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Bluebird's Lost Voucher: Lyfgenia Contains Same 'Active Ingredient' As Zynteglo, US FDA Says

by Sue Sutter

Surprise denial of rare pediatric disease priority review voucher could prompt calls for the agency to re-examine how it interprets the term 'active ingredient' for gene therapies. Bluebird asserts there are significant differences between its gene therapies for treating sickle cell and beta-thalassemia.

The US Food and Drug Administration's denial of a rare pediatric disease priority review voucher for *bluebird bio*'s sickle cell treatment Lyfgenia (lovotibeglogene autotemcel, or lovo-cel) could prompt calls for the agency to re-examine how it interprets the term "active ingredient" in the context of gene therapies.

The FDA appears to have concluded that what it previously described as "modest manufacturing differences" between Lyfgenia and bluebird's Zynteglo (betibeglogene autotemcel, or beti-cel) were not enough to distinguish the two products such that the former qualified for a rare pediatric disease priority review voucher. Both gene therapies use the same lentiviral vector and gene payload.

> ***"The agency's decision to deny bluebird's PRV request was a surprise to bluebird. There are significant differences between Lyfgenia and Zynteglo drug properties." – bluebird bio***

The agency approved Lyfgenia on 8 December but denied bluebird's request for a priority review voucher because it determined that the biologics license application "is not a human drug application for a biological product that contains no active ingredient that has been previously approved in any other application under section 351(a) or 351(k)" of the Public Health Service Act, the approval *letter* states. (Also see "*Gene Therapy: US FDA Labeling For Vertex's Casgevy, Bluebird's Lyfgenia Reflect Different Risks*" - Pink Sheet, 8 Dec, 2023.)

Specifically, the Lyfgenia BLA "is for a biological product that contains an active ingredient that was previously approved in another application under section 351(a)," that being Zynteglo.

"The agency's decision to deny bluebird's PRV request was a surprise to bluebird," the company said in a statement to the *Pink Sheet*. "There are significant differences between Lyfgenia and Zynteglo drug properties. We look forward to discussing this matter with FDA and to working with the agency to address its concerns."

Two Vouchers Sold

The FDA approved Zynteglo in August 2022 for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell transfusions. (Also see "*Keeping Track: Axsome's Auvelity Survives Long Review; Bluebird's Zynteglo Cleared For Liftoff; Omeros Appeals CRL*" - Pink Sheet, 19 Aug, 2022.) That approval came with a rare pediatric disease priority review voucher.

Bluebird also picked up a voucher with the September 2022 accelerated approval of another gene therapy, Skysona (elivaldogene autotemcel, or eli-cel) for patients with early, active cerebral adrenoleukodystrophy. (Also see "*Accelerated Approval For Bluebird's Skysona Gives Teeth To US FDA Data Questions*" - Pink Sheet, 19 Sep, 2022.)

The company sold the two PRVs for aggregate net proceeds of $102m and $93m.

Bluebird was expecting a third voucher with Lyfgenia and in October announced the sale of voucher rights to *Novartis AG* for $103m.

Bluebird really could have used the proceeds from another voucher sale. The company had only $227m cash on hand as of 30 September. While this is sufficient to fund operations into the second quarter of 2024, the PRV denial means bluebird will have to find another way to raise funds relatively quickly. (Also see "*Vertex/CRISPR Nab First-Ever Gene Editing FDA Nod, Overshadow Bluebird's Same-Day Win*" - Scrip, 9 Dec, 2023.)

PRV Eligibility Criteria

To be eligible for a rare pediatric disease PRV, an application must be for a drug or biological product:

- That is for the prevention or treatment of a rare disease; and

- Contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 355(b)(1), 355(b)(2), or 355(j) of the FD&C Act or section 351(a) or 351 (k) of the PHS Act.

A July 2019 draft *guidance* on the PRV program states that even though a drug may receive rare pediatric disease designation, "the application for the drug may not qualify as an 'application for a rare pediatric disease product application' – and hence not be likely to receive a priority review voucher – if it contains a previously approved active ingredient (including any ester or salt of the active ingredient)."

A former FDA official noted the agency's use of the term "active ingredient" in explaining the PRV denial for Lyfgenia is unusual because "it's not a CBER kind of term," especially in the gene therapy space.

The Office of Orphan Products Development and Office of Pediatric Therapeutics are responsible for determining whether a drug qualifies for a rare pediatric disease designation, the guidance states. The applicable review divisions and offices within the Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research are responsible for premarket review of the rare pediatric disease product application and determining whether an application meets the eligibility criteria for receiving a PRV.

The FDA anticipates that many rare pediatric disease drugs will qualify for designation as orphan drugs, the guidance states. "There are instances, however, where a drug may qualify as a drug for a 'rare pediatric disease' but not qualify for orphan-drug designation, or vice versa."

Lyfgenia holds rare pediatric disease designation and orphan product designation for treatment of sickle cell disease.

Principles Governing Sameness

In September 2021, the agency finalized a guidance on interpreting sameness of gene therapy products under the orphan drug regulations. (Also see "*US FDA Tweaks Guidance On Sameness Of Gene Therapies, But Questions Remain*" - Pink Sheet, 29 Sep, 2021.)

The final document was similar to the January 2020 draft version, which stated that if two gene therapy products intended for the same use express different transgenes and/or different vectors, the FDA generally intends to consider them different drugs for purposes of orphan designation and exclusivity.

However, if two gene therapy products express the same transgene and use the same vector, determining whether they are the same for orphan designation purposes may also depend upon additional features of the final product that can contribute to the therapeutic effect, such as regulatory elements or the cell type that is transduced, the guidance states. (Also see "*Orphan Exclusivity For Gene Therapies Hinges On Two Big Factors*" - Pink Sheet, 28 Jan, 2020.)

In explaining the FDA's thinking behind the guidance, an agency official cited the desire to guard against awarding "trivial" changes in a product with orphan drug designation and seven-year exclusivity. (Also see "*Gene Therapies: 'Trivial' Changes Will Not Be Rewarded With Orphan Drug Designation And Exclusivity*" - Pink Sheet, 14 Apr, 2020.)

Similar Labeling Descriptions

Some of these principles on sameness may have applied in the case of the FDA's determination on PRV eligibility for Lyfgenia.

In labeling for Zynteglo and Lyfgenia, the product descriptions are almost identical, save for the difference in nonproprietary names and reference to sickle cell patients in the latter.

Both labels state the product is "a βA-T87Q-globin gene therapy consisting of autologous CD34+ cells" containing hematopoietic stem cells "transduced with BB305 LVV encoding βA-T87Q-globin, suspended in cryopreservation solution."

Both products are "intended for one-time administration to add functional copies of a modified form of the β-globin gene (βA-T87Q-globin gene) into the patient's own HSCs."

> ***"Lovo-cel and beti-cel share the same LVV, gene cassette including target gene and promoter, and only have modest manufacturing differences." – Zynteglo clinical review***

The products are prepared using the patient's own HSCs collected through apheresis. "The autologous cells are enriched for CD34+ cells, then transduced ex vivo with BB305 LVV," which Zynteglo labeling describes as a self-inactivating lentiviral vector.

The promoter, a regulatory element that controls the expression of the transgene selected for BB305 LVV, "is a cellular (non-viral) promoter that controls gene expression specific to the erythroid lineage cells (red blood cells and their precursors). BB305 LVV encodes βA-T87Q-

globin."

Although the FDA's review documents for Lyfgenia are not yet publicly available, the clinical review for Zynteglo provides insight into how the agency has viewed the two products relative to each other.

Two sickle cell patients treated with an earlier version of Lyfgenia using a different manufacturing process and transplant procedure developed acute myeloid leukemia and subsequently died. These cases were discussed during the advisory committee review of Zynteglo because both products use the same lentiviral vector. (Also see "*Bluebird's Beta-Thalassemia Gene Therapy Faces US Panel Scrutiny On Hematologic Malignancy Risk*" - Pink Sheet, 8 Jun, 2022.)

The Zynteglo clinical review points to similarities between the products, beyond just the same vector.

"Lovo-cel and beti-cel share the same LVV, gene cassette including target gene and promoter, and only have modest manufacturing differences," the review states.

Vertex Pharmaceuticals Incorporated's sickle cell gene therapy Casgevy (exagamglogene autotemcel, or exa-cel), which incorporates CRISPR/Cas9 gene editing technology, was approved the same day as Lyfgenia and qualified for a rare pediatric disease PRV. The same product is undergoing a standard review for treatment of transfusion-dependent β-thalassemia, with a 30 March 2024 user fee goal date.