BIOPHARMA DIVE

Bluebird wins FDA approval of gene therapy for rare brain disorder

The therapy, called Skysona and cleared to treat cerebral adrenoleukodystrophy, is the product of more than a decade of work by Bluebird. It will cost $3 million.

Published Sept. 17, 2022

Ned Pagliarulo
Lead Editor

The Food and Drug Administration on Friday granted accelerated approval to a personalized gene therapy for an ultra-rare childhood brain disease, called cerebral adrenoleukodystrophy or CALD.

Built from a patient's own stem cells, the therapy is the first medicine to be made available in the U.S. for CALD, which affects young boys and typically results in severe disability or death. It was developed by the biotechnology company Bluebird bio and will be sold as Skysona.

Its approval is Bluebird's second in four weeks, following an Aug. 17 FDA decision on another gene therapy from the company for the blood disorder beta thalassemia.

The back-to-back clearances come despite FDA concerns over the risk of the treatments causing cancer. Experts convened by the agency in June to vet the two therapies voted unanimously in favor of both, agreeing their benefits outweigh their potential side effects.

Both CALD and severe beta thalassemia are uncommon, although CALD is far rarer. It's one of a small cluster of diseases that were featured in the 1992 film Lorenzo's Oil about a boy with adrenoleukodystrophy and his parents' hunt for a cure. The buildup of harmful fatty acids in the brain and nervous system causes CALD, which leads to learning and behavioral problems before progressing to more severe neurological damage.

In the U.S., an estimated 50 boys are born each year who will go on to develop CALD. Bluebird expects to treat about 10 annually.

Meant to be a one-time infusion, Skysona will cost $3 million. The price tag makes the therapy one of the most expensive ever launched on a single-use basis, exceeding the $2.8 million cost of Bluebird's other gene therapy.

'The most expeditious way'

Skysona is for children aged four to 17 years old who are in the early stages of the disease. The accelerated approval granted by the FDA means Bluebird must confirm its therapy's benefit through further testing. The company expects to use data from long-term follow-up study, as well as from commercially treated patients, it said in a Friday statement.

Bluebird was seeking full approval of Skysona, but agreed to a conditional clearance after talking with the FDA about some of the agency's concerns. "Through the course of the review after the [June meeting], we discussed this would probably be the most expeditious way to get the therapy to patients," said Bluebird CEO Andrew Obenshain in an interview Saturday.

The FDA's approval does not limit Skysona's use based on the availability of a "matched" sibling donor for a stem cell transplant, which Bluebird previously proposed for the therapy's labeling. These transplants can in some cases slow or stop the disease's progression.

The vast majority of boys with CALD don't have such a sibling, and transplants from unmatched or unrelated donors carry significant safety risks. Skysona offers an alternative that promises years of benefit by replacing the defective gene responsible for CALD.

In the main trial testing Skysona, 29 of 32 treated patients reached two years without dying or developing a major functional disability, meeting the study's main goal. Further study showed that benefit was maintained through five years in most patients who had been followed for that long. (Another trial involving 35 patients is ongoing.)

However, the FDA raised a number of issues about how that data was analyzed as well as the magnitude of benefit in patients for whom transplants are available.

Additionally, three patients given Skysona developed a type of bone marrow cancer many months later. In two, the cancer was directly linked to treatment, likely caused by the modified virus

used to create Skysona. FDA staff have indicated they think it's possible more cases will develop over time.

At the June meeting, advisers were tasked with weighing that risk and ultimately concluded it could be managed with sufficiently strong monitoring. The cancer, called myelodysplastic syndrome, can evolve into leukemia, but is treatable. Two of the three patients were in remission as of June.

"In general, families look at things as treatable versus untreatable," said Amy Waldman, medical director of the Leukodystrophy Center at Children's Hospital of Philadelphia, in an interview ahead of Friday's approval. "I have had a family say to me, "You know you're in trouble when you wish your child had a brain tumor."

The FDA's labeling for Skysona carries what's known as a "black-box" warning, the agency's strictest, for the risk of blood cancers, including myelodysplastic syndrome. Doctors are advised to monitor patients closely via blood testing at least every six months and through genetic sequencing of cells annually for 15 years after treatment.

At the June meeting, advisers agreed the tradeoff between Skysona's benefits and its potential risks is clearest in patients who don't have a matched, related donor for stem cell transplant. For patients with donors who match but are unrelated, the choice between Skysona and transplant is more complex.

"Just because someone is matched doesn't mean they are a perfect donor," Christine Duncan, a physician at Boston Children's Hospital who helped run one of the Skysona trials, said in an interview ahead of the FDA's decision. "For children who have a matched unrelated donor, it's a different risk-benefit analysis. But it's one I'm hoping we'll be able to have with patients."

Parents and family members of CALD patients who spoke in June described the uncertainty of waiting for a transplant match, as well as their fears of transplant-related side effects, which can include a serious complication known as graft-versus-host disease.

"This is a disease where time equals brain," Bradford Zakes, the father of a boy who died of CALD, said then. "Having access to an alternative therapy that can be deployed quickly, without delay, would simply be a game changer in the lives of young boys born with this devastating disease."

Duncan, as well as others at the June meeting, also noted that children who are Black or Hispanic are less likely to find a donor match through national registries.

Commercial plans

Bluebird expects Skysona to be available by the end of the year, and is planning to work with a "limited number" of centers that are experienced in treating CALD and in stem cell transplantation, including Boston Children's Hospital and CHOP.

The company is not putting in place "outcomes-based" coverage agreements with insurers for Skysona as it did with its other gene therapy, for which it's offering to reimburse part of the cost if patients don't continue to benefit.

"This is such an ultra-rare disease that these insurers are likely to see only one patient — most likely to see zero — the entire time," said Obenshain. "Neither Bluebird nor the payers want to go through the complexity of a contract for a patient population so small."

Skysona's clearance in the U.S. comes a little more than one year after it was approved in Europe. But Bluebird had trouble securing reimbursement and later withdrew the therapy from the market amid a broader wind down of its business there. Few patients were ever treated.

While the two gene therapy approvals are a boost, Bluebird remains in financial difficulty. The company is running out of money and has warned it may face insolvency in the future. Its new products could bring in needed revenue, as could the sale of special regulatory vouchers awarded to Bluebird by the FDA. The vouchers can be used to speed drug reviews and have commanded prices of around $100 million each.

Editor's note: This story has been updated with comments from Bluebird bio's CEO.