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Gene Therapy: US FDA Labeling For Vertex's Casgevy, Bluebird's Lyfgenia Reflect Different Risks

by Sue Sutter

Agency grants same-day approval to the first two gene therapies for sickle cell disease; bluebird's lentiviral-based lovo-cel carries a boxed label warning on hematologic malignancies, while Vertex's CRISPR-Cas9 exa-cel carries a warning and precaution about potential off-target effects. Only the Vertex product qualified for a rare pediatric disease priority review voucher.

Although the US Food and Drug Administration approved the first two gene therapies for sickle cell disease in a sweeping same-day action, product labeling reflects potential risks specific to each therapy's mechanism of action and clinical program to date.

On 8 December, the FDA approved *Vertex Pharmaceuticals Incorporated*/*CRISPR Therapeutics AG*'s Casgevy (exagamglogene autotemcel, or exa-cel) on the user fee goal date, and *bluebird bio*'s Lyfgenia (lovotibeglogene autotemcel, or lovo-cel) 12 days ahead of its goal date.

Both gene therapies are indicated for sickle cell patients ages 12 years and older, but the indication statements differ slightly. Casgevy is for patients with recurrent vaso-occlusive crises, while Lyfgenia is intended for patients with a history of vaso-occlusive events.

Key Takeaways

- Bluebird's Lyfgenia gets a boxed warning on hematological malignancies resulting from two leukemia cases in the clinical program.

Both are autologous hematopoietic stem cell-based gene therapies. Casgevy incorporates CRISPR/Cas9 genome-editing technology, making it the first such gene therapy

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approved. In contrast, Lyfgenia incorporates a replication-incompetent, self-inactivating lentiviral vector.

"These treatments represent a major advancement in the field of gene therapy for patients with sickle cell disease, a rare and debilitating blood disorder affecting approximately 100,000 people in the United States," Center for Biologics Evaluation and Research Director Peter Marks said during an FDA press call.

- Labeling for Vertex's Casgevy warns about potential for off-target effects, and the sponsor must conduct more preclinical analyses of these risks postapproval.
- FDA determined that Lyfgenia does not qualify for a rare pediatric disease priority review voucher because its active ingredient previously was approved, in the form of bluebird's Zynteglo.

"Casgevy and Lyfgenia are the first FDA-approved cell-based gene therapies to treat sickle cell disease in patients 12 years and older, and Casgevy is also the first FDA-approved treatment to utilize a novel genome editing technology called CRISPR/Cas9," Marks said. "The use of that technology is particularly exciting, as it more broadly signifies an innovative advancement in the field of gene therapy and, in fact, CRISPR/Cas9 was the subject for which the 2020 Nobel Prize in chemistry was awarded."

Vertex and bluebird have announced pricing of $2.2m and $3.1m for their respective products. (*See sidebar for story.*) Vertex's price is close to the $2m assumed by the Institute for Clinical and Economic Review in its clinical benefit assessment. (Also see "*As Sickle Cell Gene Therapies Move To Market, Health Inequities Could Help Pricing Debate*" - Pink Sheet, 11 Aug, 2023.)

Bluebird may face a bigger challenge in defending its higher price point, particularly given the presence of a boxed label warning on hematologic malignancies. (*See box.*)

Malignancy Warning

Lyfgenia *labeling* states that two patients treated with an earlier version of the gene therapy using a different manufacturing process and transplant procedure developed acute myeloid leukemia and subsequently died. Another patient with α-thalassemia trait has been diagnosed with myelodysplastic syndrome.

Bluebird, Vertex Gene Therapies May Answer $1m Question: Can Competition Reduce Rx Prices?

By Cathy Kelly

08 Dec 2023

Medicaid is expected to be the primary payer for the sickle cell treatments. Bluebird bio maintains outcomes-based arrangements are a key part of its access strategy and will overcome what appears to be a significant competitive disadvantage on price compared

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"The additional hematopoietic stress associated with mobilization, conditioning, and infusion of Lyfgenia, including the need to regenerate the hematopoietic system, may increase the risk of a hematologic malignancy," the warnings and precautions section of labeling states.

"Patients with sickle cell disease have an increased risk of hematologic malignancy as compared to the general population. Patients treated with Lyfgenia may develop hematologic malignancies and should have lifelong monitoring. Monitor for hematologic malignancies with a complete blood count (with differential) at least every 6 months for at least 15 years after treatment with Lyfgenia, and integration site analysis at Months 6, 12, and as warranted."

Labeling instructs that if a malignancy occurs, health care providers should contact bluebird for reporting and to obtain instructions on collection of samples for testing.

During a same-day analyst call, Rich Colvin, bluebird's chief medical officer, said the two AML cases, which involved a prior manufacturing process, have been well described in the medical literature, and neither was due to insertional oncogenesis.

Lyfgenia Boxed Warning

"Hematologic malignancy has occurred in patients treated with LYFGENIA. Monitor patients closely for evidence of malignancy through complete blood counts at least every 6 months and through integration site analysis at Months 6, 12, and as warranted."

Lyfgenia labeling does, however, include a warning and precaution about the potential risk of insertional oncogenesis.

Although the FDA did not convene an advisory committee meeting on Lyfgena, it raised the AML cases seen in the sickle cell program as a safety concern during an advisory committee meeting on another of the bluebird's gene therapies, Zynteglo (betibeglogene autotemcel, or beti-cel), which uses the same lentiviral vector as Lyfgenia. (Also see "*Bluebird's Beta-Thalassemia Gene Therapy Faces US Panel Scrutiny On Hematologic Malignancy Risk*" - Pink Sheet, 8 Jun, 2022.)

Zynteglo, which was approved in August 2022 for treatment of transfusion-dependent β-thalassemia, does not carry a boxed warning.

However, labeling for bluebird's Skysona (elivaldogene autotemcel, or eli-cel), a gene therapy for

to the Vertex product.

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cerebral adrenoleukodystrophy that uses a different lentiviral vector, includes a boxed warning on occurrence of hematologic malignancies, including life-threatening cases of myelodysplastic syndrome. The boxed warning states the cancers appear to be the result of the Lenti-D lentiviral vector integration into proto-oncogenes.

> *"What we can only do at this point is put on the label what we've seen. And I don't think that it would be fair to dismiss something to the conditioning regimen." – FDA's Peter Marks*

There is no warning about hematologic malignancy on the labeling for Vertex's Casgevy.

During the press call, FDA officials were asked why Lyfgenia got a boxed warning on hematological malignancies while Casgevy did not, and whether such a warning could be added to the Vertex product's labeling in the future.

"The black box warning in the bluebird label specifically was for myeloid malignancies, or two cases in particular of AML that happened during the clinical trials for sickle cell disease," said Nicole Verdun, director of CBER's Office of Therapeutic Products. "Those two patients actually ended up having death as a result of their malignancies. And so we thought that that rose to the level of a black box warning. Vertex at this time has not had malignancies that have occurred, and so for that reason we did not think that it warranted a black box warning at this time."

FDA officials also were asked whether the AML cases resulted from the busulfan-based conditioning regimen which is used in the administration of both gene therapies.

Marks said that with both gene therapies, patients get busulfan up-front, "and then they get the modified stem cells that have been generated by one of two means. For one of the products, it's using the CRISPR/Cas9 that is put into the cells using a nonviral means, and then by the other it's having the corrective gene therapy construct that's put into the cells using a lentiviral vector."

"It's plausible they could have the same set of side effects due to the busulfan or it's possible that there could be interactions between the busulfan and each of the different products themselves so that they might have different overall safety profiles," Marks said. "What we can only do at this point is put on the label what we've seen. And I don't think that it would be fair to dismiss something to the conditioning regimen."

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Warning On Potential Off-Target Effects

The FDA convened an October advisory committee meeting on Casgevy that focused primarily on the adequacy of Vertex's preclinical analyses of potential off-target effects. (Also see "*Gene Editing: US Panel Review Of Vertex's Exa-Cel To Focus On Nonclinical Assessment Of Off-Target Effects*" - Pink Sheet, 27 Oct, 2023.)

Although the committee found these analyses to be adequate, some members said long-term monitoring should include whole genome sequencing and monitoring to track off-target effects. (Also see "*Vertex's Exa-Cel: Off-Target Gene Editing Analyses Sufficient Given Robust Clinical Efficacy, FDA Panel Says*" - Pink Sheet, 31 Oct, 2023.)

They also raised practical questions about how such theoretical risks would be discussed in labeling and patient information. (Also see "*Gene Editing: Exa-Cel Panel Review Raises Practical Concerns About Theoretical Risks*" - Pink Sheet, 7 Nov, 2023.)

> ***"Although off-target genome editing was not observed in the edited CD34+ cells evaluated from healthy donors and patients, the risk of unintended, off-target editing in an individual's CD34+ cells cannot be ruled out due to genetic variants." – Casgevy labeling***

Casgevy *labeling* contains a warning and precaution about the risk of off-target genome editing.

"Although off-target genome editing was not observed in the edited CD34+ cells evaluated from healthy donors and patients, the risk of unintended, off-target editing in an individual's CD34+ cells cannot be ruled out due to genetic variants," labeling states. "The clinical significance of potential off-target editing is unknown."

"The way we handled it in the label and the prescribing information is to put in that potential risk into that label so that patients are informed," the FDA's Verdun said. "We will … make adjustments as needed in the future, but it is listed as a potential risk."

Both product labels also carry warnings and precautions related to delayed or potential failure of neutrophil and platelet engraftment, and hypersensitivity reactions.

Long-Term Safety Studies Required

Both sponsors must conduct long-term safety studies, in the form of prospective, observational,

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postmarketing studies with 15-year follow-up comprising 250 patients who received each of the products.

How to ensure the completion of extended follow-up studies in the face of potential insurance changes, physician retirements, or other challenges is among the gene therapy policy issues that the FDA is wrestling with. (Also see "*US FDA Struggling With Long-Term Follow-Up Requirements For Gene Therapies*" - Pink Sheet, 18 Oct, 2023.)

The Lyfgenia study must assess and characterize the risk of secondary malignancies after treatment, and it will include monitoring at prespecified intervals for clonal expansion with adequate testing strategies, the approval *letter* states.

The Casgevy study must assess and characterize the risks of secondary malignancies and off-target effects following genome editing, and the study design must include monitoring at prespecified intervals with adequate testing strategies.

Vertex also must conduct studies to comprehensively assess and screen for the impact of sequence heterogeneity on the risk of off-target editing in the patient population for Casgevy, according to the FDA's approval *letter*.

Specifically, the company must:

- Perform a new in silico, off-target analysis using publicly available databases/datasets to allow for inclusion of more variants. It must perform the analysis using all variants with at least 0.5% allele frequency in at least one of the five continental groups; and

- Perform confirmatory testing, as appropriate and feasible, of all the off-target loci nominated from the new in silico analysis, as well as those that were not accounted for in the previous study using appropriate samples harboring variants.

Priority Review Voucher Controversy

In a regulatory decision that's sure to be controversial, the FDA determined that only Casgevy qualified for a rare pediatric disease priority review voucher.

> ***The FDA denied bluebird's request for a rare pediatric disease priority review voucher because the agency determined the active ingredient in Lyfgenia was previously approved as Zynteglo, a gene***

therapy for β-thalassemia.

The FDA denied bluebird's request for a PRV because the Lyfgenia BLA is for a biological product that contains "an active ingredient that was previously approved in another application," that being Zynteglo (beti-cel), the approval letter states.

Bluebird had previously announced an agreement to sell the PRV it expected to get for Lyfgenia. The company told the analysts call it is currently reviewing the agency's denial of the PRV request and will discuss the matter with the agency.