

MEMORANDUM

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FDA / CBER / OTAT

BLA 125755 / 0

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Applicant bluebird bio, Inc.

Product / Trade Name elivaldogene autotemcel
SKYSONA

Proposed Indication Slow the progression of neurologic dysfunction in boys
4 – 17 years of age with early, active cerebral
adrenoleukodystrophy (CALD).

BACKGROUND

Bluebird bio, Inc., submitted this Biologics License Application (BLA) for marketing approval of elivaldogene autotemcel (eli-cel) to slow the progression of neurologic dysfunction in boys 4 – 17 years of age with early, active cerebral adrenoleukodystrophy (CALD). The purpose of this memo is to complement the Summary Basis for Regulatory Action (SBRA) by providing my perspective on selected critical issues regarding this BLA.

I appreciate and considered the many thoughtful reviews, memos, and internal FDA discussions that contribute to the review team's consideration of this BLA. I also appreciate and considered the proceedings of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting on June 9, 2022, including the statements submitted to the docket for that meeting.

CALD is a rare, neurodegenerative metabolic disorder caused by X-linked mutations in the *ABCD1* gene that lead to impaired expression of adrenoleukodystrophy protein (ALDP). The rate of progression is highly variable, but CALD can lead to neurologic disability and death. There are no FDA-approved treatments for CALD. The current standard of care is allogeneic hematopoietic stem cell transplant (allo-HSCT).

Please see the review documents and memos for details of this BLA.

EFFECTIVENESS

The primary evidence of effectiveness comes from two single-arm studies (ALD-102 and ALD-104). Study ALD-102 is statistically positive on the pre-specified primary endpoint of event-free survival (i.e., the proportion of subjects who were alive without Major Functional Disability (MFD) or rescue HSCT). These two studies use natural history data and data on CALD patients treated with allo-HSCT as external controls. Unfortunately, as discussed at the Advisory Committee meeting, there were challenges in comparing the two study populations to the control populations. Although allo-HSCT is the current standard of care for patients with early, active CALD, the benefit of allo-HSCT has not been established for regulatory purposes. Concerns regarding the

evidence of effectiveness of allo-HSCT include, but are not limited to, largely retrospective studies, comprising a body of literature that is highly subject to publication bias. Therefore, while comparisons of eli-cel to allo-HSCT may be of interest to the patient and caregiver community, and may provide important information regarding the relative safety of these two interventions, these comparisons are difficult to interpret with regard to the efficacy of eli-cel.

In this setting of a heterogeneous disease, single-arm studies can be difficult to interpret unless the treatment effect is very large or the outcome measures represent events that do not occur, or occur very rarely, in the absence of the study intervention. The Study ALD-102 pre-specified primary outcome measure of event-free survival does not meet this standard. In this setting, the review team went to extraordinary efforts to identify outcomes in the study populations that were not consistent with the natural history of CALD. The clinical review team identified a subgroup of subjects who were at high risk of rapid progression and had MFD-free survival at two years from symptom onset that appears to be inconsistent with the natural history of CALD. This post-hoc subgroup analysis is supported by MRI changes in the study populations, clinical pharmacology data on the association between CD14+ %ALDP+ cells and MFD-free survival at two years, and in vitro studies which demonstrated that “vector-driven *ABCD1* transgene expression and ALDP production resulted in improvements in very-long-chain fatty acid (VLCFA) metabolism in CALD fibroblasts and AMN [adrenomyeloneuropathy] patient CD34+ HSCs” [from Pharmacology / Toxicology Review].

SAFETY

The risk of hematologic malignancy is well-described in the SBRA and will require a post-marketing study to further assess this risk.

INDICATED POPULATION

The Applicant initially proposed that the indicated population be limited to patients with early CALD “who do not have an available and willing HLA-matched sibling HSC donor”. However, as noted above, the effectiveness of allo-HSCT is unclear. In the setting of uncertainty regarding the balance of benefits and risks for both allo-HSCT and eli-cel, the indication should not be restricted by whether the patient has an available and willing sibling donor; rather, the product should be indicated for all boys 4 – 17 years of age with early, active cerebral adrenoleukodystrophy (CALD).

CONCLUSION

Based on the clinical study results, MFD-free survival at 24 months is reasonably likely to predict clinical benefit, taking into account the severity and rarity of CALD and the lack of alternative treatments.

REGULATORY ACTION

Accelerated Approval of elivaldogene autotemcel (eli-cel) to slow the progression of neurologic dysfunction in boys 4 – 17 years of age with early, active cerebral adrenoleukodystrophy (CALD), with a required post-marketing study to further assess the long-term safety, and a required post-marketing study to confirm the benefit of SKYSONA.