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Allies in Rare Disease

A Call for Rational Flexibility

> **"A number of people said, 'Just find more patients.' And a number of times I've had to explain this is a completely ultra-rare condition. There's no such thing as just finding more patients. They don't exist. It's been that kind of discussion that has been incredibly frustrating."**
>
> — HILLARY VERNON, ATTENDING PHYSICIAN AT KENNEDY KRIEGER INSTITUTE AND THE PRINCIPAL INVESTIGATOR ON STEALTH BIOTHERAPEUTICS' BARTH SYNDROME CLINICAL TRIAL

Jamie Dibuque traveled from her home in Arizona to visit family in New Jersey for the holidays in December 2022 when she became concerned that her 11-month-old son Declan was refusing to eat solids. He was still breastfeeding, but he seemed to be growing weaker and she called a pediatric telehealth service that she uses, which suggested she take him to an urgent care center for a glucose test. The urgent care center didn't bother with the test and told Dibuque that Declan was dehydrated and needed to get to the emergency room at nearby Jersey Shore University Medical Center in Neptune City, New Jersey.

At the ER, Dibuque was made to wait as other patients were given priority. Dehydration wasn't a reason to push you to the head of the line in an emergency room. Realizing Declan's condition was growing worse, Dibuque finally lifted him in her arms and went back to the triage area and said, "Look at my kid! Something is seriously wrong."

It was then that doctors took Declan from her arms and rushed him to the back. Dibuque didn't know it at the time, but Declan was in heart failure and would suffer a cardiac arrest. Doctors transported him to Ocean University Medical Center, a larger hospital in Brick

Jamie and Declan Dibuque

Township, New Jersey that was able to stabilize him, but they too had limited resources. Once stabilized, he was transferred by helicopter to Children's Hospital of Philadelphia (CHOP). Genetic testing diagnosed him with Barth syndrome, a rare, mitochondrial disease. Declan is one of about 130 people in the United States known to have the condition. He was placed on heart-lung machine and would likely need a heart transplant. Surgeons later implanted a ventricular assist device to do the work his heart was unable to do.

Amy Goldstein, director of the division of genetics and metabolism at CHOP, was one of the few doctors in the country who had access to elamipretide, an experimental drug that was the subject of a clinical trial. Elamipretide is a peptide that targets the inner mitochondrial membrane where it binds to cardiolipin, which plays an essential role in energy conversion within cells. She suggested that they treat Declan with it. By August, Declan's condition had improved so much that doctors removed the ventricular assist device that they had implanted in him. There is no longer any thought that he will require a heart transplant. He's doubled in size and, except for an NG tube he still has in for feeding, he would appear to be a happy and healthy child.

But like other people with Barth syndrome who have benefited from elamipretide through a clinical trial or compassionate use, Dibuque fears Declan may lose access to the drug because the U.S. Food and Drug Administration doesn't believe Stealth Biotherapeutics, the developer of elamipretide, has studied the drug in an adequate number of patients for it to review it, let alone approve it. That's despite the fact that the principal investigator of the Stealth study believes she's screened every patient in North America that fits the clinical trial inclusion criteria. Even though Stealth filed for approval, the FDA told the company it would not consider its application. That has patients and their families worried about what will happen to them if they are unable to continue using elamipretide.

"This drug has given Declan a chance at a normal life and has allowed our family to move forward, not just move on to the next chapter of his experience with Barth syndrome, his life with Barth syndrome," said Dibuque. "It makes it hard for me to envision what his life is going

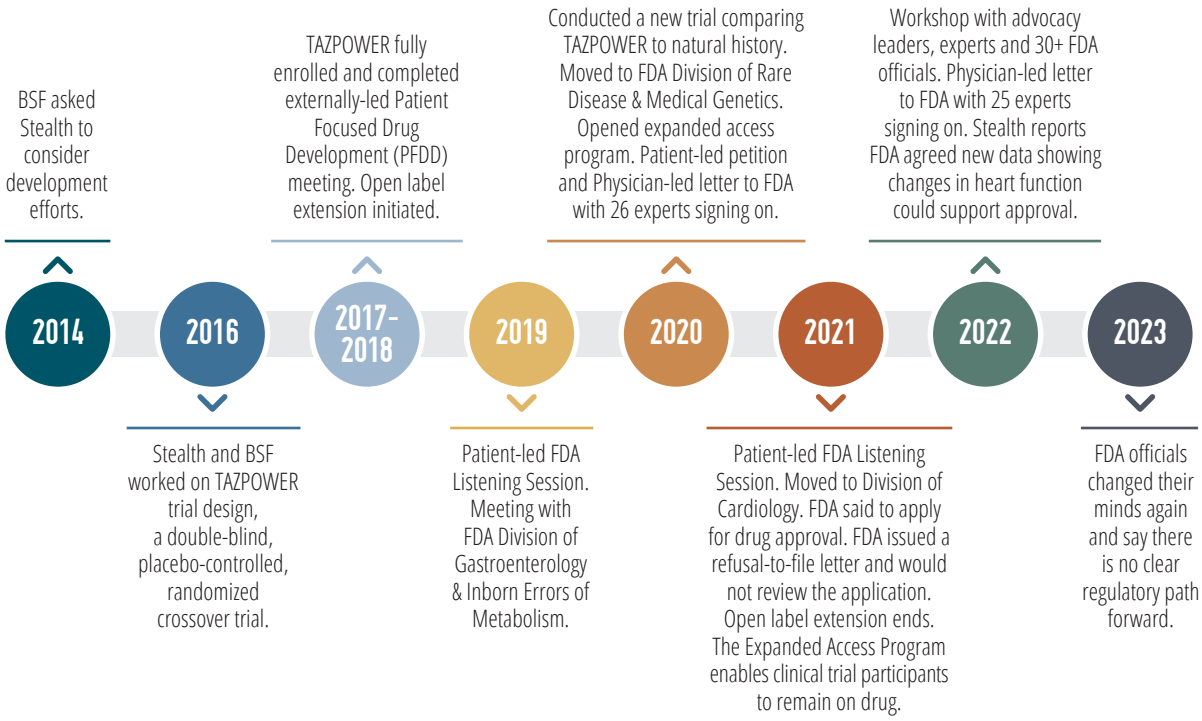
to be like if he ever has to come off of it. I had a glimpse of what it was like the first 11 months of his life. My son needs the drug. It's set him so far ahead of any expectations that any of the doctors had for him."

Balancing Evidence and Urgency

Elamipretide has traveled a tangled pathway through the FDA, but it is emblematic of the challenges therapies for ultra-rare diseases face in establishing adequate evidence of their efficacy to merit approval. At times, the agency has demonstrated flexibility and used tools, such as accelerated approval, to enable drugs to reach patients who need them while additional data is gathered to confirm what small trials may have suggested about their benefits. But there is particular concern over the inconsistency in the way the agency has approached therapies for ultra-rare diseases, with the fate of these medicines in part dependent on the particular division assigned to review a therapy. That also appears to have been exacerbated by a growing conservatism within the agency following the controversial decision to grant accelerated approval to the Alzheimer's drug Aduhelm over the negative recommendations of an advisory committee. The difficulties a number of companies have faced in recent years has alarmed drugmakers and patient advocates, who warn they could have a chilling effect on the willingness of drug companies to invest in the development of therapies for ultra-rare diseases.

Though the case of elamipretide and Stealth may seem jarring, it is by no means an isolated incident. The FDA in recent years has found itself at odds with developers of

Timeline of Stealth BioTherapeutics' Development of Elamipretide



Source: The Barth Syndrome Foundation

therapies to treat ultra-rare diseases, and the agency's insistence on studies that would provide what it would consider adequate proof of efficacy have resulted in long delays in the path to approval or caused companies to shelve promising programs in which patients had placed much hope.

In August 2021, Ipsen withdrew its application for approval for its experimental therapy palovarotene for the rare musculoskeletal condition fibrodysplasia ossificans progressive as the FDA wanted extensive additional analyses and evaluation of data from its phase 3 trial in people with the condition. Though it faced subsequent delays, it finally won FDA approval in August 2023.

Aeglea Biotherapeutics, which was developing the experimental therapy pegzilarginase to treat the ultra-rare metabolic disease arginase 1 deficiency, reported the therapy met its primary endpoint in a phase 3 study with a 76.7 percent reduction in mean plasma arginine compared to a placebo and that 90.5 percent of patients achieved normal plasma arginine levels. Nevertheless, the FDA in June 2022 refused to accept an application seeking approval for the drug. The agency wanted additional data to support effectiveness, such as evidence showing that plasma arginine and metabolite reduction predicts clinical benefit in patients with arginase 1 deficiency, or clinical data demonstrating a treatment effect on clinically meaningful outcomes. In July, the company announced that it had sold the drug to its development partner Immedica Pharma for $15 million and up to $100 million in contingent milestone payments.

> **"It's time for Califf and the FDA to fundamentally re-imagine how drugs for rare diseases are developed and remove needless obstacles that hinder clinical trials for them."**
>
> — JUDY STECKER

Taysha Gene Therapies, in September 2023, discontinued development of its lead experimental gene therapy for the ultra-rare neurodegenerative condition giant axonal neuropathy. In 2022, in an end-of-phase 2 meeting with the FDA, the agency told the company it needed to address the heterogeneity of disease progression in GAN and the use of the 32-item Motor Function Measure as a primary endpoint because it can be affected by the amount of effort a participant makes. In September 2023, following additional interactions with the agency, the company said it was discontinuing development of the therapy, known as TSHA-120, despite demonstrating its potential because of the feasibility of study designs that could support a path to approval. The agency had recommended a randomized, double-blind, placebo-controlled trial as the best way to demonstrate efficacy. When Taysha announced it was discontinuing the program it also said Astellas Gene Therapies had told the company it would not exercise its option to exclusively license the program.

Judy Stecker is a former deputy chief of staff for the Department of Health and Human Services and the mother of a young child with CLN3, a juvenile form of the ultra-rare and deadly neurodegenerative condition Batten disease. In February 2023, in an opinion piece in STAT News, she wrote about the drug miglustat, a generic drug that Theranexus and the Beyond Batten Disease Foundation are developing to treat CLN3 disease.

She noted that even though the drug is approved, private insurers and Medicaid will not cover its use for CLN3 because the FDA has not approved that indication. That means the $24,000 a month it would cost to treat her son Wheeler would be borne by her. She said the chances of getting coverage for this off-label use are "slim."

But the FDA's Division of Rare Diseases and Medical Genetics wanted a placebo-controlled trial before approving the use of the drug in CLN3. She said that's a huge obstacle and that it should be considered unethical to use a placebo in a progressive rare disease since it will

FDA Launches Pilot Program to Accelerate Development of Rare Disease Therapies

The U.S. Food and Drug Administration launched a pilot program aimed at accelerating the development of rare disease therapies by allowing for more frequent communication with agency staff to address clinical development issues.

"We hope the insight gained from this pilot will provide information on how best to facilitate more efficient development of potentially life-saving therapies with rare disease indications and help sponsors generate high-quality, compelling data to support a future marketing application," said Peter Marks, director of the FDA's Center for Biologics Evaluation and Research. "These are complex products, and we recognize the importance of sponsor communication with the FDA to facilitate development of products for patients with unmet medical needs."

> **"We recognize the importance of sponsor communication with the FDA to facilitate development of products for patients with unmet medical needs."**
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> — PETER MARKS

Selected participants of the Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program will be able to obtain frequent advice and regular ad-hoc communication with FDA staff to address product-specific development issues, including clinical study design, choice of control group, and fine-tuning the choice of patient population.

The program will be open to sponsors of products currently in clinical trials under an active Investigational New Drug application, regulated by either the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research. Eligibility criteria for the pilot differs between CBER and CDER-regulated products.

In addition to having an active IND, eligible CBER-regulated products must be a gene or cellular therapy intended to address an unmet medical need as a treatment for a rare disease or serious condition, which is likely to lead to significant disability or death within the first decade of life.

Under CDER's eligibility criteria, the product must be intended to treat rare neurodegenerative conditions, including those of rare genetic metabolic types.

The FDA will be accepting applications to the START program through March 1, 2024. Pilot participants will be selected based on application readiness. The agency will select up to three participants for each center.

likely result in irreversible harm and possibly death. She said a paradigm shift is needed at the FDA for people like Wheeler with rare diseases, particularly as FDA Commissioner Robert Califf has spoken about the essential role of patients in developing treatments.

"It's time for Califf and the FDA to fundamentally reimagine how drugs for rare diseases are developed and remove needless obstacles that hinder clinical trials for them," she wrote. "There is an urgent need to recommit to rational flexibility, not just for Wheeler but for so many others whose time is running out."[40]

Congress has given the FDA flexibility in the criteria used to approve a drug, in part because of recognition of the unmet needs for people with life-threatening rare diseases. A 2021 study in the *Annals of Internal Medicine* that reviewed 912 applications for FDA approval from 2013 to 2018 found that 117 went through multiple review cycles. Only 22 of those faced additional reviews because of issues related to clinical efficacy. Concerns about the endpoints used, the clinical meaningfulness of the observed effect, and inconsistent results were common bases for initial rejection. In seven of the 22 cases, the approval did not require new evidence but rather new interpretations of the original evidence. Perhaps most surprising, the authors found that none of the FDA decisions cited reasoning used in previous decisions.[41]

"The FDA does not have a tradition or structure to ensure consistency in its decisions," wrote Perrine Janiaud et al. "In the legal field, consistency of logic and reasoning across cases and jurisdictions is maintained through case law; arguments made by previous judges are used and cited by others, albeit in different contexts and with different evidence—exactly the FDA's situation."

The authors said that the FDA has weak structures to support institutional memory, particularly one that crosses FDA therapeutic areas, offices, or centers. Much

Industry Pushing for Legislative Fix to IRA's Rare Disease Impact

The Inflation Reduction Act of 2022 sought to increase domestic manufacturing, address climate change, and curb inflation among other things, but one of its unintended consequences has been to make the development of drugs to treat rare diseases less attractive to biopharmaceutical companies.

At issue is a provision within the act that disincentivizes drug developers from pursuing more than one indication for a drug because doing so could make them subject to price negotiations with the government.

Republican Congressman John Joyce from Pennsylvania and Democratic Congressman Wiley Nickel from North Carolina introduced H.R. 5539, legislation to address the Inflation Reduction Act's negative impact on the development of rare disease therapies.

"Encouraging R&D for drugs to treat rare diseases is difficult as is. By definition, orphan drugs benefit small patient populations, making investment in this space incredibly risky. But there is tremendous need for these treatments," said Rachel King, then president and CEO of the Biotechnology Innovation Organization.

She said by subjecting drugs that can treat more than one rare disease to government price controls, it creates additional barriers to investment into follow-on research and development for orphan drugs.

of that depends on staff memories and is lost with turnover. "This balkanization and fragility of institutional knowledge diminishes institutional efficiency and consistency," they wrote.

An Unexpected Lead Indication

Stealth Biotherapeutics was formed in 2006 to license elamipretide from Cornell Research Foundation and develop and commercialize it to treat a range of mitochondrial diseases including primary mitochondrial myopathy, Leber hereditary optic neuropathy, and dry age-related macular degeneration. The company's lead indication had been primary mitochondrial myopathy, a rare muscle disease, when the Barth Syndrome Foundation urged the company to pursue it as a treatment for Barth syndrome as well. Initially, Barth syndrome was folded into the primary mitochondrial myopathy study, but after a phase 2 study failed to demonstrate statistically significant differences to a placebo, Stealth discovered a subgroup of primary mitochondrial myopathy patients with a specific genetic mutation who had a placebo effect that skewed the results. While the company is still pursuing that indication, the FDA suggested it separate out Barth syndrome and pursue the development of that indication by itself.

That decision shifted the responsibility within FDA for elamipretide in Barth syndrome to the division of Cardiology and Nephrology, a division with a limited track record of approving rare disease therapies, no history of approving therapies for ultra-rare diseases, and one that is headed by a director who is viewed as being antagonistic to the use of accelerated approval, which the company had expected to pursue for Barth syndrome.

The Barth syndrome portion of the trial also failed to demonstrate a statistically significant benefit in the blinded, placebo-controlled portion of the study, but an analysis of subjects showed higher levels of cardiolipin and improvement in several endpoints. Cardiolipin plays an essential role in the functioning of the mitochondria. Hillary Vernon, attending physician at Kennedy Krieger Institute and the principal investigator on Stealth's Barth syndrome trial, said, "12 weeks on drug was not enough time to see the effects that we ultimately saw in retrospect." At 12 weeks, there was a significant decrease (nearly 40 percent) in the average ratio of abnormal to normal cardiolipin. There was also significantly increased exercise performance and improvements in secondary and exploratory endpoints including functional assessments and patient-reported outcomes.

> **"This balkanization and fragility of institutional knowledge diminishes institutional efficiency and consistency."**
>
> — PERRINE JANIAUD, ET AL

The company sought approval for elamipretide to treat Barth syndrome in August 2021, despite the fact that the agency had recommended that it study the drug in additional patients before applying for approval. In October 2021, the FDA notified the company it would not consider the application. It told Stealth that a preliminary

review determined that its application did not provide sufficient data to complete a substantive review because of the lack of an adequate and well-controlled trial that provides evidence of effectiveness. In a letter from the agency, it said that the phase 2 clinical trial of elamipretide for the treatment of Barth syndrome was negative during the randomized, double-blind portion of the study and that the FDA did not consider the open label extension of the study to be adequate and well-controlled.

The letter did not explain why the company's positive phase 3 trial comparing results to a retrospective natural history control, its primary basis for its submission, would not be considered an adequate and well-controlled trial, but in discussions with the company it has told Stealth that it wants a larger study.

Stealth and the FDA have previously discussed the challenges of conducting additional clinical trials in

European Trade Group Warns Proposed Overhaul to Orphan Regulations Hurts Patients

Proposed changes to the European Union's Orphan Medicinal Product Regulation will reduce investment in rare disease drug development and stymie many rare disease patients from seeing a novel therapy for their conditions come to market, according to a new analysis prepared for an industry group.

The analysis, commissioned by the European Federation of Pharmaceutical Industry Associations and prepared by the rare disease strategic consultancy Dolon, found that the European Commission's proposed changes, part of a wider overhaul to general pharmaceutical industry regulation, could reduce R&D spending by $4.8 billion (€4.5 billion) and result in 45 novel drugs to treat about 1.5 million people with rare diseases not coming to market in the next 15 years.

The European Orphan Medicinal Product Regulation was introduced in 2000 to incentivize the development of new medicines for people living with a rare disease. The number of EU-approved medicines for rare diseases was in the single digits two decades ago. To date, more than 205 new treatments for orphan diseases have been approved.

If broader changes to existing incentives for innovation are introduced, such as further reducing orphan market exclusivity and tighter criteria for securing orphan designation, Dolon warned that there could be 135 fewer orphan products between 2020 and 2035, and deeper impacts on patients, productivity, and research spending.

"Europe's policy and legislation on orphan medicines have been a success. They are a poster child for how the right combination of incentives and support can and do stimulate the development of medicines for people with rare diseases," said Nathalie Moll, director-general of the European Federation of Pharmaceutical Industries and Associations. "This robust report on the impact of the Commission's currently proposed regulatory changes should give us all pause for thought. We have come too far together to put progress for patients at risk."

Barth syndrome, an ultra-rare genetic disease affecting fewer than 130 people in the United States, but that hasn't dissuaded the agency from telling Stealth it needs to do a study with a larger number of patients.

"What has been completely surprising to me is the number of times with different people I've had to re-explain, not only the pathophysiology of the disease, but also how rare it is," said Krieger Kennedy's Vernon, the principal investigator on the study, speaking of her interactions with representatives of the agency. "A number of people said, 'Just find more patients.' And a number of times I've had to explain this is a completely ultra-rare condition. There's no such thing as just finding more patients. They don't exist. It's been that kind of discussion that has been incredibly frustrating."

Jay Randell, a father of two boys with Barth syndrome who have suffered congestive heart failure and had been on a heart transplant list, said his boys began using elamipretide as teenagers in 2017 and have thrived on the drug. They are showing increased blood profusion of oxygenated blood out through the heart and have not had a single, abnormal echocardiogram since starting the drug. Randell likens the FDA to physicians who fail to listen to their patients. "The FDA is acting like the doctor that's too pigheaded. They know everything and they're not willing to listen and come to the table and say, 'Hey, we don't know anything. What can we do to help you?'" said Randell. "That's where I think we are. You can look for another doctor, but you can't look for another FDA. That's the problem."

Stealth is running out of options for pursuing an approval of elamipretide in Barth syndrome. The company expects to file again for approval. Should the agency refuse to review the application, it could pursue an appeal. In the meantime, it expects to complete clinical development of elamipretide in primary mitochondrial myopathy and seek an approval in that indication by the end of 2024. But as for Barth syndrome, the company is facing growing pressure from investors to move on.

"Investors are not thrilled with this program. There's no way we would do another trial without clear guidance from the FDA, which we've never gotten. I can't justify spending more money. We've been doing mostly regulatory work, but investors are saying, 'This is a distraction. You're a 40-person team. You're going into phase 3 in AMD, you've got mitochondrial myopathy phase 3 readout next year. This is a distraction. Drop it. It's not worth it,'" said Reenie McCarthy, CEO of Stealth Biotherapeutics. "It's hard to justify much more work. Our team believes this drug is working in Barth syndrome, so it's hard to walk away from it, but we're closing in on that decision."

Shelly Bowen, co-founder and director of family services and advocacy for the Barth Syndrome Foundation, who lost two sons to the disease, launched a petition on Change.org in September calling on the FDA to give elamipretide a full and fair hearing. Nearly 20,000 signed the petition, which the Barth Syndrome Foundation delivered to the FDA in December. She said the agency has failed to be appropriate and consistent in the flexibility that Congress granted it to review clinical trial data for severe diseases that affect very few patients.

Kate McCurdy, board chair of Barth Syndrome Foundation delivers petition to the FDA.

CREDIT: ERIC LEE

"There's a chilling effect on what we're looking at in drug development for ultra-rare conditions. This is a fight that's bigger than just elamipretide," she said. "There needs to be to be better processes in place at the agency to review indications for ultra-rare conditions and give people the opportunity to have therapies where they can improve their life."

Drug Approvals in 2023

It was a busy year for the U.S. Food and Drug Administration. After consecutive drops in approvals of new drugs in 2021 and 2022, the FDA returned to a level of approvals in line with historical trends. The class of 2023 was notable not just because of its quantity, but its quality as well. The agency approved the first CRISPR-based gene editing therapy in 2023, as well as the first gene therapies for hemophilia A, Duchenne muscular dystrophy, and dystrophic epidermolysis bullosa. It also approved the first therapies for Rett syndrome and Friedreich's ataxia.

The FDA's Center for Drug Evaluation and Research approved 28 novel therapies for rare disease in 2023, 51 percent of the 55 novel drugs the division approved in 2022. That represented a 40 percent increase in the number of novel orphan drugs approved compared to the 20 the agency approved the previous year. It was a reversal of a two-year decline in novel rare disease drug approvals. Of the total of 28 of the novel orphan drug approvals, 35.7 percent were for medicines to treat rare cancers.

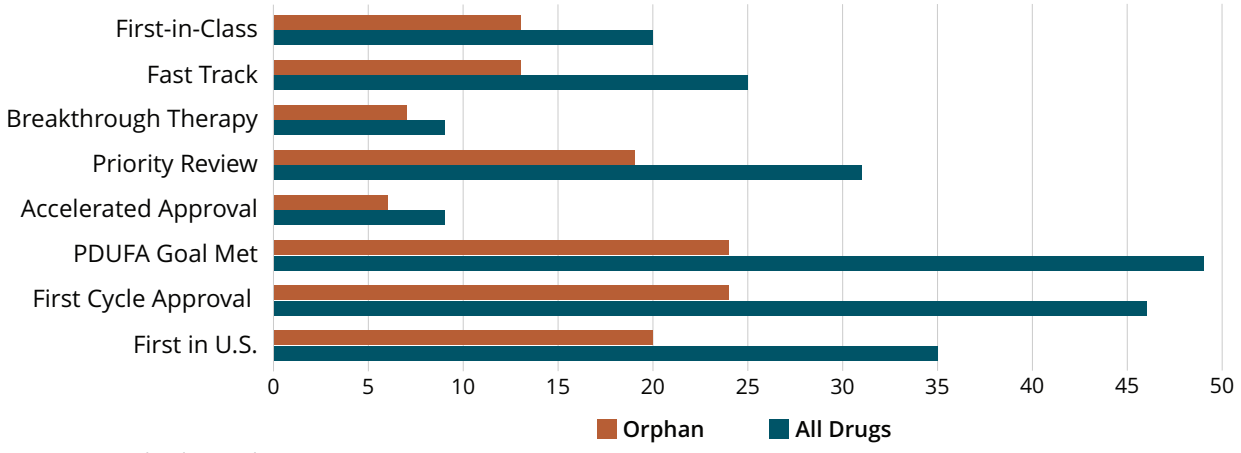
Of the 28 novel rare disease drug approvals in 2023, 13 were first-in-class therapies, seven had Breakthrough Therapy designation, and 19 benefited from Priority Review. Six of the therapies won approval through the accelerated approval pathway.

The FDA also saw an increase in the number of biologics approved for rare disease therapies in 2023, with several noteworthy approvals.

In December 2023, on the heels of the United Kingdom's Medicines and Healthcare Products Regulatory Agency granting of conditional marketing authorization, the FDA approved Casgevy, CRISPR Therapeutics' and Vertex Pharmaceuticals' CRISPR/Cas9 gene-edited therapy for the treatment of sickle cell disease. It was the first time that regulatory authorities granted approval to a CRISPR-based therapy anywhere in the world. Less than six weeks later, the agency expanded the approval of the therapy to include its use as a treatment for transfusion dependent beta thalassemia as well.

Sickle cell disease (SCD) is a genetic blood disorder that affects the red blood cells, which are essential for carrying oxygen to all organs and tissues of the body. SCD causes severe pain, organ damage, and shortened life span due to misshapen or sickled blood cells. People with SCD can

U.S. Food and Drug Administration Novel Drug Approvals in 2023 by Designation



Source: U.S. Food and Drug Administration

U.S. FDA 2023 Biological License Application Approvals for Orphan Indications

Approval Date	Trade Name	Manufacturer	Indication
2/22/2023	Altuviiio	Bioverativ Therapeutics	Indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for: (1) Routine prophylaxis to reduce the frequency of bleeding episodes; (2) On-demand treatment and control of bleeding episodes; and (3) Perioperative management of bleeding.
4/17/2023	Omisirge	Gamida Cell	Indicated for use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.
5/19/2023	Vyjuvek	Krystal Biotech	Indicated for treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.
6/22/2023	Elevidys	Sarepta Therapeutics	Indicated for treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.
6/29/2023	Roctavian	BioMarin Pharmaceutical	Valoctocogene roxaparvovec-rvox is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.
7/21/2023	Balfaxar	Octapharma Pharmazeutika	Indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure.
11/9/2023	Adzynma	Takeda Pharmaceuticals	Indicated for prophylactic or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).

Source: U.S. Food and Drug Administration

experience painful blood vessel blockages, also known as vaso-occlusive crises (VOCs), that can lead to acute chest syndrome, stroke, jaundice, and symptoms of heart failure. Individuals may also experience anemia, which can result in end-organ damage and premature death.

Though stem cell transplant from a matched donor can be curative, it is an option that is available to only a small fraction of people living with SCD. SCD requires lifelong treatment and significant use of healthcare resources. The condition causes a reduced life expectancy and reduced lifetime earnings and productivity. Current standard treatment options for SCD mostly address symptoms and do not alleviate the need for chronic care. Most often, treatment is focused on relieving pain, minimizing organ damage, maintaining hydration, and addressing fevers. In some cases, monthly blood transfusions and frequent hospital visits are necessary.

Casgevy is a one-time treatment that takes blood stem cells from a patient and, using *ex vivo* CRISPR/Cas9 editing, activates the production of fetal hemoglobin to compensate for the abnormal hemoglobin in people with sickle cell disease. The cells are then infused back into the patient. Fetal hemoglobin carries oxygen in the blood of a fetus, but production of it is shut off in early life as adult hemoglobin is activated. Casgevy has been shown to reduce or eliminate vaso-occlusive crises for patients with SCD. Vertex set the price of Casgevy at $2.2 million.

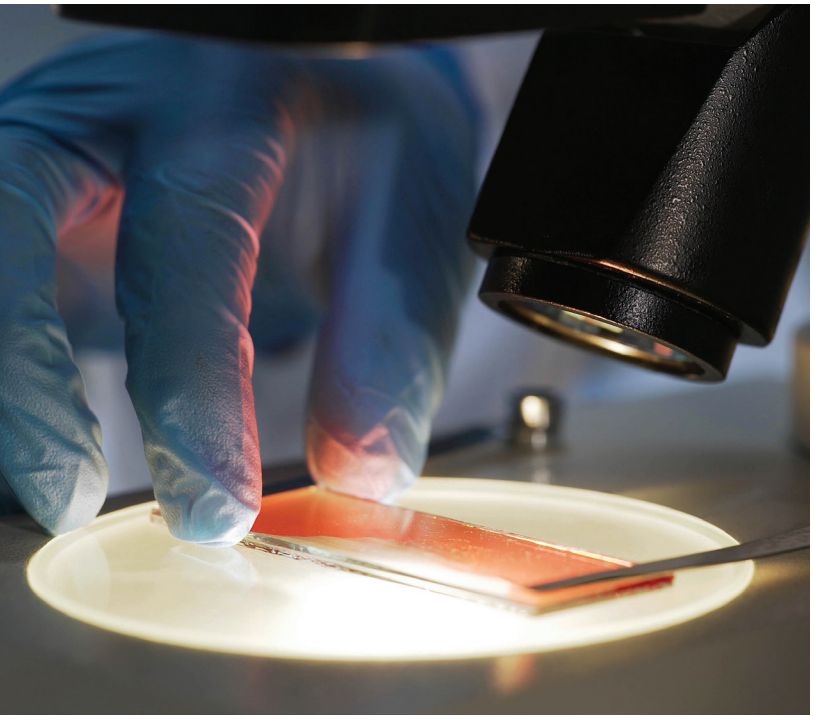
The FDA approved Casgevy based on an ongoing single-arm, multi-center trial in adult and adolescent patients with SCD. Patients had a history of at least two severe VOCs during each of the two years prior to screening. The primary efficacy outcome was freedom from severe VOC episodes for at least 12 consecutive months during the 24-month follow-up period. A total of 44 patients were treated with Casgevy. Of the 31 patients with sufficient follow-up time to be evaluable, 29 (93.5 percent) achieved this outcome.

The most common side effects were low levels of platelets and white blood cells, mouth sores, nausea, musculoskeletal pain, abdominal pain, vomiting, febrile neutropenia (fever and low white blood cell count), headache, and itching.

The same day the FDA approved Casgevy, it approved Bluebird Bio's Lyfgenia, another cell-based therapy for SCD. Lyfgenia uses a lentiviral vector to deliver a gene therapy that modifies a patient's blood stem cells *ex vivo* to produce HbA^{T87Q}. HbA^{T87Q} is similar to adult hemoglobin but has a lower risk of sickling and obstructing blood flow. The approval carried a Black Box warning because patients using Lyfgenia have developed blood cancers. Bluebird Bio set the price of Lyfgenia at $3.1 million.

Gene Therapies in the Limelight

The FDA also approved three gene therapies in 2023—BioMarin Pharmaceutical's Roctavian for the blood disorder hemophilia A, Sarepta Therapeutics' gene therapy Elevidys for the neuromuscular disease Duchenne muscular dystrophy, and Krystal Biotech's redosable topical gene therapy for the rare connective tissue disorder dystrophic epidermolysis bullosa. They each represent the first gene therapies for the condition they treat. The approvals reflect the growing pipeline of advanced therapies that are moving toward the market.



In June 2023, the FDA approved BioMarin's Roctavian, the first gene therapy the agency has approved for severe hemophilia A, a rare genetic bleeding disorder. The FDA approved Roctavian for the treatment of adults with severe hemophilia A deficiency without antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test. The approval came almost three years after the agency initially rejected BioMarin's application and a more recent delay of the review. The European Medicines Agency approved Roctavian in August 2022. BioMarin set the wholesale price at $2.9 million.

Hemophilia A is a genetic condition caused by a mutation in the gene responsible for producing a protein called factor VIII, which is necessary for blood clotting. People who have a severe deficiency in the amount of factor VIII they produce are at risk for painful and potentially life-threatening bleeds, which can occur spontaneously. With the current standard of care, individuals undergo infusions or injections at routine intervals to maintain enough clotting factor in the bloodstream to prevent bleeds. Roctavian is designed to replace the function of the mutated gene, allowing people with severe hemophilia A to produce their own factor VIII to limit bleeding episodes.

The FDA approval is based on data from the global phase 3 GENEr8-1 study, the largest phase 3 trial of any gene therapy in hemophilia. The 112 patients in whom six-month baseline annualized bleeding rate (ABR) was collected prospectively experienced a mean ABR reduction of 52 percent after receiving Roctavian (2.6 bleeds a year) through end of follow-up (median of three years) compared to their baseline ABR while receiving routine factor VIII prophylaxis (5.4 bleeds a year). These patients also reported a substantial reduction in the rate of spontaneous bleeds and joint bleeds following treatment with Roctavian.

The majority of study participants continued to respond to treatment through year three and beyond, without supplemental use of regular prophylaxis. Safety results for 134 patients through three years demonstrated that Roctavian was well-tolerated.

Results from the three-year analysis of the phase 3 GENEr8-1 study presented at the International Society on Thrombosis and Haemostasis 2023 Congress showed

that study participants had an 82.9 percent reduction in treated bleeds overall compared with baseline. It also showed Roctavian led to a 96.8 percent reduction in factor VIII usage overall compared with baseline.

Roctavian was one of two gene therapies the FDA approved in June 2023. That same month the agency granted accelerated approval to Sarepta's Elevidys, a gene therapy for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD). It is the first gene therapy approved to treat DMD. The accelerated approval is based on an increase in Elevidys micro-dystrophin protein expression in skeletal muscle. With the accelerated approval, the company has committed to the completion of a confirmatory trial. Sarepta set the wholesale price of Elevidys at $3.2 million.

DMD is caused by a change or mutation in the gene that encodes instructions for dystrophin, an essential part of the protein complex in healthy muscle. Children with DMD may experience developmental delays, such as difficulty in walking, climbing stairs or standing from a sitting position. As the disease progresses, muscle weakness in the lower limbs spreads to the arms and other areas. Most patients require full-time use of a wheelchair in their early teens, and then progressively lose the ability to independently perform activities of daily living, such as using the restroom, bathing, and feeding. Eventually, increasing difficulty in breathing due to respiratory muscle dysfunction requires ventilation support, and cardiac dysfunction can lead to heart failure. The condition is universally fatal, and patients usually succumb to the disease in their twenties.

Elevidys addresses the root genetic cause of Duchenne—mutations in the dystrophin gene that result in the lack of dystrophin protein—by delivering a gene that codes for micro-dystrophin—a shortened form of dystrophin—to muscle cells. It is a single-dose gene transfer therapy.

The FDA granted approval based on data from a two-part study. In part 1, which was randomized, double-blind, and placebo-controlled, patients were treated with either Elevidys or placebo and followed for 48 weeks. In part 2 of the study, individuals who received placebo during part 1 were treated with Elevidys, and individuals treated with Elevidys during part 1 received a placebo. All individuals were followed for an additional 48 weeks. Data from the study showed that Elevidys increased the expression of the Elevidys micro-dystrophin protein in Elevidys-treated individuals aged 4 to 5 years with DMD.

The FDA concluded that the data submitted by the applicant demonstrated that an increase in this surrogate endpoint (expression of Elevidys micro-dystrophin) is reasonably likely to predict clinical benefit in individuals 4 to 5 years of age with DMD who do not have significant pre-existing antibody titers against the AAV rh74 vector or have other contraindications based on the inclusion criteria of the clinical trials.

Results from the three-year analysis of the phase 3 GENEr8-1 study...showed that study participants had an 82.9 percent reduction in treated bleeds overall compared with baseline.

Acute serious liver injury, immune-mediated myositis and myocarditis have occurred in patients treated with Elevidys. The most common adverse reactions in clinical studies were vomiting, nausea, liver function test increases, pyrexia, and thrombocytopenia.

The other gene therapy the FDA approved in 2023 was Krystal Biotech's topical gene therapy Vyjuvek for the treatment of patients six months of age or older with dystrophic epidermolysis bullosa (DEB). It is the first redosable gene therapy approved by the agency and the first gene therapy for the treatment of both recessive and dominant DEB that can be administered by a healthcare professional in either a professional healthcare setting or in the home.

Dystrophic epidermolysis bullosa (DEB) is a rare disease that affects the skin and mucosal tissues and is caused

by one or more mutations in the COL7A1 gene. The COL7A1 gene is responsible for the production of functional COL7 protein that forms anchoring fibrils necessary to bind the inner layer of the skin, known as the dermis, and outer layer of the skin, known as the epidermis. The lack of functional anchoring fibrils in DEB patients leads to extremely fragile skin that blisters and tears with minor friction or trauma. DEB patients suffer from open wounds, which lead to recurrent skin infections and fibrosis that can cause fusion of fingers and toes, and ultimately increase the risk of developing an aggressive form of skin cancer.

> **"Vyjuvek both heals patient wounds and prevents skin from re-blistering because it actually corrects the underlying skin defect of dystrophic EB."**
>
> — M. PETER MARINKOVICH

Vyjuvek uses an engineered herpes simplex virus to deliver a gene that's much larger than the standard viral vectors can deliver. It is designed to address the genetic root cause of DEB by delivering functional copies of the human COL7A1 gene to provide wound healing and sustained functional COL7 protein expression with redosing.

"Until now, doctors and nurses had no way to stop blisters and wounds from developing on dystrophic EB patient skin and all we could do was to give them bandages and helplessly watch as new blisters formed. Vyjuvek topical gene therapy changes all of this," said M. Peter Marinkovich, primary investigator of the GEM-3 trial, director of the Blistering Disease Clinic at Stanford Health Care and associate professor of Dermatology at the Stanford University School of Medicine. "Vyjuvek both heals patient wounds and prevents skin from re-blistering because it actually corrects the underlying skin defect of dystrophic EB. Because it's safe and easy to apply directly to wounds, it doesn't require a lot of supporting technology or specialized expertise, making Vyjuvek highly accessible even to patients who live far away from specialized centers."

The FDA approval of Vyjuvek is based on two clinical studies. The GEM-1/2 trial was an intra-patient, open label, single center, randomized, placebo-controlled study showing that repeat topical applications of Vyjuvek were associated with durable wound closure, full-length cutaneous COL7 expression, and anchoring fibril assembly with minimal reported adverse events. The GEM-3 trial was an intra-patient, double-blinded, multi-center, randomized, placebo-controlled study that met both its primary endpoint of complete wound healing at six months and its key secondary endpoint of complete wound healing at three months. Vyjuvek was well tolerated with no drug-related serious adverse events or discontinuations due to treatment-related events.

First Approved Treatments

Beyond the genetic medicines, the FDA approved the first drugs to treat the progressive neuromuscular disease Friedreich's ataxia and the first drug to treat the neurodevelopmental disorder Rett syndrome.

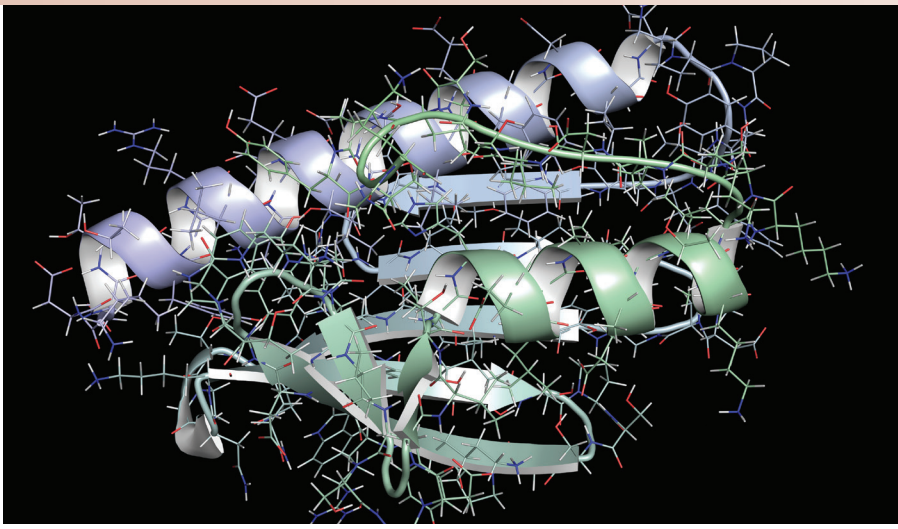
In March 2023, the FDA approved Reata Pharmaceuticals' Skyclarys as the first and only drug to treat patients with Friedreich's ataxia. The approval is for use in adults and adolescents aged 16 years and older with Friedreich's ataxia. The FDA granted a Rare Pediatric Disease Priority Review voucher to Reata as a result of the approval.

Friedreich's ataxia is an ultra-rare, inherited disorder that is typically diagnosed during adolescence. Patients with Friedreich's ataxia experience progressive loss of coordination, muscle weakness, and fatigue, which commonly progresses to motor incapacitation and wheelchair reliance by their teens or early twenties,

U.S. Food and Drug Administration Orphan Drug Approvals in 2023

Proprietary Name	Active Ingredient	Indication	Approval Date	Designations
Agamree	vamorolone	To treat Duchenne muscular dystrophy	10/26/2023	
Aphexda	motixafortide	To use with filgrastim to mobilize hematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma	9/8/2023	
Augtyro	repotrectinib	To treat ROS1-positive non-small cell lung cancer	11/15/2023	
Daybue	trofinetide	To treat Rett syndrome	3/10/2023	
Elrexfio	elranatamab-bcmm	To treat relapsed or refractory multiple myeloma after at least four lines of therapy	8/14/2023	
Fabhalta	iptacopan	To treat paroxysmal nocturnal hemoglobinuria	12/5/2023	
Filspari	sparsentan	To reduce proteinuria in primary immunoglobulin A nephropathy at risk of rapid disease progression	2/17/2023	
Filsuvez	birch triterpenes	To treat wounds associated with dystrophic and junctional epidermolysis bullosa	12/18/2023	
Jaypirca	pirtobrutinib	To treat relapsed or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a BTK inhibitor	1/27/2023	
Joenja	leniolisib	To treat activated phosphoinositide 3-kinase delta syndrome	3/24/2023	
Lamzede	velmanase alfa-tycv	To treat non-central nervous system manifestations of alpha-mannosidosis	2/16/2023	
Loqtorzi	toripalimab-tpzi	To treat recurrent or metastatic nasopharyngeal carcinoma with or following other therapies	10/27/2023	
Ngenla	somatrogon-ghla	To treat growth failure due to inadequate secretion of endogenous growth hormone	6/27/2023	
Ogsiveo	nirogacestat	To treat desmoid tumors	11/27/2023	
Ojjaara	momelotinib	To treat intermediate or high-risk myelofibrosis	9/15/2023	
Pombiliti	cipaglucosidase alfa-atga	To treat late-onset Pompe disease with miglustat	9/28/2023	
Qalsody	tofersen	To treat a form of amyotrophic lateral sclerosis	4/25/2023	
Rezzayo	rezafungin	To treat candidemia and invasive candidiasis	3/22/2023	
Rivfloza	nedosiran	To lower urinary oxalate levels in primary hyperoxaluria type 1 and relatively preserved kidney function	9/29/2023	
Rystiggo	rozanolixizumab-noli	To treat generalized myasthenia gravis	6/26/2023	
Skyclarys	omaveloxolone	To treat Friedreich's ataxia	2/28/2023	
Sohonos	palovarotene	To reduce the volume of new heterotopic ossification in fibrodysplasia ossificans progressiva	8/16/2023	
Talvey	talquetamab-tgvs	To treat relapsed or refractory multiple myeloma after at least four therapies	8/9/2023	
Vanflyta	quizartinib	To use as part of a treatment regimen for newly diagnosed acute myeloid leukemia that meets certain criteria	7/20/2023	
Veopoz	pozelimab-bbfg	To treat CD55-deficient protein-losing enteropathy (PLE) (i.e., CHAPLE disease)	8/18/2023	
Wainua	eplontersen	To treat hereditary transthyretin mediated amyloidosis	12/21/2023	
Zilbrysq	zilucoplan	To treat generalized myasthenia gravis	10/17/2023	
Zynyz	retifanlimab-dlwr	To treat metastatic or recurrent locally advanced Merkel cell carcinoma	3/22/2023	

Source: U.S. Food and Drug Administration



and eventually death. Friedreich's ataxia affects approximately 5,000 diagnosed patients in the United States.

Skyclarys is an oral, once-daily medication that activates Nrf2 and addresses mitochondrial dysfunction, oxidative stress, and chronic inflammation.

The approval of Skyclarys was based on the efficacy and safety data from the MOXIe Part 2 trial and a post hoc Propensity-Matched Analysis of the open-label MOXIe Extension trial. MOXIe Part 2 was a randomized, double-blind, placebo-controlled study. Patients with genetically confirmed Friedreich's ataxia and baseline modified Friedreich's Ataxia Rating Scale (mFARS) scores between 20 and 80 were randomized one-to-one to receive placebo or 150 mg of Skyclarys daily. The primary endpoint was change from baseline in mFARS score compared to placebo at Week 48 in the Full Analysis Population of patients without severe pes cavus, a foot morphology. The mFARS is a clinical assessment tool to assess patient function and is used in clinical trials to assess the efficacy of investigational products for use in Friedreich's ataxia.

With the emergence of artificial intelligence platform technologies…there is a potential for a significant increase in the number of new drugs and biologics seeking approval each year.

Treatment with Skyclarys resulted in statistically significant lower mFARS scores (less impairment) relative to placebo at Week 48. The placebo-corrected difference between the two groups was -2.41 points. The most common adverse reactions in MOXIe Part 2 (20 percent or more and greater than placebo) were elevated liver enzymes, headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain.

That same month the agency also approved Acadia Pharmaceutical's Daybue for the treatment of the rare, neurodevelopmental disorder Rett syndrome in adult and pediatric patients 2 years of age and older. With the FDA approval of Daybue, Acadia received a Rare Pediatric Disease Priority Review voucher.

Rett syndrome is a complex condition caused by a genetic mutation on the MECP2 gene. It is characterized by a period of normal development until 6 to 18 months of age, followed by significant developmental regression with loss of acquired communication skills and purposeful hand use. Symptoms of Rett syndrome may also include development of hand stereotypies, such as hand wringing and clapping, and gait abnormalities.

Daybue is a synthetic version of a naturally occurring molecule known as tripeptide glycine-proline-glutamate, which is part of a growth factor thought to support brain cells. The FDA approval of Daybue was supported by results from the pivotal phase 3 Lavender study evaluating the efficacy and safety of Daybue versus placebo in 187 female patients with Rett syndrome 5 to 20 years of age.

One other noteworthy approval for the FDA came in April when the agency granted accelerated approval to Biogen's Qalsody for the treatment of the neurodegenerative condition amyotrophic lateral sclerosis. The approval is for adults who have a mutation in the superoxide dismutase 1 (SOD1) gene, the first approval of an ALS therapy that targets a genetic cause of the disease.

The approval was based on a reduction in plasma neurofilament light chain (NfL) observed in patients treated with Qalsody. Neurofilaments are proteins that are released from neurons when they are damaged, making them a marker of neurodegeneration. It is the first time that there has been a consensus that neurofilament can be used as a surrogate marker reasonably likely to predict clinical benefit in SOD1-ALS.

Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials. The ongoing phase 3 ATLAS study of Qalsody in people with pre-symptomatic SOD1-ALS is being used as the confirmatory trial.

Amyotrophic lateral sclerosis (ALS) is a rare, progressive, and fatal neurodegenerative disease that results in the loss of motor neurons in the brain and the spinal cord that are responsible for controlling voluntary muscle movement. People with ALS experience muscle weakness and atrophy, causing them to lose independence as they steadily lose the ability to move, speak, eat, and eventually breathe. Average life expectancy for people with ALS is three to five years from the time of symptom onset.

Multiple genes have been implicated in ALS. Genetic testing helps determine if a person's ALS is associated with a genetic mutation, even in individuals without a known family history of the disease. SOD1-ALS is diagnosed in approximately 2 percent of all ALS cases, with about 330 people in the United States living with the disease. More than 15 percent of people with ALS are thought to have a genetic form of the disease, however, they may not have a known family history of the disease. In people with SOD1-ALS, mutations in their SOD1 gene cause their bodies to create a toxic misfolded form of SOD1 protein. This toxic protein causes motor neurons to degenerate, resulting in progressive muscle weakness, loss of function, and eventually, death.

Qalsody is an antisense oligonucleotide designed to bind to SOD1 mRNA to reduce SOD1 protein production. Qalsody is administered intrathecally as three loading doses administered at 14-day intervals followed by maintenance doses administered once every 28 days thereafter. Biogen collaborated with Ionis Pharmaceuticals on the early development of Qalsody.

With the emergence of artificial intelligence platform technologies that promise shortening the discovery and development times for new medicines and the growing interest in the development of bespoke therapies, there is a potential for a significant increase in the number of new drugs and biologics seeking approval each year. If that proves to be the case, the question will become whether the FDA will be in a position to review a far greater number of new applications to keep pace with innovation, or whether approval rates will remain static because of a lack of capacity within the agency. ■