years		—
Emergency use authorization	Active immunization to prevent COVID-19 in individuals 6 months to 11 years		Active immunization to prevent COVID-19 in individuals ≥12 years

Additional details on these and other recommendations may be viewed **here**.





Food and Drug Administration (FDA) rare disease drug and biologic development programs

On July 17, 2024, the FDA created the **Rare Disease Innovation Hub** with the goal of accelerating development of drugs and biologics for rare diseases. There are over 10,000 rare diseases that affect more than 30 million people in the U.S. The Hub will focus on treatments for rare diseases where the natural history is variable and poorly understood.

The Hub will be led by the directors of the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). The primary goal is to leverage cross-agency expertise to facilitate drug and biologic development. The Hub will have three core functions:

- Single point of connection for matters that intersect CDER and CBER for the rare disease community, including affected individuals/caregiver groups, trade organizations, and scientific organizations.
- Enhance collaboration between CBER and CDER in order to address common scientific, clinical, and policy issues related to rare disease product development.
- Advance regulatory science for consideration of novel endpoints, biomarker development and assays, innovative trial design, real world evidence, and statistical methods.

The Hub will advance a shared vision to align efforts, enable innovation, and streamline communication for the rare disease community. An open public meeting is expected to take place later this year to allow for feedback from the public.

Another recent addition to the FDA's existing rare disease development programs includes the **Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program**. This was initiated by CBER and CDER to gain insight on efficient development of treatments for rare diseases. Applicants to the program will have more frequent communication with the FDA to address early product development issues, such as clinical trial design with the goal of facilitating achievement of regulatory milestones if supported by the data. The first participants in the program have products currently in clinical trials under an active Investigational New Drug Application (IND) regulated by CBER or CDER. Treatments for the following rare diseases will be part of the program: Friedreich's ataxia, vanishing white matter disease, Mucopolysaccharidosis Type IIIA, NGLY1 deficiency, isolated methylmalonic acidemia due to complete or partial methylmalonyl-coenzyme A mutase deficiency, Canavan disease, and Rett syndrome. The FDA hopes to gain valuable insight from this pilot program to improve efficiency in developing treatments to address unmet medical needs for rare diseases.

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