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Gene therapy – FDA Advisory Committee update

- On June 9 and 10, the FDA convened a Cellular, Tissue, and Gene Therapies Advisory Committee meeting to discuss two near-term pipeline gene therapies from bluebird bio:
    - Elivaldogene autotemcel (Eli-cel) for the treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy (CALD) who do not have an available and willing HLA-matched sibling hematopoietic stem cell (HSC) donor; and
    - Betibeglogene autotemcel (Beti-cel) for the treatment of patients with β-thalassemia who require regular red blood cell transfusions.

- Both Eli-cel and Beti-cel are *ex vivo* gene therapies. After collecting the patient's hematopoietic stem cells, the CD34+ cells are isolated, activated, and then transduced with either Eli-cel (adds functional copies of the ABCD1 gene) or Beti-cel (adds functional copies of β-globin gene). Patients then undergo myeloablative conditioning before being re-infused with the transduced CD34+ cells.

- The two gene therapies reviewed are for very rare diseases. This is where many gene therapy companies are focusing: in areas where the disease burden is very high, and options are limited. The supporting data comes from single arm trials with small sample sizes and a reliance on natural history data to demonstrate impact of the gene therapy.
    - CALD is a rare, neurodegenerative disease caused by mutations in the ABCD1 gene. Most patients with CALD will die within a decade of diagnosis if they are not treated with hematopoietic stem cell transplantation (HSCT). However, only 10% have an HLA-matched donor. In the U.S., the incidence of ALD is 1 in every 20,000 to 30,000 males. CALD develops in about 40% of affected boys with ALD.
    - β-thalassemia is a blood disorder caused by β-globin gene mutations that impair hemoglobin development. Treatment includes life-long regular blood transfusions and iron chelation therapy. HSCT is the only possible curative therapy. Transfusion-dependent β-thalassemia is estimated to affect about 1,400 patients in the U.S.

Eli-Cel

- The efficacy of Eli-cel was evaluated in two single-arm studies: ALD-102 and ALD-104. Data from these studies were compared to external control data sources.
    - In the main trial, ALD-102 (N = 32), all patients received Eli-cel and 90.6% (95% CI: 75.0, 98.0) were alive and without any of the 6 pre-defined Major Functional Disabilities (MFDs) at the month 24 visit following treatment. This was better than expected based on external control data. The 6 MFDs are loss of communication, cortical blindness, tube feeding, wheelchair dependence, complete loss of voluntary movement, and total incontinence.
    - There were 3 failures of MFD-free survival: 1 patient developed total incontinence at month 9 and subsequently died at month 22, and 2 patients withdrew to receive rescue HSCT at the investigator's discretion due to progressive disease on brain MRI.
    - Of the 67 total patients treated with Eli-cel across the two studies: 14 (20.9%) have completed at least 5 years of follow-up, 13 of whom have maintained MFD-free survival.
    - Hematologic malignancy is the primary safety concern with Eli-cel. Three cases of myelodysplastic syndrome (MDS) have been diagnosed among the 67 patients treated and the FDA was very concerned that additional cases will emerge in the future.

- Despite the risk of MDS, panelists on the Advisory Committee voted unanimously in favor of the benefit vs. risk profile for Eli-cel.

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- Panelists cited the life-threatening nature of CALD and that Eli-cel could at least buy patients some time without developing overwhelming disabilities.
- Additionally, patients receiving mismatched HSCT may experience graft vs. host disease, which does not have a good treatment, and may be at least as troublesome as MDS.

Beti-Cel

- The efficacy of Beti-cel was evaluated in two single-arm studies (HGB-207 and HGB-212) in patients with transfusion dependent β-thalassemia. The primary endpoint was the proportion of patients achieving transfusion independence, at any time after drug product infusion. As the Phase 3 studies are ongoing, only 36 of 41 patients (88%) have completed the follow-up period at the time of data lock.
    - Of the 36 evaluable patients, 32 (88.9%) achieved transfusion independence. The weighted average hemoglobin during transfusion independence was 11.5 g/dL.
    - Of 32 patients who achieved transfusion independence, 20 (62.5%) were able to stop iron chelation for at least 6 months post Beti-cel infusion.
    - No malignancies were detected in Beti-cel recipients, however another product manufactured by bluebird bio with an identical lentiviral vector has been associated with two cases of acute myeloid leukemia.
- The Advisory Committee voted unanimously in favor of the benefit vs. risk profile for Beti-cel, citing the strong efficacy results, the high burden of disease associated with transfusion-dependent β-thalassemia, and risks associated with HSCT.
- Bluebird bio is expecting an FDA approval decision for Beti-cel and Eli-cel by August 19, 2022, and September 16, 2022, respectively.
- In addition to Beti-cel and Eli-cel, several other investigational gene therapies have been submitted or are expected to be submitted to the FDA for review in the near term, with a potential approval by the end of 2023.

Drug name	Manufacturer	Indication	Potential Approval Decision
Beti-cel	bluebird bio	β-thalassemia	8/19/2022
Eli-cel	bluebird bio	CALD	9/16/2022
Etranacogene dezaparvovec	CSL Behring/ uniQure	Hemophilia B	11/24/2022
Valoctocogene roxaparvovec	BioMarin	Hemophilia A	1H 2023
Eladocagene exuparvovec	PTC Therapeutics	Aromatic L-amino acid decarboxylase deficiency	2Q 2023
OTL-200	Orchard Therapeutics	Metachromatic leukodystrophy	3Q 2023
OTL-103	Orchard Therapeutics	Wiskott-Aldrich syndrome	2H 2023
Lovotibeglogene autotemcel	bluebird bio	Sickle cell disease	4Q 2023