carelon Rx

Drug and biologic pipeline update

Q1 2023

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CarelonRx's quarterly Drug and biologic pipeline update

Our Q1 2023 edition highlights emerging therapies in the pharmaceutical pipeline.

This edition provides details on three agents with the potential to reach the market this year: trofinetide for Rett syndrome, a gene therapy for Duchenne muscular dystrophy (DMD), and ritlecitinib for alopecia areata. We also highlight other significant treatments, including gene therapies and biosimilars, expected in the next few years. Also included are overviews on anticoagulants, the Food and Drug Administration (FDA)/National Institutes of Health (NIH) Critical Path for Rare Neurodegenerative Diseases partnership, and FDA Advisory Committee meetings.

CarelonRx continues to closely monitor the drug and biologic pipeline and provide this free digital 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.

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 2 required). Information in this document is accurate as of November 30, 2022.

Top emerging new therapies

TROFINETIDE

Condition:
Rett syndrome is a genetic disorder characterized by near normal development in the first two years of life followed by developmental regression of language and motor skills between the ages of 18 months and 30 months. Signs and symptoms may include repetitive hand movements, screaming fits, inconsolable crying, autistic features, panic-like attacks, teeth grinding, impaired gait, tremors, seizures, and slow head growth.[1] The disease primarily affects females and is rare, occurring in approximately 6,000 to 9,000 people in the United States. People with Rett syndrome may live into adulthood but often require constant care. They have an increased risk of sudden death due to heart irregularities.[1]

Role in treatment:
There are currently no FDA-approved therapies for Rett syndrome. Treatment consists of providing support and helping with symptoms. Trofinetide is designed to treat the symptoms of Rett syndrome by potentially reducing neuroinflammation and supporting nerve cell function.

Efficacy:
The submission was supported by results from the phase 3 LAVENDER clinical trial, which evaluated trofinetide versus placebo in 187 girls and women age 5 to 20 years. The coprimary endpoints included a caregiver assessment of core symptom change from baseline to 12 weeks and a global physician assessment of worsening or improving disease. Trofinetide demonstrated a statistically significant improvement over placebo on these endpoints. Subjects who completed this trial could choose to continue to receive trofinetide in two extension trials.

Safety:
The most common adverse events in the clinical trial were diarrhea (80.6% with trofinetide versus 19.1% with placebo) and vomiting (26.9% with trofinetide versus 9.6% with placebo). Treatment discontinuation rates were 17.2% in the trofinetide group and 2.1% in the placebo group.

Financial impact:
The current pipeline for Rett syndrome, including trofinetide, primarily consists of therapies to control symptoms. A disease-modifying therapy would be beneficial. However, the rarity of the disease has limited drug development. It is estimated that approximately 16,000 people will be affected by Rett syndrome by 2031 in the U.S., United Kingdom, and Europe.[2] Peak sales of $500 million are estimated for Rett syndrome in the U.S. market.[3]

CarelonRx view:
Trofinetide would be the first FDA-approved treatment for Rett syndrome. Effects on treatment adherence due to diarrhea and vomiting may be a concern. Long-term safety and efficacy trials are ongoing. Trofinetide is also being studied in other developmental disorders such as Fragile X syndrome.

Product:
Trofinetide

Indication:
Rett syndrome

Estimated FDA approval:
March 2023

Therapeutic class:
Synthetic tripeptide analog

Route of administration:
Oral

FDA designations:
Fast Track; Orphan; Priority

Manufacturer:
Acadia Pharmaceuticals

DELANDISTROGENE MOXEPARVOVEC

Condition:
Duchenne muscular dystrophy (DMD) is a rare neuromuscular disease characterized by muscle weakness with symptom onset before age 5 years. Affecting approximately 10,000 to 12,000 people, primarily males, in the U.S., DMD is caused by mutations in the gene responsible for making the dystrophin protein required for healthy muscle development. Muscle weakness in the heart and lungs often leads to an early death (in their 20s) for those with DMD.

Role in treatment:
Oral steroids are used as the backbone of treatment for DMD. In addition to steroids, exon-skipping agents Amondys 45, Exondys 51®, Viltepso™, and Vyondys 53 are available for people with a mutation amenable or responsive to each therapy. Exon-skipping agents were FDA-approved using an accelerated pathway based on an increased level of dystrophin found in muscle tissue. However, continued FDA approval may be contingent upon verification of a clinical benefit in trials.

Similarly, Sarepta Therapeutics has filed for approval using an accelerated pathway based on increased level of dystrophin in those given therapy. If approved, delandistrogene will introduce the first option for a one-time gene therapy infusion with the goal of inserting the micro-dystrophin gene into muscle cells, which will produce micro-dystrophin protein, a shortened version of dystrophin believed to be critical for muscle function.[4]

Efficacy:
The submission was supported by results from three early phase trials which evaluated delandistrogene in boys with DMD mostly between age 4 to 7 years. In a combined one-year analysis of these trials, boys who were given a single infusion of delandistrogene at the targeted dose showed a statistically significant improvement, 2.4 points out of 34 points, on the North Star Ambulatory Assessment (NSAA) compared to a pooled external control group which did not receive this treatment. A clinically meaningful difference results from approximately a 10-point change in the NSAA score.[5] Importantly, when results from these three trials were evaluated individually, results were inconsistent. In fact, one of these three trials that had a placebo-controlled arm found statistically increased micro-dystrophin levels 12 weeks after dosing, but boys treated did not achieve statistically superior improvement in the NSAA compared to the placebo arm one year after treatment. A phase 3, placebo-controlled, confirmatory trial, EMBARK, is fully enrolled and evaluating ambulatory boys with DMD age 4 to 7 years. The results of EMBARK will be key to understanding delandistrogene's potential role in therapy. Primary study results are expected in October 2023, with final results in November 2024.

Product:
Delandistrogene moxeparvovec (also known as SRP-9001)

Indication:
Treat ambulant patients with Duchenne muscular dystrophy

Estimated FDA approval:
May 2023

Therapeutic class:
Gene therapy

Route of administration:
Intravenous (IV) infusion

FDA designations:
Fast Track; Rare Pediatric Disease; Orphan

Manufacturer:
Sarepta Therapeutics

DELANDISTROGENE MOXEPARVOVEC

Continued

Safety:
The most common adverse events in trials were vomiting and transient liver enzyme elevations, which were managed with steroids. Serious adverse events, including inflammation affecting the heart and skeletal muscles, have occurred. As with many gene therapies, the risk of developing cancer remains a potential concern.

Financial impact:
The cost of delandistrogene is unknown. If approved, analysts anticipate it could reach peak year sales of $2 billion in the U.S.[2] While delandistrogene has potential to be the first gene therapy approved for DMD, a second micro-dystrophin gene therapy in development could create competition as soon as 2024.

CarelonRx view:
Delandistrogene could become the first gene therapy approved for DMD. It remains unclear if the micro-dystrophin gene being delivered by delandistrogene will cure or potentially lessen the disease severity in boys with DMD. The pivotal Phase 3 EMBARK trial results are essential to understanding how this micro-dystrophin protein affects clinical endpoints such as ambulation. Like other gene therapies, the durability of effect of delandistrogene remains unknown. Because delandistrogene is being studied in boys with several different DMD mutations, it is also unclear if delandistrogene will replace the exon-skipping agents or, in practice, be used in combination.

Product:
Delandistrogene moxeparvovec (also known as SRP-9001)

Indication:
Treat ambulant patients with Duchenne muscular dystrophy

Estimated FDA approval:
May 2023

Therapeutic class:
Gene therapy

Route of administration:
Intravenous (IV) infusion

FDA designations:
Fast Track; Rare Pediatric Disease; Orphan

Manufacturer:
Sarepta Therapeutics

RITLECITINIB

Condition:
Alopecia areata is a condition where a person's immune system attacks their hair follicles, which results in hair loss. Severity and duration of hair loss vary from person to person, with severe disease affecting more than 300,000 people in the U.S. each year.

Role in treatment:
If approved, ritlecitinib would become the second FDA-approved agent to treat people with alopecia areata and the first dual inhibitor of the TEC family of tyrosine kinases and of Janus kinase 3 (JAK3). Olumiant®, an oral JAK inhibitor, is currently FDA-approved to treat adults with severe alopecia areata. For those with mild disease, hair often grows back without any treatment.

Efficacy:
The ALLEGRO pivotal trial evaluated people age 12 years and older with 50% or more scalp hair loss at baseline, who were experiencing a current episode of alopecia areata lasting at least six months. After six months of treatment, a statistically significant number of people treated with the higher doses of ritlecitinib had 80% or more of their scalp covered with hair compared to placebo treatment. The FDA filing was also supported by an ongoing phase 3, open-label trial in adults with 25% or greater hair loss and adolescents age 12 years and older with 50% or greater hair loss at baseline.

Safety:
JAK inhibitors, like Olumiant, carry serious warnings in their FDA labels to communicate potential risks with their use. Examples of such risks include cardiovascular adverse events, infections, and cancer. It is unclear if ritlecitinib will carry similar warnings. The most common adverse events in ritlecitinib trials were headache, nasopharyngitis, and upper respiratory tract infections. Importantly, there were also two cases of breast cancer, one pulmonary embolism, and a handful of shingles cases in trials. No deaths or cardiac events have been reported through 48 weeks of treatment.

Financial impact:
The cost of ritlecitinib is unknown. Olumiant costs between $30,000 and $60,000 per year depending on the dosage needed to treat people with alopecia areata.[6]

CarelonRx view:
With a slightly differentiated mechanism of action, the dual inhibitor ritlecitinib could become the second FDA-approved oral JAK inhibitor approved for alopecia areata. Olumiant, the JAK inhibitor currently approved, is indicated for adults with alopecia areata. Because ritlecitinib is being studied in adolescents and adults, ritlecitinib could offer the first FDA-approved option for adolescents if it is approved. It is unclear if ritlecitinib will receive a broader indication than Olumiant or if it will also be limited to those with severe disease. It also remains unknown if ritlecitinib will carry the same FDA-labeled warnings as other JAK inhibitors. The final label may help to further differentiate it from Olumiant.

Product:
Ritlecitinib

Indication:
Treatment of people age 12 years and older with alopecia areata

Estimated FDA approval:
Second quarter 2023

Therapeutic class:
Dual kinase inhibitor that has high selectivity for Janus kinase 3 (JAK3) and members of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family

Route of administration:
Oral

FDA designations:
Breakthrough Therapy

Manufacturer:
Pfizer

Other significant product approvals

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

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

Drug or biologic Manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Lamazym (velmanase alfa) Chiesi Farmaceutici	Alpha-mannosidosis/IV	**Addition to class:** will be first FDA-approved treatment for this indication	First half of 2023	
Zavegepant Biohaven	Migraine treatment/ intranasal	**Addition to class:** first intranasal calcitonin CGRP receptor antagonist	First quarter 2023	
Trofinetide Acadia	Rett syndrome/oral	**First in class:** will be first FDA-approved treatment for this indication	3/29/2023	
Leniolisib Pharming	Activated phosphoinositide 3-kinase delta syndrome/IV	**Addition to class:** will be first FDA-approved treatment for this indication	3/29/2023	
Roctavian™ (valoctocogene roxaparvovec) BioMarin	Hemophilia/IV	**First in class:** will be first gene therapy FDA-approved for hemophilia A; questions remain on durability of effect	3/31/2023	
Tofersen Biogen	Amyotrophic lateral sclerosis/intrathecal	**Addition to class:** ASO for people with ALS with SOD1 gene mutations	4/25/2023	
Mirikizumab Eli Lilly	Ulcerative colitis/IV; SC	**Addition to class:** interleukin-23 antagonist; for use after failing other biologics	4/28/2023	

** Key

ALS: amyotrophic lateral sclerosis

ASO: antisense oligonucleotide

BCG: Bacillus Calmette-Guérin

CGRP: gene-related peptide

DMD: Duchenne muscular dystrophy

IV: intravenous

SC: subcutaneous

SOD1: superoxide dismutase 1

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 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)

Nogapendekin alfa inbakicept ImmunityBio	Bladder cancer/ intravesical	**First in class:** another option for individuals unresponsive to BCG	5/23/2023	
SRP-9001 (delandistrogene moxeparvovec) Sarepta	Duchenne muscular dystrophy/IV	**First in class:** will be first gene therapy for DMD	5/29/2023	
Zynquista™ (sotagliflozin) Lexicon	Heart failure in diabetes, reduced and preserved ejection fraction/oral	**Addition to class:** will compete with Jardiance® and Farxiga® in heart failure	5/31/2023	
Vamorolone Santhera Pharmaceuticals	Duchenne muscular dystrophy/oral	**Addition to class:** potential for better safety profile; will compete with Emflaza® and prednisone	Mid-2023	
Momelotinib Sierra Oncology	Myelofibrosis/oral	**Addition to class:** targets similar population to Vonjo®	6/16/2023	
NovaTears (perfluorohexyloctane) Bausch Health	Dry eyes/ophthalmic	**First in class:** preservative-free eye lubricant and tear film stabilizer	6/28/2023	
Ritlecitinib Pfizer	Alopecia areata/ oral	**Addition to class:** will compete with Olumiant®; also seeking approval for adolescents	6/30/2023	
Lotilaner Tarsus Pharmaceuticals	Dermodex blepharitis/ ophthalmic	**Addition to class:** will be first FDA-approved treatment for this indication	9/7/2023	
CTX001 (exa-cel) Vertex/CRISPR Therapeutics	Sickle cell disease/IV	**First in class:** first gene therapy for sickle cell disease; also under review for beta-thalassemia	2023	

*As of November 30, 2022

Currently, 39 biosimilars are FDA-approved in the United States, including four that were approved in the second half of 2022: Vegzelma® (bevacizumab-adcd), Stimufend® (pegfilgrastim-fpgk), Cimerli™ (ranibizumab-eqrn), and Idacio® (adalimumab-aacf).

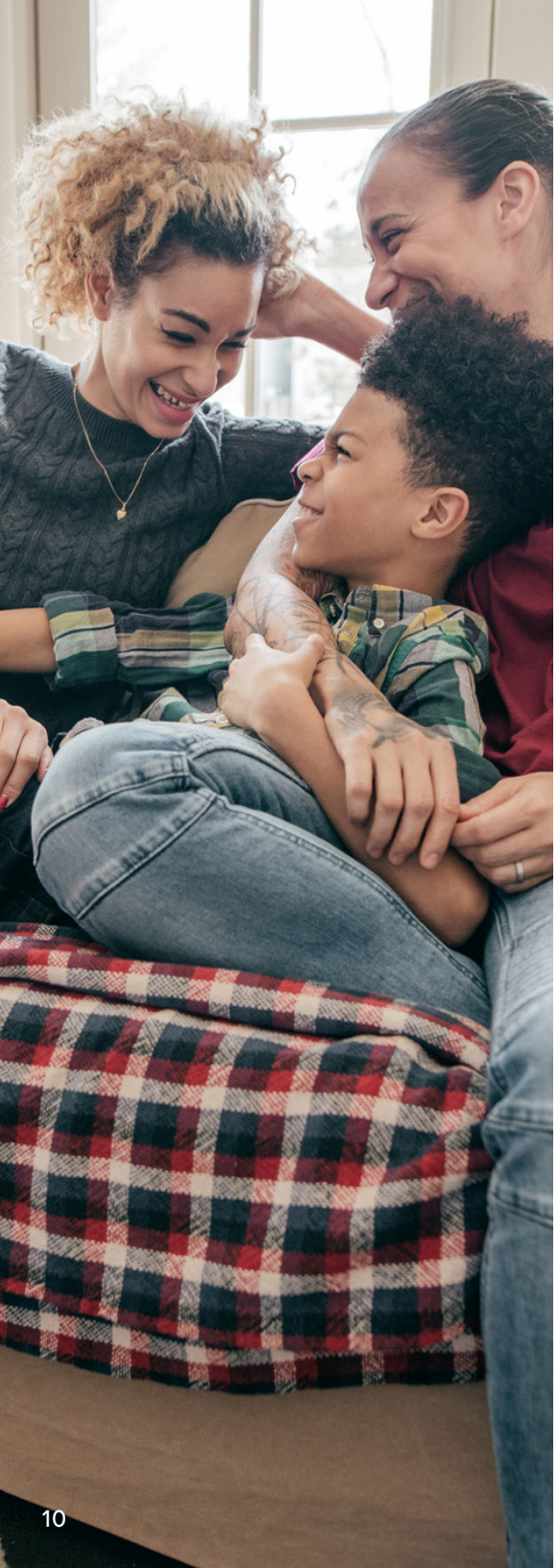
Biosimilars are highly similar to their reference product in terms of structure and function and lack clinically meaningful differences in terms of safety and efficacy. Biosimilars may be approved for all or some of the reference products indications due to patent exclusivity. Prescriptions for biosimilars need to be written for the biosimilar by name. Biosimilars that are granted interchangeability may be allowed to be substituted at the pharmacy level without the intervention of the prescriber. Currently, products that have been granted interchangeability status include Semglee™ and Rezvoglar™, biosimilars to Lantus® (insulin glargine); Cimerli™, biosimilar to Lucentis® (ranibizumab); and Cyltezo®, biosimilar to Humira® (adalimumab).

The FDA announced in March 2020 that insulins would be redefined as biologics. This allows them to go through a regulatory pathway that will better facilitate their development and serve as reference products for biosimilars. Semglee was the first approved biosimilar to Lantus.

Biosimilar pipeline update

Biosimilar products awaiting launch

Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval*
Actemra® (IV and SC)	Roche; Chugai; Genentech	MSB11456	Fresenius	Pending
Actemra (IV and SC)	Roche; Chugai; Genentech	BAT1806	Bio-Thera Solutions, Biogen	Pending
Avastin®	Genentech, Roche	Bmab-100	Biocon, Mylan	Pending
Avastin	Genentech, Roche	SB8	Samsung, Merck	Pending
Avastin	Genentech, Roche	FKB238	Centus, AstraZeneca	Pending
Avastin	Genentech, Roche	BAT1706	Bio-Thera	Pending
Avastin	Genentech, Roche	Vegzelma (CT-P16)	Celltrion	9/27/2022
Enbrel®	Amgen	Erelzi®	Sandoz	8/30/2016
Enbrel	Amgen	Eticovo™	Samsung	4/25/2019
Eylea®	Regeneron	MYL-1701P	Mylan, Momenta	Pending
Herceptin®	Genentech, Roche	EG12014	EirGenix, Sandoz	Pending
Humira® (100 mg/mL)	AbbVie	Hadlima HC™	Samsung, Merck	8/15/2022



Biosimilar products awaiting launch (continued)

Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval*
Humira® (100 mg/mL)	AbbVie	Yuflyma™	Celltrion	Pending
Humira (100 mg/mL)	AbbVie	AVT02	Alvotech, Teva	Pending; seeking interchangeability
Humira (100 mg/mL)	AbbVie	Hyrimoz HCF™	Sandoz	Pending
Humira (50 mg/mL)	AbbVie	Abrilada™	Pfizer	11/15/2019; seeking interchangeability
Humira (50 mg/mL)	AbbVie	Amjevita™	Amgen	9/23/2016
Humira (50 mg/mL)	AbbVie	Cyltezo™	BI	8/25/2017; interchangeable
Humira (50 mg/mL)	AbbVie	Hadlima™	Samsung, Merck	7/23/2019
Humira (50 mg/mL)	AbbVie	Hulio®	Fujifilm, Mylan	7/6/2020
Humira (50 mg/mL)	AbbVie	Hyrimoz™	Sandoz	10/30/2018
Humira (50 mg/mL)	AbbVie	Yusimry™	Coherus	12/17/2021
Humira (50 mg/mL)	AbbVie	Idacio	Fresenius	12/13/2022
Lantus Solostar®	Sanofi	Rezvoglar™	Eli Lilly	12/17/2021; interchangeable

Biosimilar products awaiting launch (continued)

Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval*
Neulasta®	Amgen	Fylnetra® (TPI-120)	Adello Biologics, Kashiv	5/26/2022
Neulasta	Amgen	Stimufend® (MSB11455)	Fresenius, Dr. Reddy	9/1/2022
Neulasta	Amgen	Lapelga Neupeg®	Apotex, Accord	Pending
Neulasta	Amgen	Lupifil-P™	Lupin	Pending
Neupogen®	Amgen	Grastofil®	Apotex, Accord	Pending
Neupogen	Amgen	TX01	Tanvex	Pending
Remicade®	Janssen	Ixifi PF™	Pfizer	12/13/2017
Stelara® (IV and SC)	Janssen	ABP 654	Amgen	Pending
Stelara (IV and SC)	Janssen	AVT04	Alvotech, Teva, Alvogen	Pending
Tysabri®	Biogen	PB006	Polpharma, Sandoz	Pending

*Excludes biosimilars that are FDA-approved and have launched.

Gene therapies in the pipeline

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

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

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

Gene therapy	Indication/route*	Expected use	Place in therapy*	Estimated approval date
Beremagene geperpavec (B-VEC) Krystal Biotech	Epidermolysis bullosa/topical gel	Once weekly application to wound(s)	First localized gene-based wound therapeutic for people age 1 year or older with EB	2/17/2023
Roctavian (valoctogene roxaparvovec) BioMarin	Hemophilia A/IV	One-time dose; potentially curative; however, in ongoing studies, factor levels have declined over time, introducing doubt in durability of effect	First gene therapy for this indication; will compete with FVIII products and Hemlibra®	3/31/2023 (potential for three-month delay)
Delandistrogene moxeparvovec (SRP-9001) Sarepta and Roche	Duchenne muscular dystrophy/IV	One-time dose; potentially curative	First gene therapy for this indication; will compete with Exondys 51, Vyondys 53, and Emflaza®	5/29/2023
Exagamglogene autotemcel (exa-cel; formerly CTX001) Vertex and CRISPR Therapeutics	Beta-thalassemia anemia/IV Sickle cell anemia/IV	One-time dose; potentially curative	Second gene therapy for this indication; will compete with Zynteglo First gene therapy for this indication; will compete with HCT and chronic RBC transfusions	2023

** Key

EB: epidermolysis bullosa

FVIII: factor 8

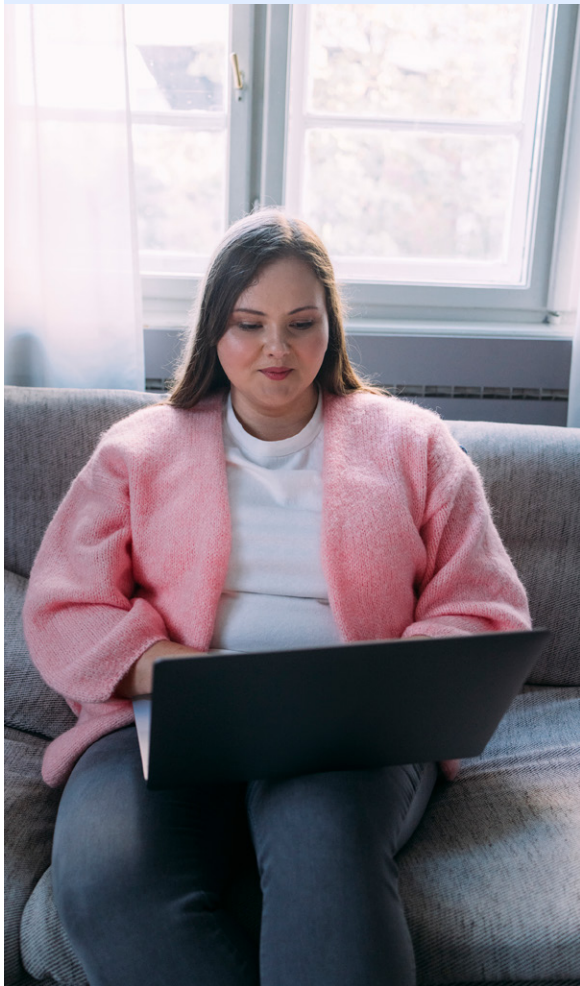
FIX: factor 9

HCT: hematopoietic cell transplantation

IV: intravenous

NMIBC: non-muscle invasive bladder cancer

RBC: red blood cell



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

Gene therapy	Indication/route*	Expected use	Place in therapy*	Estimated approval date
Lovotibeglogene autotemcel; lovo-cel (formerly LentiGlobin) bluebird bio	Sickle cell anemia/IV	One-time dose; potentially curative	Competing to be first gene therapy for this indication; will compete with HCT and chronic RBC transfusions	2023 to 2024 (plans to file 1Q23)
RP-L201 Rocket Pharmaceuticals	Leukocyte adhesion deficiency-I/IV	One-time dose; potentially curative	First gene therapy for this indication	2023 to 2024 (plans to file 1H23)
D-Fi (FCX-007; dabocemagene autoficel) Castle Creek Biosciences	Epidermolysis bullosa/autologous, gene-modified skin grafts	Multiple intradermal treatments to wound(s)	Competing to be second localized gene-based wound therapeutic for people age 2 years or older with EB	2023+
EB-101 Abeona Therapeutics	Epidermolysis bullosa/autologous, gene-modified skin grafts	One-time surgically placed skin graft to wound(s)	Competing to be second localized gene-based wound therapeutic for people age 6 years or older with EB	2023+
OTL-200 Orchard Therapeutics	Metachromatic leukodystrophy/IV	One-time dose; potentially curative	First gene therapy for this indication; will compete with HCT	2023 (plans to file early 2023)
Eladocagene exuparvovec (PTC-AADC; AGIL-AADC) PTC Therapeutics	Aromatic L-amino acid decarboxylase deficiency/ intracerebral	One-time dose; potentially curative	First gene therapy for this indication	2023 (plans to file 2023)
ABO-101 Abeona Therapeutics	Mucopolysaccharidosis IIIA (Sanfilippo Type B) /IV	One-time dose; potentially curative	First gene therapy for this indication; will compete with HCT	2023+
ABO-102 Abeona Therapeutics	Mucopolysaccharidosis IIIA (Sanfilippo Type A) /IV	One-time dose; potentially curative	Competing to be first gene therapy for this indication; will compete with HCT	2023+

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

Gene therapy	Indication/route*	Expected use	Place in therapy*	Estimated approval date
OTL-201 Orchard	Mucopolysaccharidosis IIIA (Sanfilippo Type A) /IV	One-time dose; potentially curative	Competing to be first gene therapy for this indication; will compete with HCT	2023+
Engensis (donaperminogene seltoplasmid) Helixmith	Diabetic foot ulcers/ intramuscular Diabetic peripheral neuropathy/ intramuscular	Multiple injections	First gene-based therapeutic for these indications	2023+
Fidanacogene elaparvovec (PF-06838435) Pfizer	Hemophilia B/IV	One-time dose; potentially curative	Second gene therapy for this indication; potential to compete with Hemgenix and with FIX products	2023+
TAVO (tavokinogene telseplasmid) OncoSec Medical	Advanced melanoma/ intratumoral	Administered on days 1, 5, and 8 every 6 weeks	First gene-based therapeutic for this indication; used in combination with Keytruda®	2023+ (potential to file with accelerated pathway)
RP-L102 Rocket Pharmaceuticals	Fanconi anemia (FA) /IV	One-time dose; potentially curative	First gene therapy for this indication	2023+

†As of November 30, 2022

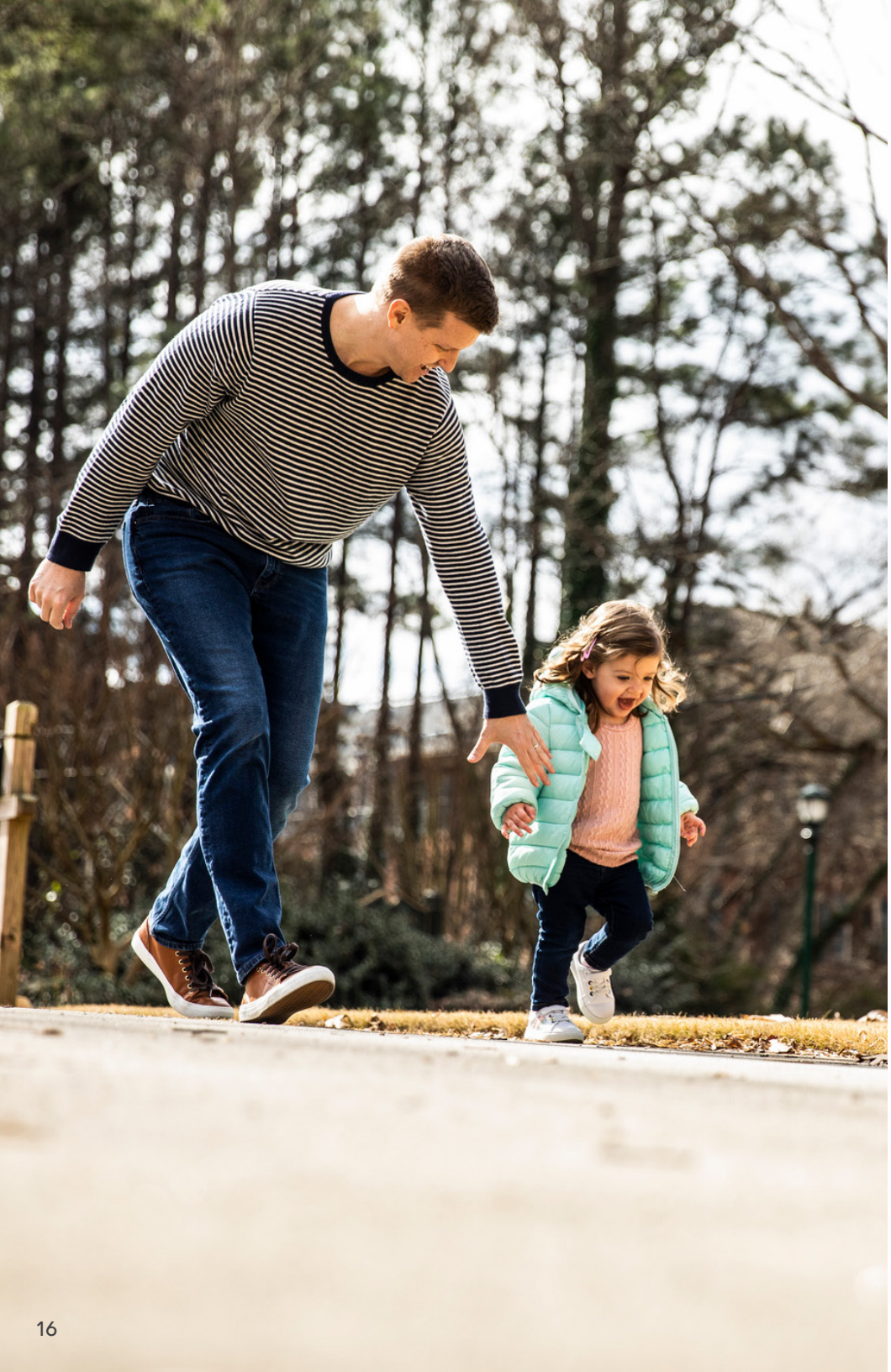
Analysis: Food and Drug Administration (FDA)/National Institutes of Health (NIH) partnership for rare neurodegenerative diseases

The FDA and NIH recently launched a new partnership called the Critical Path for Rare Neurodegenerative Diseases (CP-RND). The Critical Path Institute (C-Path) will be used to bring experts together to address issues and identify opportunities related to the treatment of neurodegenerative disease. The C-Path is an independent non-profit, public-private partnership with the FDA that aims to bring collaboration across public and private sectors.[7]

The goal of this partnership is to identify solutions to facilitate development of therapies. Some of these solutions may include characterizing the natural history of a disease or identifying molecular targets for treatment and diagnosis. The CP-RND will also encourage the use of the Rare Diseases Cures Accelerator-Data and Analytics Platform (RDCA-DAP). This FDA-funded initiative allows sharing of data and encourages standardization of new data collection.[8]

The Accelerating Access to Critical Therapies for Amyotrophic Lateral Sclerosis Act (Act for ALS) was signed into law in December 2021. The FDA released an action plan in June 2022 that included a five-year strategy for advancing therapies for ALS and improving access to ALS therapies. The CP-RND partnership is a key component of this plan.

Neurodegenerative diseases are progressive conditions that affect the nervous system and are often fatal. An unmet need exists to develop new treatments that can improve lives and extend survival of people with rare neurodegenerative diseases. The FDA/NIH partnership aims to provide needed breakthroughs in this area.



Market Trends

FDA advisory committee meetings

The FDA reviews many drugs and biologics every year. The agency sometimes relies on an advisory committee to provide input on whether a product is safe and effective. Committees are made up of independent scientific experts and members of the public, including patient representatives. An advisory committee will give the FDA recommendations regarding a potential drug or biologic approval.

Federal advisory committees are regulated by the Federal Advisory Committee Act (FACA). It states that the committee be used to give advice or recommendations and that it should not be made up entirely of government employees. Interested people can share their opinions on a drug or biologic through open public hearings or by submitting comments.

Advisory committee meetings can happen at any point during the review process or after a product has been approved and marketed if questions on safety or efficacy arise.

There were fewer advisory committee meetings for new agents held in 2021 compared with earlier years. In fact, these meetings have been steadily declining even as the number of new drugs and biologics has been increasing.[9] In 2010, over 50% of the agents approved had been reviewed by an advisory committee. By 2021, only 6% had been reviewed.[10] The FDA can decide whether an advisory committee is needed.

The FDA is not required to follow an advisory committee recommendation. Since 2010, the FDA has approved a drug or biologic after a negative recommendation about once a year. One recent example is the approval of Aduhelm™ (aducanumab) for the treatment of Alzheimer's disease. Controversy surrounded whether the FDA approved Aduhelm with sufficient evidence of efficacy.

There are sometimes questions regarding why the FDA decides not to hold an advisory committee meeting. The FDA is required to provide the reasons for not holding a meeting, but this often only consists of stating that there were no important efficacy or safety issues. In addition, there are no guidelines for what questions the FDA should ask an advisory committee. An example of this is that the FDA gave Aduhelm accelerated approval, but the advisory committee was not asked to vote on that potential outcome.[10]

Although advisory committees are valuable, issues remain. According to a recent perspective article in the *New England Journal of Medicine*, consistency and minimum requirements are needed to improve transparency and trust. A few suggestions include:[10]

- Guidance explaining how the FDA decides to hold advisory committee meetings
- Commitment to holding meetings for certain types of decisions such as accelerated approvals
- Release of questions in advance
- Standardized questions
- Procedure to publicly explain regulatory decisions that disagree with advisory committee recommendations

Oral anticoagulant prescribing

Anticoagulants are used to treat or prevent blood from clotting in conditions such as atrial fibrillation, hip or knee replacement, or thrombosis. They can prevent life-threatening conditions such as stroke, heart attack, or clots to the lungs.

The oral anticoagulants include warfarin, Eliquis® (apixaban), Pradaxa® (dabigatran), Savaysa® (edoxaban), and Xarelto® (rivaroxaban). Considering efficacy and safety is important to help select the optimal anticoagulant for patients.

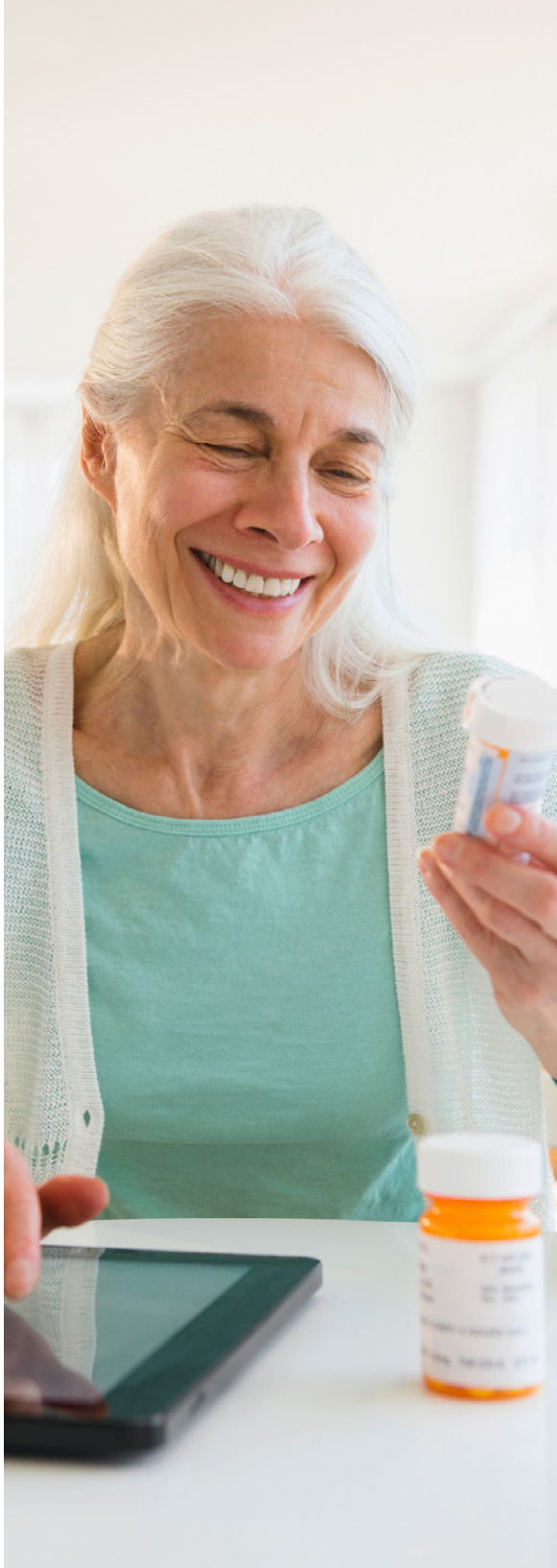
Warfarin has been studied against Eliquis, Pradaxa, Savaysa, and Xarelto in separate atrial fibrillation clinical trials. Differences among the trials makes it difficult to compare the results.

- Eliquis or Pradaxa were superior to warfarin, and Savaysa or Xarelto were non-inferior to warfarin in preventing stroke or systemic clotting.
- Eliquis or Savaysa were superior or caused less major bleeding than warfarin.
- Pradaxa or Xarelto were not statistically significantly different from warfarin for major bleeding.

Warfarin has also been studied against Eliquis, Pradaxa, Savaysa, and Xarelto in separate clinical trials for deep vein thrombosis. Differences among the trials makes it difficult to compare the results.

- All the agents were non-inferior to warfarin in preventing symptomatic clotting.
- Eliquis was superior or caused less major bleeding than warfarin.
- Pradaxa, Savaysa, and Xarelto were not statistically significantly different from warfarin for major bleeding.

Warfarin increases the risk of bleeding, requires monitoring of international normalized ratio (INR) to individualize the dosage needed, and interacts with many medications. Additionally, some dietary changes need to be implemented, like avoiding vitamin K-rich foods. There are, however, situations when a prescriber would choose warfarin over other oral anticoagulants.

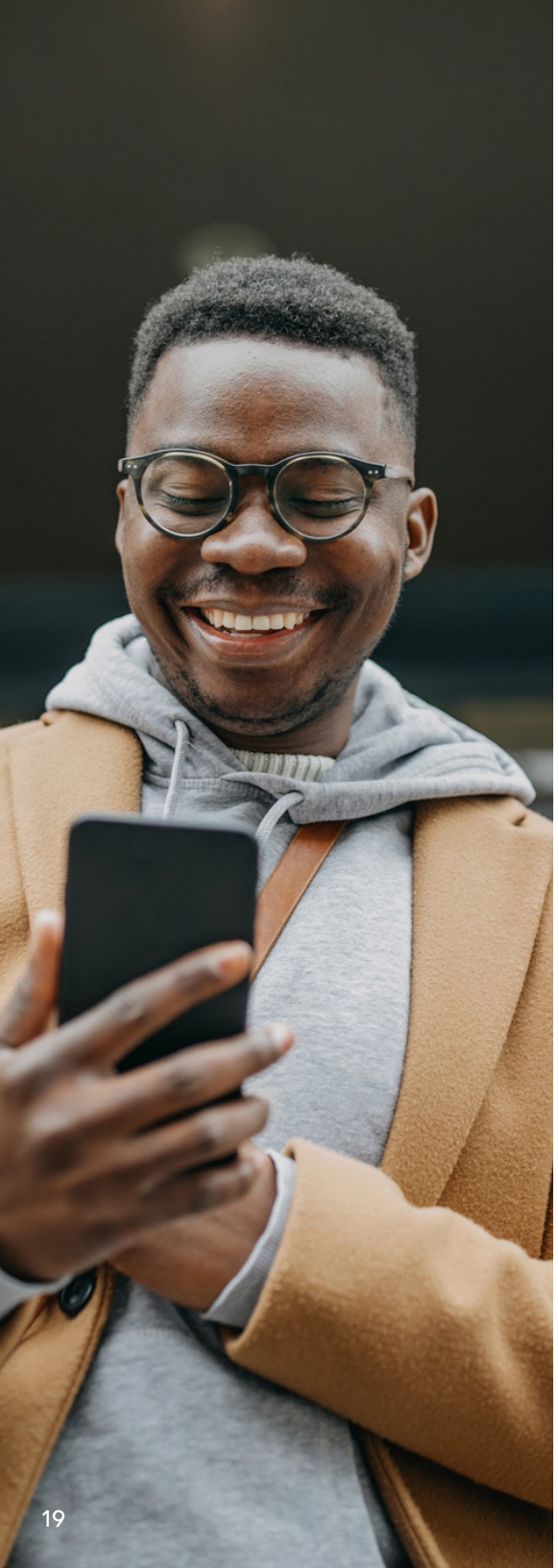


Select conditions favoring warfarin use[11,12]

Condition	Reason
Rheumatic mitral stenosis requiring anticoagulation[13]	• In INVICTUS trial, rates of death and stroke were lower with warfarin compared to Xarelto.
Mechanical heart valve[14]	• Pradaxa is contraindicated; in RE-ALIGN trial, warfarin had lower thrombotic risk and bleeding than Pradaxa. • Other oral anticoagulants have not been studied.
Creatinine clearance (CrCl) <15 mL/min requiring anticoagulation[15]	• INR monitored more frequently to maintain appropriate warfarin dose. • Pradaxa, Savaysa, and Xarelto have not been studied in CrCl <15 mL/min. • Limited data for Eliquis.
Liver disease	• Warfarin is recommended in severe hepatic impairment (Child-Pugh C) (limited data). • Other oral anticoagulants are not recommended for Child-Pugh C.

Other factors that affect the selection of an anticoagulant

Factor	Discussion
INR monitoring	• Warfarin requires INR monitoring. • Is INR monitoring feasible either through clinic or home test meter? • Will the person comply with testing and adjustments for optimal therapy?
Adherence	• Will the person take the medicine as prescribed? • Oral anticoagulants are not recommended for people who will not adhere to and continue therapy.
Pregnancy	• Warfarin can cause birth defects. • Other oral anticoagulants have not been studied in pregnancy. • Injectable anticoagulants or low-dose aspirin is often used.
Dyspepsia or gastrointestinal bleeding	• Use warfarin or Eliquis. • GI bleeding increased with Pradaxa, Savaysa, and Xarelto.
Cost[6]	• Warfarin offers a low-cost alternative as a generic agent with long history of use. It may be a clinically appropriate and cost-effective option for some individuals.



Reversal agents

Reversal agents are available to counteract the anticoagulant effects if there is life-threatening or uncontrolled bleeding.

- Andexxa® (coagulation factor Xa recomb inact-zhzo [andexanet alfa]) injection for Eliquis or Xarelto. Andexxa is not currently approved to reverse the effects of Savaysa and enoxaparin, but is being studied for this use.
- Praxbind® (idarucizumab) injection for Pradaxa.
- Kcentra® (prothrombin complex concentrate human) injection for warfarin.

Anticoagulant pipeline

The pipeline for anticoagulants includes new mechanisms of action and a new warfarin-like product with potentially fewer drug interactions. It is unclear if any of these agents in phase 3 development are substantial improvements over currently available agents.

Drug	Mechanism of action	Potential advantages
Abelacimab	• Dual-acting fully human monoclonal antibody targeting both Factor XI and Factor XIa with high affinity and selectivity	• New action targeting Factor XI and Factor XIa • Rapid onset intravenous (IV) anticoagulant for inpatient use, with a subcutaneous (SC) formulation for ongoing use
Asundexian	• Orally administered FXIa inhibitor	• New action targeting Factor XIa to prevent clots
Tecarfarin	• Vitamin K antagonist, similar to warfarin	• Potentially safer than warfarin due to fewer drug interactions with different clearance route

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