CTGTAC June 9, 2022

Day 1 Questions for BLA 125755 AC

Discussion Questions

1. The eli-cel efficacy data are difficult to interpret due to problems with the benchmark calculation, issues of comparability between populations, potential bias, concerns regarding imputation methods, few events during a limited duration of follow-up, and limited sample size for treatment and control populations.

    a. Please discuss the limitations of the primary and secondary efficacy endpoint data, and whether the data support the presence of a clinically meaningful benefit of eli-cel.

    b. Please discuss the population(s) (e.g., children without a matched and willing sibling donor, children without a matched donor) in which the efficacy data are, or are not, supportive of a clinically meaningful benefit.

2. Three eli-cel-treated subjects have developed myelodysplastic syndrome (MDS). Subjects with sickle cell disease treated with a related product, lovotibeglogene autotemcel (lovo-cel), have been diagnosed with myeloid malignancies. Please discuss the extent to which the myeloid malignancies associated with lovo-cel raise concerns regarding risk for hematologic malignancy with eli-cel.

3. Eli-cel has a risk of hematologic malignancy, a potentially fatal adverse event. The number of cases of malignancy (currently 3/67, or 4%) seems likely to increase over time. In addition to the three recognized cases of MDS, there are at least four other subjects with concern for impending MDS. Although the clinical significance is unclear, 98% of subjects in the eli-cel study population have vector integration sites in MECOM, a proto-oncogene. Please discuss the risk of insertional oncogenesis in patients with early active childhood cerebral adrenoleukodystrophy (CALD) treated with eli-cel.

Voting Questions

1. Are the lovo-cel safety data relevant to the safety assessment of eli-cel?

2. Do the benefits of eli-cel outweigh the risks, for the treatment of any sub-population of children with early active cerebral adrenoleukodystrophy (CALD)?

When explaining your vote for Question 2:

a. For Committee members who voted *yes*, please include discussion of the following:

   i. The sub-population(s) of children with early active CALD for whom you believe there is a favorable benefit-risk profile.

   ii. Any additional information you consider necessary to support a favorable benefit-risk profile in any other CALD sub-population.

   iii. Your recommendations, if any, for risk monitoring and mitigation for patients with CALD who receive eli-cel.

b. For Committee members who voted *no*, please include discussion of the following:

   i. Any additional information you consider necessary to support a favorable benefit-risk profile in a particular CALD sub-population.

   ii. Your recommendations, if any, for risk monitoring and mitigation for patients with CALD who receive eli-cel.