



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology**

**Pharmacovigilance Plan Review Memorandum
ZYNTEGLO™ (BLA 125717/0)**

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Chair, BLA Review Committee
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STN: Original BLA 125717/0

Product: Proposed brand name: ZYNTEGLO (beti-cel) and also known as LentiGlobin BB305

Proposed indication: Treatment of patients with β -thalassemia who require regular red blood cell transfusions

Sponsor: bluebird bio, Inc.

Action Due Date: August 19, 2022

1. INTRODUCTION

Objectives and Scope

The sponsor, bluebird bio, Inc., submitted an original BLA 125717/0 on 09/20/2021, seeking licensure for the product proposed proprietary name "ZYNTÉGLO™" for the treatment of patients with β -thalassemia who require regular red blood cell transfusions. The product is also referred to by the name LentiGlobin BB305, betibeglogene autotemcel, and beti-cel in the submission. The purpose of this memorandum is to review the pharmacovigilance plan proposed by the sponsor for postmarketing safety monitoring and to identify potential safety concerns that may require further additional postmarketing safety surveillance, studies, or other pharmacovigilance activities if the product is licensed.

Product Description

ZYNTÉGLO™ is a 20mL suspension for IV infusion containing (b) (4) to 20×10^6 CD34 + hematopoietic human stem cells suspended in cryopreservation solution 5% DMSO, proposed for autologous infusion.

Per the sponsor, the process of administration of ZYNTÉGLO™ begins with hematopoietic stem cell mobilization with granulocyte colony-stimulating factor (GC-SF). Peripheral blood mononuclear cells (PBMCs) are collected by apheresis (up to 2 mobilization cycles separated by at least 2 weeks) for both drug product manufacture and to provide back-up cells for rescue (in the event of an engraftment failure). These autologous CD34+ stem cells derived from the patient are exposed to an attenuated lentivirus carrying the gene for beta globin and cryopreserved. The recipient then undergoes myeloablative conditioning for 4 consecutive days followed by at least 48 hours of washout. On Day 1, the cryopreserved cells (ZYNTÉGLO™) are reintroduced to the patient via IV infusion at a dose of $\geq 5.0 \times 10^6$ CD34+ cells/kg, (median dose of (b) (4) $\times 10^6$ CD34+ cells/kg (range 5.0, (b) (4))). Upon engraftment, the patient is expected to produce hemoglobin expressing this transgenic β -globin.

Mechanism of action

Long-term expression of transgenic β -globin from engrafted autologous hematopoietic stem cells.

Proposed indication

The indication sought is for treatment of patients with β -thalassemia, who require regular red blood cell transfusions.

Regulatory and Development History

Beti-cel was granted an accelerated assessment by the Committee for Medicinal Products for Human Use (CHMP) of the EMA in July 2018. Bluebird bio submitted the Marketing Authorization Application (MAA) on August 21, 2018. On March 28, 2019, the CHMP adopted a positive opinion recommending conditional marketing authorization for beti-cel under the proprietary name of ZYNTÉGLO for *"patients 12 years and older with transfusion-dependent β -thalassaemia (TDT) who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available."* Global marketing

authorization approval was granted on May 29, 2019 in the EU/European Economic Area/United Kingdom and ZYNTEGLO launched for marketing in Germany on November 13, 2019.

On February 12, 2021, the Marketing Authorization Holder (MAH) temporarily suspended marketing of ZYNTEGLO following a report of a case of acute myeloid leukemia in a patient with sickle cell disease treated with investigational product bb1111 which uses a similar lentiviral vector as used in ZYNTEGLO. The case represented the second case of acute myeloid leukemia occurring in a patient with sickle cell disease treated with bb1111. The first case, reported in 2018, was an event of myelodysplastic syndrome progressing to acute myeloid leukemia. This case was ultimately assessed as not related to bb1111 or the lentiviral vector. It was determined that the 2 cases of myelodysplastic syndrome in patients with sickle cell disease (occurring 3 and 5.5 years post treatment with bb1111) did not result from insertional oncogenesis. The signal was closed in March 2021.

In the US, the initial IND (IND 15324) was submitted to the FDA on December 19, 2012, and beti-cel was subsequently granted Fast Track, Rare Pediatric Disease (RPD), Breakthrough Therapy (BT), and Orphan Drug Designation (ODD) for the treatment of β -thalassemia major and intermedia. A pre-BLA meeting was held in November of 2019. On February 17, 2021, a clinical hold was issued by the FDA, due to safety concerns related to reports of acute myeloid leukemia and myelodysplastic syndrome in a patient with sickle cell disease treated with LentiGlobin BB305 on a different IND (IND 15905); the hold was subsequently removed on June 03, 2021.

On September 20, 2021, the sponsor submitted BLA STN 125717 for licensure of ZYNTEGLO in the US.

In December of 2021, the sponsor submitted a request to the EMA to withdraw EU Marketing Authorization for beti-cel due to commercial reasons. The withdrawal became effective on April 15, 2022. Per the sponsor, the decision was based on the inability to be reimbursed by the European Authority, making sustainability of operations in Europe infeasible.

2. MATERIALS REVIEWED

Materials reviewed in support of this pharmacovigilance plan assessment are listed below.

Original BLA submission STN 125717/0

- Module 1.16.1: Pharmacovigilance Plan/Risk Management Plans
- Module 1.14.1.2: Draft Labeling (annotated draft labeling)
- Module 2.5: Clinical Overview
- Module 2.7.4: Summary of Clinical Safety
- Module 5.3.5.2: Study Reports
 - Clinical trial HGB-207 study report body
 - Clinical trial HGB-212 study report body
 - Clinical trial LTF-303 study report body
- Module 5.3.5.4 Other Study Reports: Post Approval Registry REG-501 protocol

- STN 125717/0/12 Module 5.3.5.3: 90-Day Safety Update (dated 12/17/2021)
- Module 5.3.5.4 STN 125717/0/12 Late Breaking SAEs Monthly submissions
- Module 5.3.6: Periodic Safety Update Report
- Module 5.3.5: Monthly MDS reports February 01, 2022 – August 01, 2022
- Module 1.11.3: Clinical Information Amendment
 - Response to IR dated December 15, 2021 STN 125717/0/14 Module 1.11.3 (dated 12/21/2021)
 - Response to IR dated December 16, 2021 STN 125717/0/15 Module 1.11.3 (date 12/21/2021)
 - Response to IR dated January 4, 2021 STN 125717/0/21 Module 1.11.3 (dated 1/12/2022)
 - Response to request during external midcycle meeting to provide revised milestones and number of patients anticipated for enrolment pertaining to REG-501 - STN 125717/0/28 module 1.11.3 (dated 2/2/2022)
 - Response to IR dated February 16, 2022 STN 125717/0/41 Module 5.3.5.4 (Appendices 16.1.1) (dated 2/28/2022)
 - Response to IR dated April 20, 2022 STN 12571/0/56 Module 1.11.3 (Clinical Information Amendment (dated April 25, 2022)

3. CLINICAL STUDIES

In support of the BLA submission, the sponsor submitted safety data from two completed Phase 3 safety/efficacy clinical trials: “HGB-207” and “HGB-212,” as well as 1 long term follow up study of safety and efficacy, “LTF-303.”

3.1 Clinical Trial HGB-207

Study HGB-207, titled “A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent β -Thalassemia, who do not have a β^0/β^0 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral β^{A-T87Q} -Globin Vector in Subjects ≤ 50 Years of Age,” involved 23 beti-cel treated patients (safety population). Among these 23 subjects were 15 patients ≥ 12 years of age (cohort 1) and 8 patients < 12 years of age (cohort 2).

Study duration: The study was initiated on August 08, 2016. Per the sponsor, enrollment for Study HGB-207 is complete as of March 09, 2021; however, the study was ongoing at the time of submission of the BLA, and the submitted interim data had a database lock point of March 09, 2021. Initial subject follow-up was planned for approximately 24 months after beti-cell infusion, followed by enrollment in long-term follow up study LTF-303 (discussed later in this review) for up to an additional 13 years (total follow up time of 15 years following beti-cel infusion). At the time of submission, 19 patients in safety population had completed the 24 month visit with median follow up of 24.28 months (ranging between 13 to 27.5 months).

Main inclusion criteria:

- Age ≤ 50 years of age at the time of consent and with a history of at least 100 mL/kg/year of packed red blood cells (pRBCs) transfusions in the 2 years preceding

enrollment (all patients) or managed under standard thalassemia guidelines with ≥ 8 transfusions of pRBCs per year in the 2 years preceding enrollment (for patients ≥ 12 years).

- Clinically stable and eligible to undergo hematopoietic stem cell transplantation (HSCT)

Main exclusion criteria:

- Mutation consisting of either β^0 or IVS-I-110 on both HBB alleles (genotypes of β^0/β^0 , $\beta^0/\text{IVS-I-110}$, or $\text{IVS-I-110}/\text{IVS-I-110}$).
- Positive test for HIV, hepatitis B or C, and syphilis
- Clinically significant and active bacterial, viral, fungal, or parasitic infection
- WBC count $< 3 \times 10^9/\text{L}$, and/or platelet count $< 100 \times 10^9/\text{L}$ unrelated to hypersplenism
- Uncorrected bleeding disorder
- History of malignancy or myeloproliferative or immunodeficiency disorder
- Immediate family member with Familial Cancer Syndrome, Prior HSCT, advanced liver disease, estimated glomerular filtration rate $< 70 \text{ ml/min/1.73m}^2$
- Pregnancy/absence of adequate (2 methods of) contraception

Safety endpoints:

Safety endpoints consist of incidence of transplant-related mortality through 100 days and through 365 days post-drug product, overall survival, detection of vector-derived replication competent lentivirus in any subject, monitoring of laboratory parameters, frequency and severity of clinical adverse events, incidence of acute and/or chronic graft versus host disease, and incidence of adverse events related to insertional oncogenesis, such as myelodysplasia, leukemia, and lymphoma.

Safety Review HGB-207

Treatment Emergent Adverse Events (TEAEs)

AEs that occurred during or after drug product infusion (Day 1 to Month 24) were considered TEAEs. There were 614 total TEAEs, and all 23 patients experienced at least 1 TEAE, and 24 serious TEAEs were experienced by 12 patients.

Thrombocytopenia was experienced by all 23 patients (23/23, 100%). Other common TEAEs experienced (by ≥ 5 patients) were neutropenia in 8 patients (78.3%), stomatitis in 8 patients (78.3%), anemia in 16 patients (69.6%), leukopenia in 13 patients (56.5%), pyrexia in 13 patients (56.5%), vomiting in 12 patients (52.2%), nausea in 11 patients (47.8%), epistaxis in 10 patients (43.5%), febrile neutropenia in 9 patients (39.1%), alanine aminotransferase increase in 9 patients (39.1%), cough in 9 patients (39.1%), abdominal pain in 8 patients (34.8%), alopecia in 7 patients (30.4%), headache in 7 patients (30.4%), diarrhea in 7 (30.4%), nausea in 7 patients (30.4%), constipation in 6 patients (26.1%), aspartate aminotransferase increased in 6 patients (26.1%), pruritus in 6 patients (26.1%), upper respiratory tract infection in 5 patients (21.7%), and decreased appetite in 5 patients (21.7%).

The 90 Day Safety Update reported 2 additional nonserious AEs in 2 patients between initial data cutoff date 3/09/2021 and 90 day safety report cutoff date of August 18,

2021, consisting of ligament pain in 1 patient and blood alkaline phosphatase increased in the other patient.

Serious Treatment Emergent Adverse Events

The 24 serious TEAEs experienced by 12 patients are summarized in Table 1 below.

Table 1. Serious TEAEs Study HGB-207

Patient ID	SERIOUS AE(s)	Outcome(s)	Comments/Days post ZYNTEGLO
207-(b) (6)	Hypotension	Resolved	Hypotension occurred on day 11 and was reported as resulting from blood loss from multiple episodes of epistaxis, and resolved by day 12
207-(b) (6)	Venoocclusive liver disease, hypoxia	All resolved	Hypoxia occurred on day 33 and resolved on day 36 in setting of ascites and venoocclusive liver disease occurred as non-serious initially on day 26 and serious on day 34 and resolved by day 84.
207-(b) (6)	Epistaxis	Resolved	
207-(b) (6)	Pyrexia, viral pneumonia, viral infection	All Resolved	Pyrexia occurred on day 44 in setting of 2 weeks of dry cough and resolved on day 46; cultures were negative; subsequently viral pneumonia/viral infection with COVID 19 was diagnosed on day 53.
207-(b) (6)	Bacterial sepsis	Resolved	Bacterial sepsis was diagnosed on day 149 and 152 with cultures positive for <i>Streptococcus mitis</i> and coagulase negative Staphylococci and resolved by day 162.
207-(b) (6)	Transfusion reaction	Resolved	Hemolytic transfusion reaction
207-(b) (6)	Venoocclusive liver disease	Resolved	Venoocclusive liver disease occurred on day 23 and resolved by day 37
207-(b) (6)	Contusion	Resolved	Contusion occurred on day 505 as a result of trauma during an altercation.
207-(b) (6)	Pyrexia	Resolved	Pyrexia occurred on day 37 and cultures and imaging were negative and was resolved by day 44.
207-(b) (6)	Neutropenic sepsis, thrombocytopenia, femur fracture	All resolved	Neutropenic sepsis occurred on day 9 and resolved on day 10. Platelet engraftment had occurred on day 53. Thrombocytopenia occurred on day 114 which resolved on day 163. Femur

			fracture was related to removal of a pre-existing metal device placed for skeletal malformation correction and resolved on day 677 with osteosynthesis with PediLoc.
207-(b) (6)	Neutropenia, febrile neutropenia, thrombocytopenia, stomatitis, sepsis, appendicitis	All resolved	Neutropenia occurred on day 10 and resolved on day 23 Thrombocytopenia occurred on day 12 and resolved on day 50 Febrile neutropenia occurred in setting of sepsis due to <i>Klebsiella pneumoniae</i> and along with stomatitis, all resolved by day 18. Appendicitis occurred on day 200 and resolved after appendectomy and IV antibiotics by day 204.
207-(b) (6)	*Venoocclusive disease, atrial fibrillation, lower respiratory tract infection	All resolved	Patient history includes preexisting atrial fibrillation and iron overload from longer RBC transfusions. *Liver MRI subsequently ruled out venoocclusive liver disease.

Additionally, in January of 2021, a 5 year old patient participating in study HGB-207 experienced tachycardia which was determined to have been associated with infusion. "Tachycardia" was added to the Company Core Data Sheet under the category of infusion-related reactions. Of note, tachycardia is a well documented response to infusion.

There were no additional serious TEAEs reported in the 90 day safety update report between initial data cutoff date March 09, 2021 and 90 day safety report cutoff date of August 18, 2021 in study HGB-207.

Adverse Events of Special Interest

All 23 patients achieved neutrophil engraftment; median time to engraftment was 23 days (range 13, 32). No patient was reported as having met predefined criteria of neutrophil engraftment failure (engraftment failure is defined as failure to achieve an absolute neutrophil count (ANC) ≥ 500 cells/ μ L for 3 consecutive days by Day 43, or receiving back-up cells at any time during the neutropenic phase).

All patients also achieved platelet engraftment, defined as more than $>20 \times 10^9/L$ for 3 consecutive platelet values post-transplant without transfusion support. The median time to engraftment was 46.0 days (range 20 to 94 days). There was no predefined value for platelet engraftment failure specified in the study, but the sponsor did note that median time to platelet engraftment in patients who received ZYNTGLO exceeded standard engraftment times for allogeneic hematopoietic stem cell transplant (an alternative treatment to gene therapy), which is expected to be on average around 20-

30 days^{1 2 3}. The sponsor acknowledged that it is unclear if delayed engraftment is specific to beti-cel or consistent with what would be expected for autologous transplantation in β -thalassemia. Of note, patients who experienced platelet engraftment times above the median 46 days were not found to sustain more bleeding events than patients who experienced more rapid engraftment.

None of the patients who received treatment with ZYNTEGLO discontinued study participation (i.e. no TEAEs lead to discontinuation).

There were no reports of acute or chronic graft versus host disease or graft failure.

There was no report of lentiviral vector replication competent lentivirus.

Integration site analysis reported polyclonal reconstitution with no clonal predominance. Patients were evaluated for persistent oligoclonality, defined as $\geq 10\%$ relative frequency on 2 occasions 3 months apart. No patient met criteria for oligoclonality.

There was no evidence of insertional oncogenesis in this study.

There were no deaths reported in study HGB-207.

Reviewer comment: The majority of adverse events are expected and related to the indication for use or are reactions to the procedures involved in beti-cel administration. Beti-cel is indicated for a population that undergoes chronic transfusion with red blood cells. Chronic red blood cell transfusion can cause hemochromatosis. Transplant conditioning with use of the alkylating agent busulfan is associated with venoocclusive liver disease. Adverse events related to blood cell depletion are understood risks of post-transplant neutropenia. These adverse events can include thrombocytopenia, which can lead to increased risk of bleeding, and neutropenia or lymphopenia which can increase the risk of infection.

3.2 Clinical Trial HGB-212

Study HGB-212, titled “A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent β -Thalassemia by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral

¹ Bernardo. ME, Piras E, Vacca A, et al. Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan. *Blood*. 2012;120:473–6.

² Sellathamby S, Lakshmi KM, Busson M, et al (2012) Polymorphisms in the immunoregulatory genes are associated with hematopoietic recovery and increased susceptibility to bacterial infections in patients with thalassaemia major undergoing matched related hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2012;18:1219–26.

³ Anurathapan U, Hongeng S, Pakakasama S, et al (2016) Hematopoietic stem cell transplantation for homozygous beta-thalassemia and beta-thalassemia/hemoglobin E patients from haploidentical donors. *Bone Marrow Transplant*. 2016; 51:813–8.

β^{A-T87Q} -Globin Vector in Subjects ≤ 50 Years of Age,” enrolled 19 patients; 1 patient discontinued prior to ZYNTEGLO administration (after 1 cycle of mobilization) due to “withdrawal of consent” not further specified. The safety population of 18 patients was comprised of a cohort of 10 patients ≥ 12 years of age (cohort 1) and a cohort of 8 patients <12 years of age (cohort 2). In contrast to trial HGB-207, conducted in patients without a β^0/β^0 genotype at the β -globin (HBB) gene), trial HGB-212 included patients with β^0/β^0 , $\beta^0/\text{IVS-I-110}$, or $\text{IVS-I-110}/\text{IVS-I-110}$ genotype at the HBB gene.

Study duration: The study was initiated on June 08, 2017. Initial subject follow-up was planned for approximately 24 months after beti-cell infusion, followed by enrollment in long-term follow up study LTF-303 (discussed later in this review) for up to an additional 13 years (total follow up time of 15 years following beti-cel infusion). At the time of submission, 10 patients from the safety population had completed the 24 month visit with median follow up of 23.98 months (range 20.4, 26.8 months).

Main inclusion criteria:

- Age ≤ 50 years of age at the time of consent and with a history of at least 100 mL/kg/year of packed red blood cells (pRBCs) transfusions in the 2 years preceding enrollment (all patients) or managed under standard thalassemia guidelines with ≥ 8 transfusions of pRBCs per year in the 2 years preceding enrollment (for patients ≥ 12 years).
- Clinically stable and eligible to undergo hematopoietic stem cell transplantation (HSCT)

Main exclusion criteria:

- Mutation characterized as other than β^0 (e.g., β^+ , β^E , β^C) on at least one *HBB* allele (*HBB* mutation IVS-I-110 [HGVS nomenclature: *HBB*:c.93-21G>A] was considered equivalent to a β^0 mutation for screening/enrollment purposes)
- Positive test for HIV, hepatitis B or C, and syphilis
- Clinically significant and active bacterial, viral, fungal, or parasitic infection
- WBC count $< 3 \times 10^9/\text{L}$, and/or platelet count $< 100 \times 10^9/\text{L}$ unrelated to hypersplenism
- Uncorrected bleeding disorder
- History of malignancy or myeloproliferative or immunodeficiency disorder
- Immediate family member with Familial Cancer Syndrome, Prior HSCT, advanced liver disease, estimated glomerular filtration rate $< 70 \text{ mL/min/1.73 m}^2$
- Pregnancy/absence of adequate (2 methods) of contraception

Safety endpoints:

Safety endpoints consisted of incidence of transplant related mortality through 100 days and through 365 days post-drug product, overall survival, detection of vector-derived replication competent lentivirus in any subject, monitoring of laboratory parameters, frequency and severity of clinical adverse events, incidence of acute and/or chronic graft versus host disease, and incidence of adverse events related to insertional oncogenesis such as myelodysplasia, leukemia, lymphoma.

Safety Review HGB-212

Treatment Emergent Adverse Events

All 18 patients experienced at least 1 TEAE. There were 408 total TEAEs. 8 serious TEAEs were experienced by 3 patients.

Thrombocytopenia was the most common TEAE, experienced by 17 of the 18 patients (94.4%). Other common TEAEs, experienced (by ≥ 5 patients), in addition to thrombocytopenia were neutropenia in 16 patients (88.9%), anemia in 15 patients (83.3%), febrile neutropenia in 12 patients (66.7%), stomatitis in 11 patients (61.1%), alopecia in 11 patients (61.1%), vomiting in 8 patients (44.4%), mucosal inflammation in 7 patients (38.9%), abdominal pain in 7 patients (38.9%), pyrexia in 7 patients (38.9%), epistaxis in 7 patients (38.9%), leukopenia in 6 patients (33.3%), procedural pain in 6 patients (33.3%), decreased appetite in 5 patients (27.8%), headache in 5 patients (27.8%), and skin hyperpigmentation in 5 patients (27.8%).

The 90 Day Safety Update reported 6 additional TEAEs (5 nonserious and 1 serious) in 3 patients between initial data cutoff date March 09, 2021, and 90 day safety report cutoff date of August 18, 2021. These TEAEs included contact dermatitis in 1 patient, bone pain in 1 patient, and COVID-19, hepatic mass, osteopenia, and serious pyrexia in a third patient.

Serious Treatment Emergent Adverse Events

The 8 serious TEAEs experienced by 3 patients in the initial submitted data consisted of congestive cardiac failure, pyrexia (experienced by 2 of the 3 patients), headache, thrombocytopenia, stomatitis, febrile neutropenia, neutropenia. All outcomes were reported as resolved.

There was 1 additional serious TEAE of pyrexia reported in the 90 safety update report (between initial data cutoff date 3/09/2021 and 90 day safety report cutoff date of August 18, 2021 in this study).

Table 2. Serious TEAEs Study HGB-212

Patient ID	SERIOUS AE(s)	Outcome(s)	Comments/Days post ZYNTGLO
212-(b) (6)	Cardiac failure	Resolved	Patient had mild to moderate cardiac muscle iron overload at screening. The patient experienced sudden palpitations and shortness of breath on day 18 and was found to have dilated left ventricle and received supportive care and iron chelation therapy symptomatically improved and ejection fraction improved (increased) and by day 144 cardiac failure was considered resolved
212-(b) (6)	Pyrexia	Resolved	Pyrexia occurred on day 53 and ended on day 54. Cultures were

			negative and by day 58 the event of pyrexia was considered resolved (after culture results).
212-(b) (6)	Pyrexia, headache, thrombocytopenia, neutropenia, febrile neutropenia, stomatitis	All Resolved	<p>Neutropenia occurred on day 11 and the patient received GCSF and neutropenia resolved by day 35 and the patient achieved neutrophil engraftment on day 36.</p> <p>Febrile neutropenia and stomatitis both occurred on day 12 in the setting of nasal culture positive for <i>Staphylococcus aureus</i>, and urine culture positive for <i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i> (blood cultures results were negative); antibiotics were administered; febrile neutropenia and stomatitis both resolved on day 17</p> <p>Thrombocytopenia (serious) occurred on day 13 (started as nonserious on day 12) and patient received platelets and thrombocytopenia resolved by day 31 and patient achieved platelet engraftment by day 39.</p> <p>Pyrexia and headache occurred on day 60; blood and urine cultures were negative; paracetamol was administered (stopped on day 61) and both pyrexia and headache resolved by day 62.</p>
212-(b) (6)	Pyrexia (reported in the 90 Day Safety Update Report)	Resolved	<p>Pyrexia occurred on day 666 accompanied by increased white blood cell counts and increased absolute neutrophil count in the setting of urine culture showing 20,000 colonies of mixed urogenital flora and blood in urine; the patient received antibiotic therapy and pyrexia resolved by day 668</p>

Adverse Events of Special Interest

All 18 patients achieved neutrophil engraftment; median time to engraftment was 26 days (range 14, 39), and no patient was reported as having met predefined criteria (described above in HGB-207) of neutrophil engraftment failure.

All patients achieved platelet engraftment (criteria defined above in HGB-207); median time to engraftment was 49.5 days (range 21, 64). Median engraftment times thus again exceeded standard engraftment times for allogeneic hematopoietic stem cell transplant.

However, patients with engraftment times above 49.5 days did not exhibit more bleeding episodes than patients with engraftment times below 49.5 days. Of note, patients who experienced platelet engraftment times above the median 49.5 days were not found to sustain more bleeding events than patients who experienced more rapid engraftment.

None of the patients who received treatment with ZYNTEGLO discontinued study participation (i.e. no TEAEs lead to discontinuation).

There were no reports of acute or chronic graft versus host disease or graft failure.

There was no report of lentiviral vector replication competent lentivirus or malignancies.

Integration site analysis reported polyclonal reconstitution with no clonal predominance. Patients were evaluated for persistent oligoclonality, defined as $\geq 10\%$ relative frequency on 2 occasions 3 months apart. No patient met criteria for oligoclonality.

There was no evidence of insertional oncogenesis in this study.

There were no deaths reported in study HGB-212.

Reviewer comment: The majority of adverse events were expected and related to indication for use or were related to conditioning or procedures involved in beti-cel administration. Chronic transfusion with red blood cells can cause hemochromatosis which can affect various tissues/organs, including the cardiac muscle. Adverse events related to blood cell depletion are understood risks of post-transplant neutropenia. These adverse events can include thrombocytopenia, which can lead to increased risk of bleeding, and neutropenia or lymphopenia which can increase the risk of infection.

3.3 Long Term Followup Study LTF-303

The ongoing long term follow up study LTF-303, titled “Long-term Follow-up of Subjects with Hemoglobinopathies Treated with Ex Vivo Gene Therapy Using Autologous Hematopoietic Stem Cells Transduced with a Lentiviral Vector,” monitors the long-term efficacy and safety of the gene therapy product in patients previously enrolled in studies HGB-207 and HGB-212. At the time of data cut off for the interim report submitted in support of this BLA, LTF-303 had enrolled 19 patients from parent study HGB-207 and 10 patients from parent study HGB-212.

Study duration: The study was initiated on January 06, 2014, and the interim database lock is April 13, 2021. During Study LTF-303, subjects are evaluated every 6 months through 5 years post-drug product infusion and then annually from 5 years through 15 years post-drug product infusion. As of the interim data, the longest duration of follow-up for a subject since drug product infusion in their parent study was approximately 7 years (86.5 months), with median follow up of 44.2 months (range 22.9 to 86.5 months) for subjects treated with beti-cel.

Main inclusion criteria:

- Eligible patients (based on parent study criteria for enrollment into REG-303) who were treated with drug product for therapy of a hemoglobinopathy in a bluebird bio-sponsored clinical study

Main exclusion criteria:

- None

Safety endpoints:

Safety endpoints were overall survival, all product related adverse events and serious adverse events regardless of relatedness to drug product through Year 15, immune related adverse events (e.g. autoimmune disorders, graft-versus-host-disease, opportunistic infections, HIV), new or worsening hematologic disorders, new or worsening neurologic disorders, malignancies, incidence of vector-derived replication competent lentivirus (as clinically indicated), incidence of adverse events related to insertional oncogenesis (e.g myelodysplasia, leukemia, lymphoma).

Safety Review LTF-303

Adverse Events

There was 1 adverse event reported during study LTF-303 in a patient enrolled from parent study HGB-207 as of the original data cutoff of March 09, 2021. The reported event was a serious event of cholelithiasis, further discussed below.

There was an additional AE reported during study LTF-303 in a different patient enrolled from parent study HGB-207 as of data cutoff of the 90 Day Safety Report of August 18, 2021. The reported event was a serious event of gastritis, further discussed below.

No AEs were reported in patients who had enrolled in study LTF-3030 from study HGB-212, as of data cutoff of the 90 Day Safety Report of August 18, 2021.

Serious Adverse Events

The serious adverse events occurring during LTF-303 are described in the Table below:

Table 3. Serious AEs Study LTF-303

Patient ID	Serious AE	Outcome(s)	Comments/Days post ZYNTGLO
207-(b) (6)	Cholelithiasis	Resolved	Cholelithiasis occurred on day 800 and a laparoscopic cholecystectomy was performed and cholelithiasis was reported as resolved on day 839. Cholelithiasis is a known complication of β -thalassemia, and the event was likely related to underlying condition.

207-(b) (6)	Gastritis (reported in the 90 Day Safety Update Report)	Resolved	Gastritis occurred on day 900 and the patient experienced vomiting and was hospitalized and found to have increased amylase and iron overload. Abdominal ultrasound was normal, X ray showed constipation, acute abdomen was ruled out, and the patient was diagnosed with viral gastritis, which resolved on day 905. Amylase elevation/exocrine pancreas dysfunction can be associated with the effects of hemochromatosis from chronic transfusion in patients with β -thalassemia.
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Adverse Events of Special Interest

There have been no deaths reported in study LTF-303.

There have been no discontinuations reported due to AEs in study LTF-303.

There have been no AEs associated with graft rejection or GVHD reported in study LTF-303.

There have been no AEs of malignancies reported in study LTF-303.

3.4 Late Breaking Information

Monthly updates (late breaking information) were submitted by the sponsor beginning on February 1, 2022, to provide information regarding insertional oncogenesis and MDS. No cases of insertional oncogenesis/MDS in ZYNTEGLO BLA 125717 studies have been reported as of latest submission STN 125717/0/90 dated August 01, 2022.

5. SPONSOR-PROPOSED PHARMACOVIGILANCE PLAN

The pharmacovigilance plan (PVP) (dated August 23, 2021) proposed by the sponsor is summarized in the table below:

Table 4. Safety Concerns and Sponsor Proposed Risk Mitigation Plan

Type of Concern	Safety Concern	Planned Pharmacovigilance Activity/Risk Minimization
Important Identified	Delayed Platelet Engraftment	Routine and/or Additional Pharmacovigilance Activity Routine pharmacovigilance Registry Study Risk Minimization Activity Routine risk communication (drug labeling and HCP and Patient Communication)

Important Potential	Insertional Oncogenesis	Routine and/or Additional Pharmacovigilance Activity Routine pharmacovigilance Registry Study Ongoing clinical studies, including long-term follow-up Study LTF-303 Risk Minimization Activity Routine risk communication (drug labeling and HCP and Patient Communication)
Important Potential	Lack or Loss of Gene Therapy Response	Routine and/or Additional Pharmacovigilance Activity Routine pharmacovigilance Registry Study Ongoing clinical studies, including long-term follow-up Study LTF-303 Risk Minimization Activity Routine risk communication (drug labeling and HCP and Patient Communication)
Important Potential	Neutrophil Engraftment Failure	Routine and/or Additional Pharmacovigilance Activity Routine pharmacovigilance Registry Study Risk Minimization Activity Routine risk communication (drug labeling and HCP and Patient Communication)
Missing Information	Long-Term Safety and Efficacy	Routine and/or Additional Pharmacovigilance Activity Routine pharmacovigilance Registry Study Ongoing clinical studies, including long-term follow-up Study LTF-303 Risk Minimization Activity Routine risk communication (drug labeling and HCP and Patient Communication)
	Use in Pregnancy	Routine and/or Additional Pharmacovigilance Activity Routine pharmacovigilance Registry Study Ongoing clinical studies, including long-term follow-up Study LTF-303

		Risk Minimization Activity Routine risk communication (drug labeling and HCP and Patient Communication)
	Use in Patients > 35 years of age	Routine and/or Additional Pharmacovigilance Activity Routine pharmacovigilance Registry Study Ongoing clinical studies, including long-term follow-up Study LTF-303 Risk Minimization Activity Routine risk communication (drug labeling and HCP and Patient Communication)

HCP = Health Care Provider

Source: PVP plan submission BLA 125717/0 Module 1.16.1 Pharmacovigilance Plan dated August 23, 2021 pp. 9-10

The sponsor proposes routine pharmacovigilance including targeted follow up questionnaires to obtain information regarding identified risk of delayed platelet engraftment and associated bleeding events from the reporting/treating health care practitioner (HCP). The applicant provides information pertaining to identified and potential risks in the label.

The sponsor proposes additional pharmacovigilance activities in the form of long-term follow up study LTF-303 (discussed above), registry study REG-501 (discussed below), and ongoing phase III clinical trials HGB-207 and HGB-212, to address the following safety concerns:

- Delayed platelet engraftment
- Insertional oncogenesis
- Lack or loss of response to gene therapy
- Neutrophil engraftment failure
- Long-term safety and efficacy
- Use in patients > 35 years of age
- Use in pregnancy and lactation

To address the identified and potential safety concerns above, the sponsor will produce risk communication, including the Health Care Provider (HCP) Educational Brochure and Website, the Patient Package Insert, a Patient Educational Brochure, a Patient-Specific Website. The sponsor also plans to communicate with relevant patient advocacy groups. The sponsor will also be conducting long-term follow-up study LTF-303, described and discussed earlier in this review, and a registry study REG-501 discussed below.

Registry Study REG-501

The sponsor has submitted a post approval/postmarketing observational registry (REG-501, dated February 21, 2022) which per concurrence from the April 28, 2022 Safety

Working Group meeting, will constitute a PMR the long-term followup for patients treated with gene therapy drug products/ ZYNTGLO for 15 years after administration of ZYNTGLO.

Study description: REG-501 is a multicenter, single-arm, observational registry that will collect real world longitudinal data on patients treated with beti-cel in the postmarketing setting. No study medication is provided as a part of participation, and the decision to treat patients with beti-cel will have been made independently by patients and their health care providers in accordance with the prescribing/product information and in a qualified treatment center by a physician with experience in hematopoietic stem cell transplant and in the treatment of patients with β -thalassemia. The registry places no restrictions on concomitant treatments or therapies, and no registry assessments will be mandated. The registry will be descriptive, and no formal hypothesis will be tested.

Study population: The registry is anticipated to enroll 150 patients based on epidemiology/incidence of transfusion dependent thalassemia in the US and expected number of patients that may be eligible for treatment in the postmarketing setting in the US, per the sponsor. Study enrollment begins once beti-cel has become commercially available in the US following the first patient enrollment in the US and ends 5 years after enrollment of the first beti-cel patient into the registry. Each enrolled patient will be followed for 15 years from time of enrollment.

The sponsor's rationale for the proposed anticipated number of registry participants was reported to have been based on epidemiology/incidence of transfusion dependent thalassemia in the US and expected number of patients that may be eligible for treatment in the postmarketing setting in the US. Search of literature regarding the epidemiology of transfusion dependent thalassemia noted prevalence values consistent with those provided by the sponsor.^{4,5} Based on this information, the sponsor's rationale for planning to enroll 150 patients appears adequate.

Patients who have not had data captured within 60 months of last data entry and for whom 3 attempts during the last year of attempted follow up have been unsuccessful, will be deemed lost to follow up. However, if after being deemed lost to follow up, contact is made, the patient can be reenrolled into the registry.

If the Registry remains open after an individual patient in the registry has been followed for 15 years post treatment with beti-cel, areas/adverse events of long-term interest (i.e. death, oncogenesis, malignancy, and pregnancy-related events and outcomes) will continue to be solicited from the patient/patient's care provider every 2 years until the registry closes, and these data will be included in the registry dataset.

Data collection: The registry will provide for routine integration site analysis, via quantitative polymerase chain reaction (qPCR) using whole blood samples after beti-cel

⁴ Lal A, Wong T, Keel S, Pagano M, Chung J, Kamdar A, et al. The transfusion management of beta thalassemia in the United States. *Transfusion*. 2021;61:3027–39.

⁵ Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis*. 2010 May 21;5:11.

administration, to identify predominant clone(s). Findings of a persistent, predominant clone will be shared with regulatory authorities.

The registry will also provide safety data and monitoring for serious adverse events and adverse events of special interest of neutrophil engraftment failure (defined as requiring back-up cells per health care provider decision), malignancies (including leukemia, lymphoma, and myelodysplastic syndrome), newly acquired HIV1, HIV2, HTLV infection, autoimmune disorders, hepatic venoocclusive disease, and clinically significant bleeding events, and will assess clinical response/recovery. Additional safety assessments will include time to neutrophil and platelet engraftments post beti-cel administration, transplant related mortality, incidence of vector-derived replication competent lentivirus, incidence of insertional oncogenesis, incidence of persistent clonal predominance, and overall survival 15 years post beti-cel infusion.

Of note, if any patient develops hematologic malignancy during registry participation, patient blood samples are to be submitted to the sponsor for integration site analysis to determine if the gene therapy integration site was contributory to the development of hematologic malignancy/oncogenesis. If any patient is found to have HIV or HTLV infection, blood samples will be submitted to the sponsor to assess for presence of vector-derived replication competent lentivirus.

An abnormal pregnancy outcome is considered an AE, and any pregnancy that occurs during participation in the registry (in a pregnant patient or female partner of a male patient (except in cases of sperm banked prior to receipt of drug product) is to be reported to the sponsor within 2 weeks of awareness, and the pregnancy is to be followed to determine outcome (including elective termination). Any SAE occurring in association with a pregnancy/pregnancy outcome is to be reported promptly to the sponsor. Elective terminations for medical reasons and spontaneous abortions are to be reported as SAEs. Information is to be provided on the status of the mother and infant at 6 weeks of age and annually thereafter for 2 years.

Per the registry protocol, these adverse events of special interest and any serious adverse events are to be reported to the sponsor within 24 hours of discovery of the adverse event and include reporting of newly diagnosed malignancies to facilitate prompt initiation of workup and obtainment of clinical samples. FDA sent an information request to confirm with the sponsor that secondary malignancies must be reported to sponsor by treating physicians within 72 hours of diagnosis and specimen are to be collected for insertional site analysis to investigate vector persistence.

Analysis plan: Data is to be submitted to the registry at regular intervals of 100 days, 6 months, and 12 months for the first year and then annually thereafter (and may also be submitted more frequently), until completion of 15 years of follow up.

Interim analyses are planned every 5 years (from first patient enrolled) with the first interim analysis planned for 2027, 5 years after first enrollment. Additional interim analyses may be planned in support of regulatory submissions, per the sponsor. Final analysis will be performed when all enrolled patients have been followed for followed for up to 15 years post-treatment.

6. REVIEW OF THE SPONSOR'S PHARMACOVIGILANCE PLAN

The Pharmacovigilance Plan (PVP) (dated August 23, 2021) includes the sponsor's assessment of identified and potential risks and missing information based on the pre-licensure clinical trial data, published literature, known product-class effects, and other relevant sources of safety information. Review of the safety data did not suggest any additional safety concerns not addressed by the sponsor's proposed PVP.

The sponsor's proposed plan for routine pharmacovigilance is consistent with 21 CFR 600.80.

FDA Guidance *Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020)* available at <https://www.fda.gov/media/113768/download> recommends 15-year long term follow up for products with integrating vectors. In keeping with this Guidance, the sponsor is also conducting a long-term follow up study for patients receiving the product in the premarket clinical trial setting (study LTF-303, discussed above), and a post approval registry, REG-501, for patient receiving the marketed product post-licensure. Based on concerns regarding the risk of insertional oncogenesis and secondary malignancy, OPBV/DPV obtained a Sentinel Sufficiency Assessment (discussed in section 6.4). REG-501 was presented as a potential safety potmarketing requirement (PMR) under Section 505(o) of Federal Food, Drug, and Cosmetic Act (FDCA), to further characterize the serious risk of secondary malignancies, at the Safety Working Group meeting on April 28, 2022. The Safety Working Group concurred with need for this safety-related PMR study and the sponsor was notified of this PMR on July 8, 2022. The sponsor provided written acknowledgment of the PMR on July 14, 2022.

6.1 Safety concerns and Proposed Actions – Identified Risks

Delayed platelet engraftment is the single identified risk for this product at this time.

Delayed platelet engraftment can result in increased frequency and severity of bleeding. Of note in ZYNTGLO studies severity and frequency of bleeding was generally not found to be increased despite delayed platelet engraftment times, except in 1 patient who experienced severe epistaxis in association with delayed engraftment 69 days post ZYNTGLO administration (subject 207-(b) (6)). Risk of delayed platelet engraftment/thrombocytopenia and bleeding is included as a warning in Section 5 of the label. This risk will be further characterized in long-term followup study LTF-303, PMR registry study REG-501, and in routine PV. This risk mitigation plan is adequate.

6.2 Safety concerns and Proposed Actions – Potential risks

Potential risks include insertional oncogenesis, neutrophil engraftment failure, and lack or loss of response to gene therapy.

Insertional oncogenesis is a long-term safety concern in association with gene therapy. Beti-cel is a lentivirus vector (LVV) is used to deliver the beta globin gene to target hematopoietic stem cells. LVVs integrate into the DNA of target cells upon transduction, and there is concern that the LVV could potentially affect expression of nearby genes. As such, there is a concern that after engraftment a progenitor cell

derived from the transduced hematopoietic stem cells may potentially undergo preferential expansion due to altered expression of nearby genes. This expansion can potentially result in development of a predominant clone and subsequent malignancy.

Although oligoclonality was reported, no clonal predominance or MDS was reported in patients treated with ZYNTEGLO as of the latest safety update (June 01, 2022). In a meeting on June 10, 2022, the Advisory Committee concurred with this finding. However, LVV integration into oncogenes remains a potential risk given that there have been reports of cases of AML in patients with sickle cell disease treated with the same LVV product, although a relationship between AML and the LVV has not been established. Given this potential risk, it is reasonable that integration site analysis (ISA) be performed in treated patients to assess for clonal expansion in the postmarket setting. The sponsor has proposed monitoring for insertional oncogenesis with routine pharmacovigilance, long-term followup study LTF-303, and PMR registry study REG-501. This risk mitigation plan is adequate.

Should the BLA be approved, the PMR protocol design and data analysis plan will be discussed with the sponsor post-licensure. Of note, an algorithm for monitoring for insertional oncogenesis, including a schedule for conducting ISAs, will be agreed upon. On August 8, 2022, the review team provided additional recommendations on the REG-501 study design for the PMR, including the need for monitoring (at pre-specified intervals) with additional testing for safety outcome assessments. Additional testing will include bone marrow biopsy, peripheral blood sample with blood smear, integration site analysis, vector copy number, gene expression studies. FDA will review the final study protocol upon submission to ensure that FDA recommendations on study design were appropriately incorporated.

Although not reported in the clinical trial data, neutrophil engraftment failure is a potential risk with beti-cel therapy. Neutrophil engraftment failure can result in increased risk of infections. As part of the treatment plan, autologous hematopoietic stem cells are retained prior to ZYNTEGLO administration and can be used as rescue therapy in the event of neutrophil engraftment failure. The sponsor proposes monitoring for delayed neutrophil engraftment with routine pharmacovigilance and PMR registry study REG-501. This plan for risk mitigation is adequate.

The anticipated duration of beti-cel effects is for the lifetime of the recipient. Lack or loss of response is defined as less than 0.0003 vector copies per diploid genome in peripheral blood cells on 2 consecutive measurements which are taken at least 1 month apart. There was no report of lack or loss of response to gene therapy with beti-cel in any subject at a median follow up time of 35.48 months of follow up (range 4.1 to 86.5 months). The sponsor proposes monitoring for lack or delayed response to gene therapy with routine pharmacovigilance, long-term followup study LTF-303, and PMR registry study REG-501. This proposed plan is adequate.

6.3 Missing information

Long term safety, relative to the expected effect over a patient's lifetime will be followed and evaluated in long-term followup study LTF-303, and in post approval PMR registry study REG-501.

None of the patients enrolled in clinical trials for ZYNTEGLO were older than 35 years of age despite inclusion criteria for some studies allowing for participation of patients up to 50 years of age. Therefore, use in patients over 35 years of age will be evaluated with routine pharmacovigilance and in post approval PMR registry study REG-501 in the postmarketing setting.

Pregnant and lactating patients were not included in clinical trials. Therefore, safety in pregnancy and lactation will be evaluated with routine surveillance, in long-term follow up study LTF-303, and in post approval PMR registry study REG-501. Of note, ZYNTEGLO is not indicated during pregnancy.

The sponsor's proposed pharmacovigilance plan with respect to long-term safety, use in patients over 35 years of age, and pregnancy and lactation is adequate.

6.4 Sentinel Sufficiency Assessment

Insertional oncogenesis and secondary malignancy is a potential serious risk associated with ZYNTEGLO. The sponsor's registry study REG-501 will include at least 15 years of follow up for this potential serious risk post ZYNTEGLO administration. As required by regulations under Section 901 of the Food and Drug Administration Amendments Act (FDAAA) and as described in CBER SOPP 8415: Procedures for Developing Post-marketing Requirements and Commitments, a Sentinel sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to characterize the serious risk of secondary malignancy associated with ZYNTEGLO. As outlined in the Sentinel sufficiency memorandum, the CBER Sentinel Team has determined that CBER Sentinel will not be sufficient to characterize the serious risk of secondary malignancy/insertional mutagenesis for 15 years of follow-up. Additionally, collection of tissue samples are needed and this is not feasible in a claims-based system such as Sentinel.

Sentinel insufficiency serves as a justification for requiring a safety-related post-marketing study under Section 901, Title IX of FDAAA. Therefore, if the product is approved, the sponsor will be required to conduct a PMR safety study under FDAAA Title IX to identify the serious risk of secondary malignancy after treatment with beti-cel (ZYNTEGLO). The PMR will be conducted for up to 15 years in accordance with the FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020). Similar PMR safety studies have been required for approved CAR T-cell products. DE presented the PMR to the CBER Safety Working Group on April 28, 2022. Further discussion at the June 10, 2022 Advisory Committee raised no concern that would warrant institution of REMS. On July 08, 2022, the sponsor was notified that the registry study will be a PMR.

The sponsor has provided the following milestones for the postmarketing registry study protocol REG-501:

Final protocol submission	November 18, 2022
Study completion	March 18, 2043
Final study report	March 18, 2044

An information request was submitted to the sponsor on August 09, 2022, requesting that the milestone dates be updated to reflect last day of the month submission in keeping with the *SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments*.

In the event of BLA licensure, the sponsor will submit PMR reports for Post Approval Registry study REG-501 to the FDA annually in addition to quarterly (for the first 3 years post approval) and periodic safety update reports (PSURs) as per FDA requirements.

7. Labeling

There is no Postmarketing Section. The sponsor's proposed Adverse Reactions and Warnings and Precautions labeling sections of the package insert are consistent with the above discussed adverse events in the studies submitted in support of the BLA and final decision regarding overall adequacy of the label is deferred to the product office primary clinical review team.

8. DPV ASSESSMENT AND RECOMMENDATIONS

- Should ZYNTÉGLO be approved, OBPV/DPV agrees with the sponsor's proposed pharmacovigilance plan (dated August 23, 2021) to include routine pharmacovigilance in accordance with 21 CFR 600.80, completion of long-term follow up study LTF-303*, and safety PMR under Section 505(o) of FDCA (study REG-501), to assess the potential serious risk of insertional oncogenesis and secondary malignancies. Please see the approval letter for the PMR study milestone dates.
- The available data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS) at this time.

Please see the final version of the package insert submitted by the sponsor for the final agreed upon language for the label.

*Note that OBPV defers to OTAT for review of LTF-303 study, which includes long term follow up of patients who received Zynteglo in the premarket clinical trial setting.