Zynteglo® (betibeglogene autotemcel) – New orphan drug approval

- On August 17, 2022, the FDA announced the approval of bluebird bio's Zynteglo (betibeglogene autotemcel), for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.

- β-thalassemia is an inherited blood disorder that causes a reduction of normal hemoglobin and RBCs in the blood, through mutations in the beta-globin subunit. Transfusion-dependent β-thalassemia, the most severe form of the condition, generally requires life-long RBC transfusions as the standard course of treatment. These regular transfusions can be associated with multiple health complications of their own, including problems in the heart, liver, and other organs due to an excessive build-up of iron in the body.

    - Bluebird estimates that there are approximately 1,300 to 1,500 individuals with transfusion-dependent β-thalassemia in the U.S.

- Zynteglo is an autologous hematopoietic stem cell-based gene therapy product administered as a single dose. Each dose of Zynteglo is a customized treatment created using the patient's own bone marrow stem cells that are genetically modified to produce functional beta-globin (a hemoglobin component).

- The efficacy of Zynteglo was established in two ongoing open-label, single-arm, 24-month studies (Study 1 and Study 2) in 41 patients aged 4 to 34 years with β-thalassemia requiring regular transfusions. All patients were administered granulocyte-colony stimulating factor and plerixafor to mobilize stem cells prior to an apheresis procedure and then full myeloablative conditioning with busulfan prior to treatment with a one-time dose of Zynteglo.

- Study 1 was conducted in 23 patients with β-thalassemia requiring regular transfusions and with a non-β0 /β0 genotype. The median duration of follow-up is 29.5 months. The primary endpoint was achievement of transfusion independence (TI), defined as a weighted average Hb ≥ 9 g/dL without any packed RBC transfusions for a continuous period of ≥ 12 months at any time during the study, after infusion of Zynteglo.

    - Of 22 patients evaluable for TI, 91% (95% CI: 71, 99) achieved TI with a median weighted average hemoglobin during TI of 11.8 g/dL.
    - All patients who achieved TI maintained TI, with a min, max duration of ongoing TI of 15.7+, 39.4+ months.

- Study 2 was conducted in 18 patients with β-thalassemia requiring regular transfusions and a β0 /β0 or non-β0 /β0 genotype. The median duration of follow-up is 24.6 months. The primary endpoint was achievement of TI.

    - Of 14 patients evaluable for TI, 86% (95% CI: 57, 98) achieved TI with a median weighted average hemoglobin during TI of 10.20 g/dL.
    - All patients who achieved TI maintained TI, with a min, max duration of ongoing TI of 12.5+, 32.8+ months.

- Warnings and precautions for Zynteglo include delayed platelet engraftment; risk of neutrophil engraftment failure; risk of insertional oncogenesis; hypersensitivity reactions; anti-retroviral and hydroxyurea use; and interference with serology testing.

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- The most common non-laboratory adverse reactions (≥ 20%) with Zynteglo use were mucositis, febrile neutropenia, vomiting, pyrexia, alopecia, epistaxis, abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus.

- The most common Grade 3 or 4 laboratory abnormalities (> 50%) with Zynteglo use were include neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia.

- Zynteglo is provided as a single dose for infusion containing a suspension of CD34+ cells in one or more infusion bags. The minimum recommended dose of Zynteglo is 5.0×10^6 CD34+ cells/kg.

    - Zynteglo is designed to be administered to the patient once, but the treatment process is comprised of several steps that may take place over the course of several months.
    - Refer to the Zynteglo drug label for complete dosing and administration recommendations.

- Zynteglo will be priced at $2.8 million for a one-time dose.

- Bluebird bio expects to start the treatment process for patients with Zynteglo in the fourth quarter of 2022.