Study of Safety & PK of Luspatercept (ACE-536) in Pediatric Participants Who Require Regular RBC Transfusions Due to Beta (β)-Thalassemia.

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT04143724	RECRUITING	OCTOBER 29, 2019	MAY 27, 2022

STUDY DESCRIPTION

Brief Summary

This is a Phase 2a study to evaluate the safety and pharmacokinetics (PK) of luspatercept in pediatric participants who require regular red blood cell transfusions due to β-thalassemia. The study will be conducted in 2 parts: Part A will be in adolescent participants aged 12 to <18 years with two dose escalation cohorts of 6 participants each, followed by a dose expansion cohort of 30 participants. Part B will begin after a review of the safety in participants completing at least one year of treatment in Part A and will be in participants aged 6 to <12 with two dose escalation cohorts of 6 participants each. Upon completion of the Treatment Period, participants of any cohort who are benefiting from the study treatment, will be offered the opportunity to continue luspatercept treatment in the Long-term Treatment Period for up to 5 years from their first dose (Cycle 1 Day 1). Participants who discontinue study treatment any time will continue in the Posttreatment Follow-up Period for at least 5 years from their first dose of luspatercept (Cycle 1 Day 1), or 3 years from their last dose, whichever occurs later, or until they withdraw consent/assent, are lost to follow-up, or the End of Trial, whichever occurs first.

Condition or Disease: Beta-Thalassemia

Intervention/treatment: Drug: ACE-536
Drug: ACE-536
Drug: ACE-536
Drug: ACE-536
Drug: ACE-536

Phase: Phase 2

DETAILED DESCRIPTION

This is a Phase 2a study to evaluate the safety and pharmacokinetics (PK) of luspatercept in pediatric participants who require regular red blood cell (RBC) transfusions due to β-thalassemia and to determine the recommended dose (RD).
The primary endpoints are the determination of the RD and PK parameters (including Cmax, AUC, t1/2, CL/F and Vd/F).
The secondary endpoints include the safety of luspatercept in pediatric participants, the immunogenicity (frequency of antidrug antibodies) of luspatercept, mean change in RBC transfusion burden, mean change in hemoglobin levels, mean change from baseline in mean daily dose of iron chelation therapy (ICT), and mean change from baseline in serum ferritin.
The study will consist of the following periods:
Screening/Run-in Period
Treatment Period
Long-term Treatment Period
Posttreatment Follow-up Period
Participant screening procedures will occur during the Screening/Run-in Period, within 12 weeks prior to the start of study treatment. Participants who meet the study eligibility criteria will be enrolled into the Treatment Period.
The study will be conducted in a staggered manner, in descending order of age, with 2 parts as described below.
Part A
Adolescent participants aged 12 to < 18 years: Luspatercept 0.75 will be enrolled as outlined below: Part A Dose Escalation Phase Part A Dose Escalation Phase will explore up to 2 dose levels of luspatercept, 0.75 mg/kg and 1.0 mg/kg, to evaluate the safety and tolerability of luspatercept in this age group and determine the RD to be used for Part A Expansion Phase: Cohort 1: 6 adolescent participants 12 to < 18 years of age receiving luspatercept 0.75 mg/kg, administered subcutaneously (SC) once every 21 days (for up to 4 cycles in the Treatment Period) Cohort 2: 6 adolescent participants 12 to < 18 years of age receiving luspatercept 1.0 mg/kg, administered SC once every 21 days (for up to 4 cycles in the Treatment Period) Part A Expansion Phase • Cohort 3 - The Expansion Cohort: 30 adolescent participants (12 to < 18 years of age) receiving luspatercept at the RD for up to 12 months in the Treatment Period. Children from 6 years to < 12 years of age will be enrolled into Part B as outlined below: Part B Dose Escalation Phase will explore 2 dose levels of luspatercept, 1.0 mg/kg and 1.25 mg/kg, to evaluate the safety and tolerability of luspatercept in this age group and determine the RD. Cohort 4: 6 participants (6 to < 12 years of age) receiving luspatercept 1.0 mg/kg, administered SC once every 21 days (for up to 4 cycles in the Treatment Period) Cohort 5: 6 participants (6 to <12 years of age) receiving luspatercept 1.25 mg/kg, administered SC once every 21 days (for up to 4 cycles in the Treatment Period) During the Treatment Period of both Part A Dose Escalation Phase and Part B Dose Escalation Phase, once all 6 participants in a dose escalation cohort have completed the first cycle (Study Day 22), the Dose Review Team (DRT), will review all available safety data, including dose-limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), and laboratory results (including hematology and chemistry) reported during Cycle 1 of each dose level. A DLT, using the current active version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, is defined as any of the following toxicities at any dose level occurring within 21 days of the first administered dose: Treatment-related SAE of ≥ Grade 3 Treatment-related nonhematologic AE of ≥ Grade 3 Treatment-related hematologic AE of ≥ Grade 4 The DRT will make a recommendation as to whether or not to enroll the next cohort at the next planned dose level based in part upon the following criteria: If a DLT occurs in ≤ 1 participant (out of 6) in a cohort within 21 days following the initial dose of luspatercept, the next planned dose level may proceed; If a DLT occurs in ≥ 2 participants (out of 6) in a cohort within 21 days following the initial dose of luspatercept, the next planned dose level should not proceed; If a hemoglobin increase of ≥ 2.0 g/dL (confirmed by central lab after initial study treatment administration and not attributable to RBC transfusion) occurs in ≥ 2 participants (out of 6) in a cohort, the decision to proceed to the next planned dose level will need to be evaluated by the DRT. At least 6 participants eligible for the Dose Determining Set (DDS) are planned to be enrolled per dose escalation cohort with up to 2 cohorts per age group. With up to 4 2 age groups being considered, a total of up to 24 participants are to be included in the DDS. To minimize safety risk to participants, best supportive care will be available, including RBC transfusions, iron-chelating agents, use of antibiotic therapy, antiviral and antifungal therapy, and/or nutritional support as needed.

STUDY DESIGN

Study Type:	Interventional
Estimated Enrollment :	54 participants
Allocation :	Non-Randomized
Intervention Model :	Sequential Assignment
Masking:	None (Open Label) ()
Primary Purpose:	Treatment
Official Title:	Study of Safety & PK of Luspatercept (ACE-536) in Pediatric Participants Who Require Regular RBC Transfusions Due to Beta (β)-Thalassemia.

Actual Study Start Date:	November 2019
Estimated Primary Completion Date:	February 2031
Estimated Study Completion Date:	September 2033

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Cohort 1: 12 to < 18 years - Luspatercept 0.75 mg/kg Luspatercept 0.75 mg/kg, administered SC once every 21 days (for up to 4 cycles)	Drug: ACE-536 Up to 6 participants will start with luspatercept at 0.75mg/kg and the Dose Review Team (DRT) will evaluate all toxicities of each participant after Cycle 1 and determine whether or not to enroll the next cohort at the next planned dose level
Experimental: Cohort 2: 12 to < 18 years: Luspatercept 1.0 mg/kg, Luspatercept 1.0 mg/kg, administered SC once every 21 days (for up to 4 cycles)	Drug: ACE-536 Up to 6 participants will start with luspatercept at 1.0mg/kg and the Dose review team (DRT) will evaluate all toxicities of each participant after Cycle 1 and determine whether or not to enroll the next cohort (Expansion Cohort)
Experimental: Cohort 3 (Expansion Cohort): 12 to <18 years Luspatercept administered SC once every 21 days (for up to 12 months)	Drug: ACE-536 Up to 30 participants will start with luspatercept (at the Recommended Dose (RD) determined by the Dose Review Team (DRT)). Overall safety data from all cohorts in part A (Cohorts 1, 2 & 3) will be assessed before Part B (Cohorts 4 & 5) can be initiated
Experimental: Cohort 4: 6 to < 12 years: Luspatercept 1.0 mg/kg Luspatercept 1.0 mg/kg, administered SC once every 21 days (for up to 4 cycles)	Drug: ACE-536 Up to 6 participants will start with luspatercept at 1.0mg/kg and the Dose Review Team (DRT) will evaluate all toxicities of each participant after Cycle 1 and determine whether or not to enroll the next cohort at the next planned dose level
Experimental: Cohort 5: 6 to <12 years: Luspatercept 1.25 mg/kg Luspatercept 1.25 mg/kg, administered SC once every 21 days (for up to 4 cycles)	Drug: ACE-536 Up to 6 participants will start with luspatercept at 1.25 mg/kg and the Dose Review Team (DRT) will evaluate all toxicities of each participant after Cycle 1.

OUTCOME MEASURES

Primary Outcome Measures:
1. Determination of the Recommended Dose (RD [Time Frame: Cycle 1 Day 1 through Cycle 1 Day 22 (each Cycle is 21 days)]
Determine the recommended dose of luspatercept that is safe and tolerable in pediatric participants with transfusion-dependent B-thalassemia
2. Pharmacokinetics - Cmax [Time Frame: Time from Cycle 1 Day 1 of Treatment Period up to a maximum of 1 year]
Maximum serum concentration of drug
3. Pharmacokinetics - AUC [Time Frame: Time from Cycle 1 Day 1 of Treatment Period up to a maximum of 1 year]
Area under the curve
4. Pharmacokinetics (PK) - t1/2 [Time Frame: Time from Cycle 1 Day 1 of Treatment Period up to a maximum of 1 year]
Half-life
5. Pharmacokinetics (PK) - CL/F [Time Frame: Time from Cycle 1 Day 1 of Treatment Period up to a maximum of 1 year]
Apparent oral clearance
6. Pharmacokinetics (PK) - Vd/F [Time Frame: Time from Cycle 1 Day 1 of Treatment Period up to a maximum of 1 year]
Apparent volume of distribution

Secondary Outcome Measures:
1. Mean change in Red Blood Cell (RBC) Transfusion Burden [Time Frame: 12 weeks prior to enrollment; Treatment Period and Long-term Treatment Period through End of Treatment - Up to 5 years]
Change from baseline as continuous variable
2. Mean change in hemoglobin levels [Time Frame: 12 weeks prior to enrollment; Treatment Period and Long-term Treatment Period through End of Treatment - Up to 5 years]
Change from baseline as continuous variable
3. Immunogenicity [Time Frame: Time from Cycle 1 Day 1 of Treatment Period up to a maximum of 1 year]
Frequency of antidrug antibodies (ADA)
4. Mean change from baseline in mean daily dose of iron chelation therapy (ICT) [Time Frame: 12 weeks prior to enrollment; Treatment Period and Long-term Treatment Period through End of Treatment - Up to 5 years]
Change from baseline as continuous variable
5. Mean change from baseline in serum ferritin [Time Frame: 12 weeks prior to enrollment; Treatment Period and Long-term Treatment Period through End of Treatment - Up to 5 years]
Change from baseline as continuous variable
6. Safety - Incidence of Adverse Events (AEs) [Time Frame: From enrollment until at least 9 weeks after last dose of study treatment]
An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE

ELIGIBILITY CRITERIA

Ages Eligible for Study: 6 to 18 Years (Child, Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
Participants must satisfy the following criteria to be enrolled into the study:
Participant must be 6 years to < 18 years of age at the time of signing the informed consent form (ICF)/informed assent form (IAF). Participant (and when applicable, parent/legal representative) must understand and voluntarily sign an ICF/IAF prior to conducting any study-related assessments/procedures. Participant (and when applicable, parent/legal representative) is willing and able to adhere to the study visit schedule and other protocol requirements. Participant must have documented diagnosis of β-thalassemia or Hemoglobin/β-thalassemia. Participant is regularly transfused, defined as: ≥ 4 red blood cell transfusions in the 24 weeks prior to enrollment with no transfusion-free period ≥ 42 days during that period. Note: For the purpose of the study, transfusions administered over 2 or 3 consecutive days are considered as part of a single transfusion event. Participant must have a history of regular transfusions for at least 2 years. Participant has Karnofsky (age ≥16 years) or Lansky (age 1000 x 109/L. Participant has poorly controlled diabetes mellitus within 24 weeks prior to enrollment as defined by short term (eg, hyperosmolar or ketoacidotic crisis) and/or history of diabetic cardiovascular complications (eg, stroke or myocardial infarction). Participant has treatment with another investigational drug or device ≤ 28 days prior to enrollment. Participant has prior exposure to sotatercept (ACE-011) or luspatercept (ACE-536). Participant underwent or is scheduled for HSCT or gene therapy Participant has used an erythropoiesis-stimulating agent (ESA) ≤ 24 weeks prior to enrollment. Participant use of iron chelation therapy (ICT), if initiated ≤ 8 weeks prior to enrollment (allowed if initiated > 8 weeks before or during treatment). Participant use of hydroxyurea treatment ≤ 24 weeks prior to enrollment. Participant is pregnant or breastfeeding female. Participant has uncontrolled hypertension. Controlled hypertension for this protocol is considered ≤ Grade 1 according to NCI CTCAE version 5.0.
Participant has major organ damage, including:
Symptomatic splenomegaly Liver disease with alanine aminotransferase (ALT)/aspartate aminotransferase (AST) > 3X the upper limit of normal (ULN) for age Heart disease, heart failure as classified by the New York Heart Association (NYHA) classification 3 or higher, or significant arrhythmia requiring treatment, or recent myocardial infarction within 6 years of enrollment Lung disease, including pulmonary fibrosis or pulmonary hypertension which are clinically significant Renal insufficiency defined as:
A serum creatinine based on age/gender based on threshold derived from Schwartz formula for estimating GFR utilizing child length and stature data published by the Centers for Disease Control Participant has proteinuria ≥ Grade 3 according to NCI CTCAE version 5.0. Participant use of chronic systemic glucocorticoids ≤ 12 weeks prior to enrollment (physiologic replacement therapy for adrenal insufficiency is allowed). Single day glucocorticoid treatment (eg, for prevention or treatment of transfusion reactions) is allowed. Participant has major surgery ≤ 12 weeks prior to enrollment (participants must have completely recovered from any previous surgery prior to enrollment). Participant has history of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the IP (see IB). Participant use of cytotoxic agents, immunosuppressants ≤ 28 days prior to enrollment (ie, antithymocite globulin (ATG) or cyclosporine).
Participant has history of malignancy with the exception of:
Curatively resected nonmelanoma skin cancer. Curatively treated cervical carcinoma in situ. Other solid tumor with no known active disease in the opinion of the Investigator.

CONTACTS AND LOCATIONS

Contacts

Contact: BMS Study Connect Contact Center www.BMSStudyConnect.com 855-907-3286 Clinical.Trials@bms.com
Contact: First line of email MUST contain NCT # and Site #.

Locations

United States, California	Children's Hospital of Los Angeles	Los Angeles
Germany	Universitatsklinikum Ulm	Ulm
Greece	General Children's Hospital "Agia Sophia"	Athens
Italy	Ente Ospedaliero Ospedali Galliera - Centro della Microcitemia e delle Anemie Congenite	Genoa
Italy	Azienda Ospedaliera Universitaria "Federico II"	Napoli
Italy	Azienda Ospedaliero Universitaria S. Luigi Gonzaga	Orbassano
Italy	Local Institution - 301	Orbassano
Thailand	Siriraj Hospital Mahidol University	Bangkok
Turkey	Ege Universitesi Tip Fakultesi Hastanesi	Izmir

Sponsors and Collaborators

Celgene

Acceleron Pharma Inc.

Investigator

Study Director :	Bristol-Myers Squibb	Bristol-Myers Squibb

MORE INFORMATION

Responsible Party : Celgene

ClinicalTrials.gov Identifier : NCT04143724

Other Study ID Numbers : ACE-536-B-THAL-004, U1111-1241-4168, 2019-000208-13

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Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	Yes
Plan Description:	Information relating to our policy on data sharing and the process for requesting data can be found at the following link: https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Supporting Materials:	Study Protocol, Statistical Analysis Plan (SAP), Informed Consent Form (ICF), Clinical Study Report (CSR), Analytic Code
Time Frame:	See Plan Description
Access Criteria:	See Plan Description
URL:	https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No
Keywords provided by Celgene:	*ACE-536* *Luspatercept* *Pharmacokinetics Beta-Thalassemia* *Red Blood Cell Transfusion*
Additional relevant MeSH terms :	*Thalassemia* *beta-Thalassemia* *Anemia, Hemolytic, Congenital* *Anemia, Hemolytic* *Anemia* *Hematologic Diseases* *Hemoglobinopathies* *Genetic Diseases, Inborn*