CTGTAC June 10, 2022

Day 2 Questions for BLA 125717 AC

Discussion Questions

1. Hematologic malignancies have not occurred in transfusion-dependent β-thalassemia (TDT) subjects treated with beti-cel. However, the beti-cel lentiviral vector (LVV) is similar to the vector used in sickle cell disease (SCD) and is related to the vector used for cerebral adrenoleukodystrophy (CALD), and there have been cases of hematologic malignancies in both SCD and CALD subjects in other studies. In this setting, what is the likelihood that the constellation of delayed platelet reconstitution, abnormal marrow morphology findings, and insertion site analyses will predict future development of hematologic malignancies in TDT patients treated with beti-cel?

2. Please discuss whether patients with TDT should be screened for potential germline and somatic mutations predisposing to hematologic malignancy prior to administration of beti-cel. What screening tests, if any, for such mutations would you recommend?

3. Please discuss the adequacy of the proposed postmarketing pharmacovigilance program, including the long-term follow-up study and registry study and discuss additional recommendations for safety monitoring for hematologic malignancies.

4. Please discuss recommendations for specific testing for hematologic malignancies following administration of beti-cel, to include frequency of testing, in patients with TDT.

Voting Question

1. Do the benefits of beti-cel outweigh the risks for the treatment of subjects with transfusion-dependent β-thalassemia?

   When explaining your vote:

   a. For Committee members who voted *yes*, please include discussion of your recommendations, if any, for risk monitoring and mitigation for patients who receive beti-cel for treatment of TDT.

   b. For Committee members who voted *no*, please discuss the following:

      i. Any additional information you consider necessary to support a favorable benefit-risk profile.

      ii. Your recommendations, if any, for risk monitoring and mitigation for patients who receive beti-cel for treatment of TDT.