carelon Rx

# Drug and biologic pipeline update Q4 2023

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# CarelonRx's quarterly Drug and biologic pipeline update

CarelonRx continues to closely monitor the drug and biologic pipeline. We provide this free publication as part of our mission to improve health; reduce waste; lower total cost of care for pharmacy and medical; and estimate future cost impact. Information contained within this document is compiled from various publicly available resources and is provided for informational purposes only. This document does not provide information on confidential CarelonRx proprietary clinical programs or management strategies.

Our Q4 2023 edition provides summaries of three agents of interest with the potential to reach the market this year or early next year: aprocitentan for resistant hypertension; NVK-002 (low dose atropine) for myopia in children; and OTL-200, a gene therapy for metachromatic leukodystrophy. Other select drugs and biologics in the pipeline, including gene therapies and biosimilars, are highlighted. An overview of the new Centers for Disease Control and Prevention (CDC) recommendations for hepatitis B and an update on the hepatitis pipeline are provided. Finally, summaries of drug shortages and prescription to over-the-counter (OTC) switches will be spotlighted.



This document should not be relied on solely for decision-making purposes, and should not be considered clinical, legal, or financial advice. Projections on future drug approvals, availability, and/or pricing are based on information available at the time of publication and are not within the control of CarelonRx.

Unless otherwise noted, information contained in this document was obtained from the Centers for Disease Control and Prevention (CDC) (cdc.gov), the Food and Drug Administration (FDA) (fda.gov), clinicaltrials.gov, releases from pharmaceutical manufacturers, National Institutes of Health (NIH) (nih.gov), and UpToDate.com (registration required). Information in this document is accurate as of September 14, 2023.

## Top emerging new therapies

# Aprocitentan

### Condition:

Resistant hypertension is diagnosed when a person's blood pressure remains above treatment goal despite concurrent treatment with three optimized antihypertensive medications from different therapeutic classes. The most common classes include calcium channel blockers (e.g., amlodipine oral), renin-angiotensin system blockers [e.g., angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB, or ARB-neprilysin inhibitor), and diuretics (e.g., hydrochlorothiazide)]. The diagnosis of resistant hypertension further involves consideration of pseudoresistance (e.g., white coat hypertension, medication nonadherence) and ruling out secondary causes of hypertension (e.g., obstructive sleep apnea, primary aldosteronism). Of note, people who have achieved target blood pressure levels on four or more antihypertensive medications are considered to have resistant hypertension.

People with resistant hypertension are at higher risk for medication-adverse effects and multiple cardiovascular and renal adverse outcomes (e.g., stroke, heart disease, kidney failure, death). Prevalence of the condition is unknown but estimated to affect 10% to 20% of people with hypertension.

### Role in treatment:

Currently available add-on therapies to standard hypertensive treatment include mineralocorticoid receptor antagonists (MRAs), beta-blockers, and vasodilators. Results of the PATHWAY-2 trial have placed the MRA spironolactone oral as a compelling selection as the fourth agent for treatment.

Aprocitentan targets the endothelin pathway, which is implicated in the pathogenesis of hypertension, and provides a unique mechanism of action for treatment. Blocking the endothelin peptide results in blood vessel relaxation and a resultant decrease in blood pressure. In some people, it may be an alternative fourth-line treatment option for resistant hypertension.

### Efficacy:

The New Drug Application submitted to the FDA was supported by data from PRECISION, a phase 3 clinical trial. When added to a standardized triple antihypertensive regimen including a diuretic, for treatment of resistant hypertension aprocitentan demonstrated a clinically meaningful reduction in blood pressure at four weeks compared to placebo. The effect was maintained for up to 48 weeks.

**Product:**
Aprocitentan

**Indication:**
Difficult-to-control (resistant) hypertension

**Estimated FDA approval:**
March 2024

**Therapeutic class:**
Dual endothelin receptor antagonist

**Route of administration:**
Oral

**FDA designations:**
None

**Manufacturer:**
Idorsia in collaboration with Janssen Biotech

# Aprocitentan

## (continued)

### Safety:
Aprocitentan was well tolerated in PRECISION trial subjects. The most common adverse effect was mild-to-moderate fluid retention, primarily peripheral edema, which led to discontinuation in a small number of subjects.

### Financial impact:
If approved, aprocitentan will be a first-in-class oral agent used as add-on therapy for resistant hypertension. It is expected to compete most directly with spironolactone as a fourth-line antihypertensive. While treatment cost is not available, it will likely be higher than the cost associated with generic options. A news release has estimated peak sales at $2.5 billion.[1]

### CarelonRx view:
The availability of a new drug class for treating difficult-to-treat hypertension is promising. However, questions remain about what the best use of aprocitentan in clinical practice will be. Although spironolactone is associated with increased potassium levels that are concerning in specific populations, aprocitentan's association with fluid retention, anticipated higher cost, and comparable effects on blood pressure reduction may limit uptake over spironolactone initially.

**Product:**
Aprocitentan

**Indication:**
Difficult-to-control (resistant) hypertension

**Estimated FDA approval:**
March 2024

**Therapeutic class:**
Dual endothelin receptor antagonist

**Route of administration:**
Oral

**FDA designations:**
None

**Manufacturer:**
Idorsia in collaboration with Janssen Biotech

# NVK 002 (atropine low dose)

### Condition:
Pediatric myopia (nearsightedness) is very common. It begins in children as young as ages 3 or 4 years and progresses in the early years of life. It is caused by a steeply curved cornea. This makes objects far away appear blurry. Myopia can increase the risk of cataracts, glaucoma, and retinal detachment later in life.

Myopia is becoming more common among children. It has been suggested that this is due to an increase in activities such as computer work and video games. Myopia affects 30% of the world's population and is estimated to affect 5 billion people by 2050.

### Role in treatment:
There are no FDA-approved pharmacological treatments for myopia. It is corrected with glasses, contact lenses, or surgery. Myopia cannot be reversed, but doctors have been studying ways to slow progression in children. The goal is to keep vision from getting worse. One therapy that has been tried in recent years is low-dose atropine eye drops. This product, which currently must be compounded, may slow myopia progression by preventing the eye from lengthening too much when administered for several years.[2] NVK 002 (atropine 0.01%) is the first atropine eye drop to seek FDA approval for this use.

### Efficacy:
The FDA submission was supported by a three-year, placebo-controlled phase 3 clinical trial in 600 children. Statistically significant improvements compared with placebo were observed at month 36 in the primary outcome measure of proportion of people responding to therapy. Myopia is measured in units called diopters (D).[3] A positive response in this trial was measured as less than 0.50 D myopia progression.[4]

### Safety:
In the clinical trial, tolerability was similar to placebo. The most common ocular adverse events were redness, photophobia, allergic conjunctivitis, itching, and irritation. There were no serious ocular events.[4]

### Financial impact:
The cost of a commercially available low-dose atropine ophthalmic product compared with a compounded version is unknown. The rate of adoption will also affect financial impact of NVK 002.

### CarelonRx view:
The use of ophthalmic atropine will not reverse myopia. It will only slow progression. It is uncertain the number of people who may choose atropine treatment. Adoption may depend on the answers to several lingering questions, including optimal age to begin therapy, how long treatment should continue, and how to avoid potential rebound effect after treatment is stopped.[5]

**Product:**
NVK 002 (atropine low dose)

**Indication:**
Myopia in children ages 3 to 17

**Estimated FDA approval:**
January 2024

**Therapeutic class:**
Muscarinic acetylcholine receptor

**Route of administration:**
Ophthalmic

**FDA designations:**
None

**Manufacturer:**
Vyluma

# Atidarsagene autotemcel (arsa-cel; OTL-200)

### Condition:
Metachromatic leukodystrophy (MLD) is a rare disorder due to mutations in the arylsulfatase-A (ARSA) or prosaposin (PSAP) genes that causes a toxic buildup of lipids that results in destruction of nerve fibers. There are three main subtypes of MLD, categorized primarily by the age at symptom onset: late infantile, juvenile, and adult onset. Symptoms vary by subtype, with the most severe affecting the central nervous system (CNS), resulting in neurological problems, rapid functional and cognitive decline, and ultimately death. It is estimated that MLD, including all subtypes, occurs in 1 in 100,000 births.

### Role in treatment:
Currently the only treatment known to slow or stop progression of MLD is a hematopoietic stem cell (HSC) transplant. This is for people identified in early stages of MLD with a matched HSC transplant donor. HSC transplants are not a cure for MLD. They can treat CNS symptoms; however, peripheral neuropathies remain.

Atidarsagene autotemcel (arsa-cel) is a one-time, personalized therapy that requires removal and modification of each person's own HSCs. Arsa-cel uses a lentiviral vector to insert two functional copies of the ARSA gene. After a chemotherapy-conditioning regimen, the modified HSCs are reinfused with the goal to slow or stop MLD progression. Arsa-cel, approved in the European Union (EU) in 2020 under the brand name Libmeldy™, is an option for children with late infantile or early juvenile forms of MLD who can still walk and before the onset of cognitive decline.

### Efficacy:
Integrated data from two phase 1/2 studies evaluated 39 children younger than age 7 years with pre-symptomatic late infantile MLD or pre- or early-symptomatic juvenile MLD. Compared to natural history cohorts, treatment with arsa-cel provided a statistically significant improvement in severe motor impairment-free survival in each subgroup. Participants have been followed for a median of six years after arsa-cel administration.

A third study, a phase 3 trial, is currently recruiting children age 17 years and younger with MLD and normal cognitive function.

### Safety:
There were six cases of anti-ARSA antibodies that resolved either spontaneously or with B-cell depleting therapy. No serious adverse events or deaths have been considered as related to treatment with arsa-cel. Most adverse events were due to the chemotherapy conditioning regimen or were related to the course of MLD disease.

### Financial impact:
The price of arsa-cel is unknown. However, it will likely be priced similarly to other gene therapies for rare diseases at $3 million or more for each one-time treatment.

### CarelonRx view:
Arsa-cel would be the first gene therapy approved for MLD introducing an option for children who do not have a matched HSC donor. While emerging data supports improvements in severe motor impairment, it remains unclear if arsa-cel prevents or improves peripheral neuropathies. The question remains whether the efficacy effects established to date will continue to modify the course of disease long term.

**Product:**
Atidarsagene autotemcel (arsa-cel; OTL-200)

**Indication:**
Children with early-onset metachromatic leukodystrophy (MLD)

**Estimated FDA approval:**
March 2024

**Therapeutic class:**
Gene therapy

**Route of administration:**
Intravenous

**FDA designations:**
Orphan; Rare Pediatric Disease (RPD); Regenerative Medicine Advanced Therapy (RMAT)

**Manufacturer:**
Orchard Therapeutics

# Other significant product approvals

We expect these products to reach the market in late 2023 to mid-2024:*

| Drug or biologic manufacturer | Indication/route** | Place in therapy | Estimated approval date | Impact on overall drug or medical spend** |
|---|---|---|---|---|
| **CTX001 (exa-cel)** Vertex/CRISPR Therapeutics | Sickle cell disease/IV | **First in class:** first gene therapy for sickle cell disease; also under review for beta-thalassemia, where it would compete with Zynteglo® | 12/08/2023 |  |
| **ARQ-154 (roflumilast)** Arcutis Biotherapeutics | Seborrheic dermatitis in people age 9 years and older/topical | **Addition to class:** foam formulation of roflumilast for dermatitis of the scalp | 12/16/2023 |  |
| **Lovotibeglogene autotemcel; lovo-cel (formerly LentiGlobin)** bluebird bio | Sickle cell disease/IV | **Addition to class:** would likely be second gene therapy for sickle cell disease | 12/20/2023 |  |
| **Givinostat** Italfarmaco | Duchenne muscular dystrophy (DMD)/oral | **First in class:** new mechanism of action for treatment of DMD | 12/21/2023 |  |
| **Eplontersen** Ionis | Familial amyloid polyneuropathy/SC | **Addition to class:** second generation LICA agent targeting transthyretin | 12/22/2023 |  |
| **iDose TR (travoprost implant)** Glaukos Corporation | Glaucoma; ocular hypertension/ ophthalmic implant | **Addition to class:** novel formulation of travoprost designed to continuously release therapeutic levels for at least one year; will compete with Durysta®, another bimatroprost implant | 12/22/2023 |  |

* As of September 14, 2023

**In addition to treatments listed previously, these important drugs and biologics are scheduled to receive FDA approval within the next 12 months.**

** Key

**CLDN18.2:** claudin 18.2

**ESA:** erythropoiesis-stimulating agents

**IM:** intramuscular

**IV:** intravenous

**Ligand-conjugated antisense:** LICA

**LRTD:** lower respiratory tract disease

**PD-1:** programmed cell death protein 1

**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** |
|---|---|---|---|---|
| **Gefapixant**<br>Merck | Chronic cough/oral | **First in class:**<br>non-narcotic option for chronic cough | 12/27/2023 | ⊗ |
| **Tirzepatide**<br>Eli Lilly | Chronic weight management/SC | **Addition to class:**<br>data available in people with and without diabetes; would compete with Wegovy®; currently approved as Mounjaro™ for type 2 diabetes | Approved | 📈 |
| **Donanemab**<br>Eli Lilly | Alzheimer's disease/IV | **Addition to class:**<br>would compete with Leqembi® in early-stage disease | 2023 | 📈 |
| **Mirikizumab**<br>Eli Lilly | Ulcerative colitis/IV; SC | **Addition to class:**<br>interleukin-23 antagonist; for use after failing other biologics | Approved | 📈 |
| **Capivasertib**<br>AstraZeneca | Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer/oral | **Addition to class:**<br>used in combination with Faslodex® following recurrence or progression on or after an endocrine-based regimen | Fourth quarter 2023 | 📈 |

## Other significant product approvals (continued)

| Drug or biologic manufacturer | Indication/route** | Place in therapy | Estimated approval date | Impact on overall drug or medical spend** |
|---|---|---|---|---|
| **Cosibelimab** Checkpoint Therapeutics | Metastatic cutaneous squamous cell carcinoma/IV | **Addition to class:** would compete with other PD-1 inhibitors | 01/03/2024 | |
| **Zolbetuximab** Astellas | Gastric cancer/IV | **First in class:** CLDN18.2-targeted monoclonal antibody | 01/12/2024 | |
| **TAK-755** Takeda | Thrombotic thrombocytopenic purpura (TTP), congenital/IV | **First in class:** would be first FDA-approved treatment for this indication | Approved | |
| **NVK-002 (atropine low dose)** Nevakar | Myopia in children and adolescents/ ophthalmic | **Addition to class:** would be first FDA-approved treatment for this indication | 01/31/2024 | |
| **Imetelstat** Geron Corporation | Myelodysplastic syndrome (MDS)/IV | **First in class:** for those who have failed to respond or have lost response to or are ineligible for ESAs | 02/20/2024 | |
| **Roluperidone** Minerva Neurosciences | Schizophrenia/oral | **First in class:** would be first FDA-approved treatment for negative symptoms of schizophrenia | 02/26/2024 | |
| **Resmetirom** Madrigal Pharmaceuticals | Nonalcoholic steatohepatitis (NASH)/oral | **First in class:** would be first FDA-approved treatment for this indication | 03/17/2024 | |

## Other significant product approvals (continued)

| Drug or biologic manufacturer | Indication/route** | Place in therapy | Estimated approval date | Impact on overall drug or medical spend** |
|---|---|---|---|---|
| **OTL-200**<br>Orchard Therapeutics | Metachromatic leukodystrophy/IV | **First in class:**<br>would be first FDA-approved treatment for this indication; gene therapy | 03/18/2024 | |
| **Aprocitentan**<br>Johnson & Johnson | Hypertension, resistant/oral | **First in class:**<br>would be first FDA-approved product specifically for resistant hypertension | 03/19/2024 | |
| **RP-L201**<br>Rocket Pharmaceuticals | Leukocyte adhesion deficiency-1/IV | **First in class:**<br>would be first FDA-approved treatment for this indication | 3/31/2024 | |
| **mRNA-1345**<br>Moderna | Prevention of LRTD caused by respiratory syncytial virus (RSV) in people age 60 years and older/IM | **Addition to class:**<br>would be third RSV vaccine for older adults | 04/05/2024 | |
| **Fidanacogene elaparvovec**<br>Pfizer | Hemophilia B/IV | **Addition to class:**<br>would compete with Hemgenix® as the second gene therapy for hemophilia B | 04/27/2024 | |
| **Ensifentrine**<br>Verona Pharma | Chronic obstructive pulmonary disease (COPD)/nebulization | **First in class:**<br>moderate to severe COPD; bronchodilator and anti-inflammatory | 06/27/2024 | |
| **Iptacopan**<br>Novartis | Paroxysmal nocturnal hemoglobinuria (PNH)/oral | **First in class:**<br>would compete with injectable agents Soliris®, Ultomiris®, and Empaveli® | 06/30/2024 | |

## Other significant product approvals (continued)

| Drug or biologic manufacturer | Indication/route** | Place in therapy | Estimated approval date | Impact on overall drug or medical spend** |
|---|---|---|---|---|
| **Crovalimab**<br>Roche | Paroxysmal nocturnal hemoglobinuria (PNH)/IV; SC | **Addition to class:**<br>first dose is intravenous infusion; maintenance dosing is self-administered SC injection | 07/27/2024 | ⊗ |
| **Danicopan**<br>AstraZeneca | Paroxysmal nocturnal hemoglobinuria (PNH)/oral | **First in class:**<br>add-on therapy with Soliris® or Ultomiris® in people who also have clinically evident extravascular hemolysis | 07/27/2024 | ⊗ |
| **Sotatercept**<br>Merck | Pulmonary arterial hypertension/SC | **First in class:**<br>novel mechanism of action; still uncertain whether this will be self-administered | 08/01/2024 | ⊗ |

The FDA requires all approved biological products, including reference, biosimilar, and interchangeable products, to 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 need to be written for the biosimilar by name. 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.

# Biosimilar pipeline update

The table below presents key biologic products that have biosimilar competition in phase 3 clinical trials. Some of these reference biologic products have existing FDA-approved and launched biosimilar competition. FDA approval of additional biosimilars in phase 3 clinical trials would allow for more options.

## Biologic products with biosimilars in phase 3 clinical trials

| Reference biologic | Therapeutic use | FDA-approved biosimilar | Launched biosimilar |
|---|---|---|---|
| Actemra® | Inflammatory conditions | No | No |
| 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 | No | No |
| Herceptin® | Cancer | Yes | Yes |
| Humira® | Inflammatory conditions | Yes | Yes |
| Keytruda® | Cancer | No | No |
| Lantus®, Solostar® | Insulin | Yes | Yes |
| Lucentis® | Eye conditions | Yes | Yes |

## Biologic products with biosimilars in phase 3 clinical trials (continued)

| Reference biologic | Therapeutic use | FDA-approved biosimilar | Launched biosimilar |
|---|---|---|---|
| Novolog® products | Insulin | Yes | Yes |
| Ocrevus® | Multiple sclerosis | No | No |
| Perjeta® | Cancer | No | No |
| Prolia® | Bone conditions | No | No |
| Remicade® | Inflammatory conditions | Yes | Yes |
| Rituxan® | Cancer | Yes | Yes |
| Simponi®/ Simponi Aria® | Inflammatory conditions | No | No |
| Soliris® | Blood modifying | No | No |
| Stelara® (IV and SC) | Inflammatory conditions | Yes | No |
| Xgeva® | Bone conditions | No | No |
| Xolair® | Asthma | No | No |

# Gene therapies in the pipeline

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

The following gene therapies and gene-based therapeutics are scheduled to receive an FDA decision in the next 12 months or we expect them to file a Biologics License Application (BLA) with the FDA in 2023/2024.

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

| Gene therapy/ gene-based therapy | Indication/route** | Expected use | Place in therapy | Estimated approval date |
|---|---|---|---|---|
| **Exagamglogene autotemcel (exa-cel; formerly CTX001)** Vertex and CRISPR Therapeutics | Beta-thalassemia anemia/IV | One-time dose | Second gene therapy for this indication; will compete with Zynteglo®. Uses gene editing. | 03/30/2024 (standard review) |
| | Sickle cell anemia/IV | | First gene therapy for this indication; will compete with HCT and chronic RBC transfusions. Uses gene editing. | 12/08/2023 (priority review) |
| **Lovotibeglogene autotemcel; lovo-cel (formerly LentiGlobin)** bluebird bio | Sickle cell anemia/IV | One-time dose | Second gene therapy for this indication; will compete with HCT, chronic RBC transfusions, and, if FDA-approved, exa-cel gene therapy. Uses viral vector (lentivirus). | 12/20/2023 (priority review) |
| **OTL-200** Orchard Therapeutics | Metachromatic leukodystrophy/IV | One-time dose | First gene therapy for this indication; will compete with HCT. Uses viral vector (lentivirus). | 03/18/2024 |
| **RP-L201** Rocket Pharmaceuticals | Leukocyte adhesion deficiency-1/IV | One-time dose | First gene therapy for this indication. Uses viral vector (lentivirus). | 03/31/2024 |
| **Fidanacogene elaparvovec (PF-06838435)** Pfizer | Hemophilia B/IV | One-time dose | Second gene therapy for this indication; will compete with Hemgenix® and with FIX products. Uses viral vector (adeno-associated virus). | 04/27/2024 |

** Key

**BLA:** biologics license application

**DNA:** deoxyribonucleic acid

**EB:** epidermolysis bullosa

**FVIII:** factor 8

**FIX:** factor 9

**HCT:** hematopoietic cell transplantation

**IV:** intravenous

**RBC:** red blood cell

## Gene and gene-based therapies of significant interest with potential FDA submissions in 2023/2024† (continued)

| 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). | 2024 (plans to file 2023) |
| **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 age 6 years and older with DEB; will compete with Vyjuvek™. Uses viral vector (adeno-associated virus). | 2024 (submitted) |
| **RP-L102** Rocket Pharmaceuticals | Fanconi anemia (FA)/IV | One-time dose | First gene therapy for this indication. Uses viral vector (lentivirus). | 2024 (plans to file in 4Q23) |
| **Fordadistrogene movaparvovec** Pfizer | Duchenne muscular dystrophy/IV | One-time dose | Second gene therapy for this indication. Uses viral vector (adeno-associated virus). | 2024 (potential to file by end of 2023) |
| **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 (filing possible in 2H23-2024) |
| **RGX-121** Regenxbio | Mucopolysaccharidosis II (MPS II; Hunter Syndrome)/ intracisternal or intracerebroventricular injection | One-time dose | First gene therapy for this indication. Uses viral vector (adeno-associated virus). | 2024/2025 (plans to file in 2024) |
| **Giroctocogene fitelparvovec (PF-07055480; SB-525)** Pfizer and Sangamo Therapeutics | Hemophilia A/IV | One-time dose | Competing with SPK-8011 to be second gene therapy for hemophilia A; will compete with FVIII products, Hemlibra, and Roctavian. Uses viral vector (adeno-associated virus). | 2024/2025 (plans to file in 2H24) |

## Gene and gene-based therapies of significant interest with potential FDA submissions in 2023/2024† (continued)

| Gene therapy/ gene-based therapy | Indication/route** | Expected use | Place in therapy | Estimated approval date |
|---|---|---|---|---|
| **AGTC-501** Beacon Therapeutics | X-linked retinitis pigmentosa (XLRP)/ intraocular injection | One-time dose | Second gene therapy for this indication; will compete with botaretigene if FDA-approved. Uses viral vector (adeno-associated virus). | 2024/2025 (potential to file in 2024) |
| **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 (plans to file in 2024 if phase 3 successful) |
| **Cretostimogene grenadenorepvec (CG0070)** Novartis | Non-muscle invasive bladder cancer (NMIBC)/intravesical | Multiple dosing | Second gene-based therapeutic; would compete with Adstiladrin®. Uses viral vector (adeno-associated virus). | 2024/2025 (plans to file late 2024 or early 2025) |
| **DTX401** Ultragenyx Pharmaceutical | Glycogen storage disease type Ia/IV | One-time dose | First gene therapy for this indication. Uses viral vector (adeno-associated virus). | 2024/2025 (potential to file in 2024) |
| **Generx® (alferminogene tadenovec)** Gene Biotherapeutics | Angina/ intracoronary infusion | One-time dose | First gene therapy for this indication. Uses viral vector (adeno-associated virus). | 2024/2025 (potential to file in 2024) |
| **RGX-111** Regenxbio | Mucopolysaccharidosis I (MPS I; Hurler Syndrome)/ intracerebroventricular infusion | One-time dose | First gene therapy for this indication. Uses viral vector (adeno-associated virus). | 2024/2025 (potential to file in 2024) |
| **RP-A501** Rocket Pharmaceuticals | Danon disease/IV | One-time dose | First gene therapy for this indication. Uses viral vector (adeno-associated virus). | 2024/2025 (potential to file in 2024) |

## Gene and gene-based therapies of significant interest with potential FDA submissions in 2023/2024† (continued)

| Gene therapy/ gene-based therapy | Indication/route** | Expected use | Place in therapy | Estimated approval date |
|---|---|---|---|---|
| **UX701**<br>Ultragenyx | Wilson disease/IV | One-time dose | First gene therapy for this indication. Uses viral vector (adeno-associated virus). | 2024/2025 (potential to file in 2024) |
| **ABO-102**<br>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). | 2024+ |
| **D-Fi (FCX-007; dabocemagene autoficel)**<br>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 age 2 years and older with DEB; will compete with Vyjuvek. Uses viral vector (lentivirus). | 2024+ |
| **Engensis; donaperminogene seltoplasmid**<br>Helixmith | Diabetic peripheral neuropathy and diabetic foot and other ulcers/ intramuscular injections | Intramuscular injections (multiple doses) | First gene-based therapy for these indications. Uses non-viral vector (plasmid DNA). | 2024+ |
| **OTL-201**<br>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+ |
| **TAVO (tavokinogene telseplasmid)**<br>OncoSec Medical | Metastatic melanoma/ intratumoral injections | Intratumoral injections (multiple doses) | First gene therapy for this indication. Uses non-viral vector (plasmid DNA). | 2024+ |

† As of September 7, 2023

# Updated Centers for Disease Control and Prevention (CDC) recommendations: Screening and testing for hepatitis B virus infection

**Acute hepatitis B virus (HBV) infection leads to developing chronic, or lifelong, HBV infection in approximately 4% of infected people.** While the majority of people are likely unaware they have chronic HBV infection, the estimated prevalence is up to 2.4 million people in the United States. Having a chronic HBV infection increases a person's risk of developing liver cancer, cirrhosis, and premature death. There is no cure for HBV infection; however, there are several hepatitis B vaccines available that are highly effective and are recommended for the prevention of HBV infection. Self-reported HBV vaccination rates are low; less than 40% of adults report being vaccinated.

In 2023, the CDC released updated recommendations to guide screening and testing for HBV infection in the United States. Compared to the prior 2008 publication, the new recommendations vastly expand the population that should receive screening and testing. The CDC now recommends testing all adults at least once in their lifetime for HBV infection and has expanded risk-based testing recommendations to include a broader group of people who require more frequent testing. It is unknown if the expanded screening and testing recommendations will increase HBV vaccination rates.

Increased testing will inevitably lead to more people diagnosed with chronic HBV infections. On a related tangent, hepatitis D is a liver infection caused by the hepatitis D virus (HDV). HDV infection only occurs in people already infected with HBV. Chronic HDV infection is the most severe form of viral hepatitis, progresses more rapidly than chronic HBV infections alone, and can have mortality rates as high as 50% within five years in people with cirrhosis. An increase in HBV infection diagnoses may also increase HDV infection diagnoses. Although prevalence of HDV is likely low, there are currently no FDA-approved treatments for HDV. The pipeline agent Hepcludex® (bulevirtide) is in development with the goal of becoming the first FDA-approved treatment for adults with chronic HDV infection. If approved, Hepcludex may be costly and spark interest from the medical community.

# Market trends

## Drug shortages

**In 2023, drug shortages hit a 10-year high with 309 active shortages by the end of second quarter (all-time high 320).** The top drug classes in shortage include drugs for attention deficit hyperactivity disorder, cancer, diabetes and weight management, and antibiotics.[6,7] Drug shortages can lead prescribers to use less effective alternatives that may pose additional risks compared to a drug in shortage. Many times a generic or similar therapeutic alternative can be prescribed.

Manufacturers must notify the FDA about manufacturing interruptions or product discontinuations. While the FDA cannot require manufacturers to make drugs, the FDA can expedite reviews of production lines and material sources, extend expiration dates, and import drugs into the United States to help prevent and resolve shortages.

An FDA report from 2019 identified three major root causes for drug shortages:

1. There is a lack of incentives to produce less profitable drugs (e.g., older generics).
2. The market does not recognize and reward manufacturers for mature quality management systems.
3. Logistical and regulatory challenges make it difficult for the market to recover after a disruption.

The FDA and American Society of Health-System Pharmacists[7] (ASHP) each have searchable databases where users can access drug shortage information. Both are updated daily and provide similar information; however, there are some key differences.

| | FDA | ASHP |
|---|---|---|
| Audience | Public | Healthcare provider |
| Scope of shortage | All drugs confirmed to be a national shortage (i.e., period of time when demand within the U.S. exceeds supply of the drug)<br>**Note:** Separate shortage site maintained by Center for Biologics Evaluation and Research for vaccines and some biologics. | All drug and biologic shortages reported and confirmed with manufacturers that are national in impact<br>**Note:** ASHP frequently lists more shortages than FDA. |
| Source of shortage report | Manufacturers notify FDA of production disruption and voluntarily provide updates. Reports also received from ASHP and the public.<br>**Note**: Represents shortage status at drug manufacturer level | Voluntary reports from practitioners, individuals, pharmaceutical industry, and others<br>**Note:** Represents status at healthcare provider level; information is updated based on release dates from manufacturers |
| Inclusion criteria | Manufacturers unable to meet current market demand | Verified with manufacturer and affects how pharmacies prepare/dispense product or requires use of alternative drugs |
| Resolution criteria | One or more manufacturers are in production and able to meet full market demand. | All manufacturers restore all formulations/dosages to full availability. |
| Alternative therapies suggested | No | Yes |

## Drug shortages (continued)

At CarelonRx, we carefully monitor drug shortages using various sources (e.g., FDA, ASHP, media reports) and internal monitoring (e.g., prescriber, network pharmacy, or customer service feedback). Our clinical policies help prevent overprescribing and encourage clinically appropriate use of drugs, helping to prevent shortages. We will modify our formularies or clinical policies as needed to provide access to alternative drugs where clinically appropriate. Although the responsibility for mitigating drug shortages resides primarily with manufacturers, CarelonRx's clinical strategies help mitigate impact to our members.

# Prescription to over-the-counter switches

Over the last couple of decades, the FDA has approved switches from prescription to nonprescription status for a number of drug products. This process allows consumers over-the-counter (OTC) access, which could be a more convenient and affordable option. In order to receive OTC status, the product must be effective and safe in a nonprescription setting with labeling that is easy to understand.  Examples of drugs that have switched status are allergy medications and nicotine replacement therapies. Estimates of OTC allergy medication users went up from 66% in 2009 to 75% in 2015. Use of nicotine replacement products increased 150% to 200% during the first year after the switch to OTC status.[8] A full listing of prescription to over-the-counter (Rx-to-OTC, or RTO) switches from January 2001 through July 2023 is available on the FDA website.

A recent analysis evaluated how innovative RTO switches have been in the past two decades. An exceptional innovation was defined as a product with a new-to-OTC active ingredient, pharmacological class, and indication. There were 45 RTO switches that occurred between January 2002 and August 2022, and 6.6% were considered exceptional, meaning a truly novel OTC product. These included levonorgestrel for emergency contraception, orlistat for weight loss, and oxybutynin for overactive bladder. The authors concluded that in order to help reduce healthcare spending and address public health challenges, more RTO switches that expand access to new OTC active ingredients for new indications are necessary.[9]

Two important switches occurred in 2023. Opill® (norgestrel, oral) was approved for nonprescription use in the prevention of pregnancy, and Narcan® (naloxone, nasal spray) was approved for nonprescription use in the treatment of known or suspected opioid overdose.

There is ongoing discussion on other therapeutic classes that may have potential RTO switch candidates. However, proving that a drug would be safe with OTC status is difficult. The potential for missed self-diagnosis and inappropriate self-medication is an issue. The FDA has proposed a rule that would require a drug product to have an additional condition for nonprescription use (ACNU). An ACNU is an FDA-approved condition that must be implemented to ensure appropriate self-selection and use of a nonprescription drug product by a consumer. Examples include requiring responses to a test available by mobile application or an automated telephone response system in order to purchase the nonprescription product. The rule is intended to increase options for safe and effective nonprescription drugs. It is still under review, and many issues need to be considered regarding operationalizing such a program.

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