A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF LUSPATERCEPT (ACE-536) VERSUS PLACEBO IN ADULTS WITH NON-TRANSFUSION DEPENDENT BETA (β)-THALASSEMIA

(The BEYOND™ Study)

PROTOCOL NUMBER:	**ACE-536-B-THAL-002**
DATE FINAL:	**12 MAY 2017**
DATE AMENDMENT 1 FINAL:	**21 DEC 2018**
DATE AMENDMENT 2 FINAL:	**12 Jun 2020**
EudraCT NUMBER:	**2015-003225-33**
IND NUMBER:	**112562**
SPONSOR NAME/ ADDRESS:	Celgene Corporation [redacted]

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MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information:
Name: Jeevan Shetty, MBChB, FRCP
Title: Medical Director, Clinical Development
[redacted]
[redacted]
[redacted]

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

Back-up 24-hour Global Emergency Contact Call Center: [redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.	

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:** _____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:** _____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

A Phase 2, Double-blind, Randomized, Placebo-controlled Multicenter Study to Determine the Efficacy and Safety of Luspatercept (ACE-536) versus Placebo in Adults with Non-transfusion Dependent Beta (β)-Thalassemia

Indication

Adults with non-transfusion dependent β-thalassemia (NTDT)

Objectives

The primary objective is:

- To evaluate the effect of luspatercept versus placebo on anemia, as measured by mean hemoglobin concentration in the absence of transfusions over a continuous 12-week interval, from Week 13 to Week 24, compared to baseline.

The secondary objectives are:

- To evaluate the effect of luspatercept versus placebo in anemia-related symptoms in patients with β-thalassemia, as measured by non-transfusion dependent β-thalassemia-patient reported outcome (NTDT-PRO) over continuous 12-week intervals (from Weeks 13 to 24 and from Weeks 37 to 48) compared to baseline
- To evaluate the effect of luspatercept versus placebo on functional and health-related quality of life (QoL) as measured by the Medical Outcomes Study 36-Item Short Form (SF-36) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaires
- To evaluate the long-term effect of luspatercept versus placebo on anemia, as measured by mean hemoglobin concentration in the absence of transfusions over a continuous 12-week interval from Week 37 to Week 48, compared to baseline
- To evaluate the effect of luspatercept versus placebo on iron overload, as measured by liver iron concentration (LIC) and iron chelation therapy (ICT) daily dose
- To evaluate the effect of luspatercept versus placebo on iron overload, as measured by serum ferritin
- To evaluate the duration of erythroid response
- To evaluate the effect of luspatercept versus placebo on physical activity measured by 6-minute walk test (6MWT)

Safety and Pharmacokinetics (PK) Objectives

- To evaluate safety and tolerability of luspatercept, including immunogenicity
- To evaluate population pharmacokinetics (PK) of luspatercept in subjects with β-thalassemia

[redacted]

Study Design

This is a Phase 2, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in adults with non-transfusion dependent beta (β)-thalassemia. The study is divided into the Screening Period, Double-blind Treatment Period (DBTP), Open-label Phase (OLP) and Post-treatment Follow-up Period (PTFP). The overall study design is described in Figure 7.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

Subjects diagnosed with NTDT, with a documented diagnosis of β-thalassemia or hemoglobin E/β-thalassemia, aged ≥ 18 years and who received 0 to 5 units of red blood cells (RBCs) during the 24-week period prior to randomization, with a mean baseline hemoglobin level ≤ 10.0 g/dL.

A total of approximately 150 eligible subjects will be enrolled.

Length of Study

Study participation for each individual subject will be approximately 4 weeks in the Screening Period, at least 48 weeks in the DBTP, up to 15 months in the Open-label Phase (OLP) and the PTFP will be for 5 years from first dose of IP, or 3 years from last dose (whichever occurs later) to complete the Post-treatment Follow-up Period under this study or the rollover protocol.

End of Treatment for each individual subject is defined as the date of the last IP dose in the DBTP or OLP, whichever occurs later.

End of Study for each individual subject should occur after the study is unblinded and the OLP, or the PTFP have been completed, as appropriate or at the **End of Trial** as defined below, whichever occurs later.

The End of Trial is defined as the date all subjects complete the OLP, if eligible (see Section 3.1.3), or discontinue earlier, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis as prespecified in the protocol, whichever is the later date.

The Sponsor may end the trial when all key endpoints and objectives of the study have been analyzed, and the availability of a rollover protocol exists.

Any subjects remaining on the parent study may be consented and continue to receive access to luspatercept, and/or complete the long-term follow-up of 5 years from first dose of IP, or 3 years from last dose (whichever occurs later), to complete the Post-treatment Follow-up Period under this study or the rollover protocol.

Study Treatments

Experimental arm. Luspatercept will be provided by the Sponsor as a lyophilized powder in vial. Luspatercept will be administered after reconstitution (see Section 7) as a subcutaneous (SC) injection to the subjects by the study staff at the clinical site. Subcutaneous injections will be given in the upper arm, abdomen, or thigh, every 3 weeks during the Treatment Periods, unless dose delay or treatment discontinuation is indicated. Subjects will start luspatercept at 1.0 mg/kg dose level and can be dose escalated up to 1.25 mg/kg.

Control arm. Placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection) administered as a SC injection. Designated individuals will prepare the placebo syringes to match the active syringe. Subcutaneous injections will be given in the upper arm, abdomen, or thigh every 3 weeks during the DBTP, unless dose delay or treatment discontinuation is indicated.

Overview of Key Efficacy Assessments

- The primary efficacy assessment will include:
    - Hemoglobin values over a continuous 12-week interval from Week 13 to Week 24 of treatment in the absence of transfusions
- Secondary efficacy assessments:
    - Quality of life (QoL) assessment using the non-transfusion dependent β-thalassemia-patient reported outcome (NTDT-PRO)
    - Hemoglobin values over a continuous 12-week interval from Week 37 to Week 48 of treatment
    - Quality of Life assessed using SF-36 and FACIT-F
    - Liver iron concentration (LIC, mg/g dry weight [dw]) measured by magnetic resonance imaging (MRI)
    - Daily dose of iron chelation therapy (ICT) use
    - Serum ferritin
    - Six-minute walk test (6MWT) distance
    - Transfusion free intervals

Overview of Key Safety Assessments

All subjects will be assessed for safety by monitoring adverse events (AEs), clinical laboratory parameters, vital signs, physical examination, electrocardiogram (ECG), echocardiography,

erythropoietin, anti-drug antibody (ADA) testing, and Eastern Cooperative Oncology Group (ECOG) performance status.

Overview of Pharmacokinetic Assessments

Population pharmacokinetics will be evaluated, and the relationship between serum drug exposure and clinical endpoints of interest will be explored.

Statistical Methods

The analysis populations for this study include: intent-to-treat subjects (ITT), per protocol set (PPS), and safety population (definition of each population is provided in Section 9).

Subjects will be randomized to receive luspatercept or placebo in a 2:1 ratio. Subjects will be stratified as described in the Section 3, Overall Study Design.

Based on the assumption of a targeted primary endpoint response rates at least 50% in the luspatercept group and 10% for the placebo group, and 2:1 randomization, a total sample size of 150 (100 in the luspatercept group, 50 in the placebo group) will have at least 99% power to detect the difference between the 2 groups with a 2-sided alpha of 0.05 and assumed 10% drop-out rate.

For NTDT-PRO tiredness and weakness (T/W) domain scores, assume the mean change from baseline scores at Week 24 are 1.2 and 0.5 for luspatercept and placebo group, respectively, with a common standard deviation of 1.2, the statistical power will be 91%.

Primary Efficacy Analysis: The primary efficacy endpoint of this study is erythroid response, defined as an increase from baseline ≥1.0 g/dL in mean of hemoglobin values over a continuous 12-week interval from Weeks 13 to 24 of treatment in the absence of transfusions.

Hemoglobin (Hb) values within 21 days following a transfusion may be influenced by the transfusion and will be excluded from this analysis. Baseline Hb is the average of 2 or more Hb measurements at least 1 week apart within 4 weeks before Dose 1. For discontinued subjects who

do not complete 24 weeks of the Double-blind Treatment Period, Hb data will continue to be collected in the post-treatment follow-up.

Further description of the analyses is provided in Section 9.

Secondary Efficacy Analyses. Secondary endpoints will be measured at Week 24 and Week 48.

The results will be presented by treatment groups. The statistical tests will be conducted to compare the treatment groups. Detailed descriptions of the analyses are provided in Section 9.

Secondary efficacy analyses will include: Mean change in NTDT-PRO, mean change and responder analysis in Hemoglobin, mean change in FACIT-F Fatigue subscale, mean change in SF-36 v2, LIC / ICT responder analysis, mean change in LIC, mean change in serum ferritin**,** transfusion-free period, duration of mean hemoglobin increase, mean change in the 6MWT.

Interim Analysis: No interim analysis is planned.

Timing of Analyses: The primary clinical study report (CSR) will include safety and efficacy parameters with a cut-off date at the time when the last subject enrolled in the DBTP has completed 48 weeks in the DBTP or discontinued earlier (ie, at the time of the unblinding of the study), whichever occurs later. Thus, the analysis will be conducted after all required information is available for these endpoints (ie, after all subjects have completed 48 weeks in the study or discontinued earlier).

The final CSR will include efficacy and safety data at the time of the End of the Trial (EOT definition in Section 3.3).

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2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
• To evaluate the effect of luspatercept versus placebo on anemia, as measured by mean hemoglobin values in the absence of transfusions over continuous 12-week intervals, from Week 13 to Week 24, compared to baseline
Secondary Objectives
• To evaluate the effect of luspatercept versus placebo on anemia-related symptoms in patients with β-thalassemia, as measured by non-transfusion dependent β-thalassemia-patient reported outcome (NTDT-PRO) over 2 continuous 12-week interval (Weeks 13 to 24, Weeks 37 to 48) compared to baseline • To evaluate the effect of luspatercept versus placebo on functional and health-related quality of life (QoL) as measured by the Medical Outcomes Study 36-Item Short Form (SF-36) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaires • To evaluate the long-term effect of luspatercept versus placebo on anemia, as measured by mean hemoglobin concentration in the absence of transfusions over a continuous 12-week interval from Week 37 to Week 48, compared to baseline • To evaluate the effect of luspatercept versus placebo on iron overload, as measured by liver iron concentration (LIC) and iron chelation therapy (ICT) daily dose • To evaluate the effect of luspatercept versus placebo on iron overload, as measured by serum ferritin • To evaluate the duration of erythroid response • To evaluate the effect of luspatercept versus placebo on physical activity measured by 6-minute walk (6MWT) **Safety and PK Objectives** • To evaluate safety and tolerability of luspatercept, including immunogenicity • To evaluate population pharmacokinetics (PK) of luspatercept in subjects with β-thalassemia
[redacted]
[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Endpoint Measurement	
			Wk 24	Wk 48
Primary Efficacy Endpoint	Proportion of subjects who have an increase from baseline ≥1.0 g/dL in mean of hemoglobin values over a continuous 12-week interval from Week 13 to Week 24 in the absence of transfusions	Baseline hemoglobin (Hb) is the average of 2 or more Hb measurements at least 1 week apart within 4 weeks prior to Dose 1.	X	
Key Secondary Efficacy Endpoints	Mean change from baseline in non-transfusion dependent β-thalassemia-patient reported outcome (NTDT-PRO) Tiredness and Weakness (T/W) domain score over a continuous 12-week interval from Week 13 to Week 24	NTDT-PRO is administered as a daily diary for 24 weeks and after that over the 7 days prior to receiving IP dose.	X	
	Mean change from baseline in mean of hemoglobin values over a continuous 12-week interval from Week 13 to Week 24 in the absence of transfusions	See description above for baseline Hb	X	
	Proportion of subjects who have an increase from baseline ≥1.0 g/dL in mean of hemoglobin values over a continuous 12-week interval from Week 37 to Week 48 in the absence of transfusions	See description above for baseline Hb		X
Secondary Efficacy Endpoints	Mean change from baseline in mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Fatigue subscale score over a continuous 12-week interval from Week 13 to Week 24	FACIT-F is administered to subjects every other dose prior to receiving IP dose.	X	
	Mean change from baseline in mean NTDT-PRO Shortness of Breath (SoB) domain over a continuous 12-week interval from Week 13 to Week 24	See description above for NTDT-PRO	X	
	Mean change from baseline in mean hemoglobin values over a continuous 12-week interval from Week 37 to Week 48 in the absence of transfusions	See description above for baseline Hb		X

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Endpoint Measurement	
			Wk 24	Wk 48
Secondary Efficacy Endpoints	Mean change from baseline in mean FACIT-F Fatigue subscale, mean NTDT-PRO T/W domain and mean NTDT-PRO SoB domain over a continuous 12-week interval from Week 37 to Week 48	See description above for FACIT-F and NTDT-PRO		X
	Proportion of subjects with an increase from baseline ≥ 3 in mean FACIT-F Fatigue subscale score over a continuous 12-week interval from Week 13 to Week 24	See description above for FACIT-F	X	
	Proportion of subjects with an increase from baseline ≥ 3 in mean FACIT-F Fatigue subscale score over a continuous 12-week interval from Week 37 to Week 48	See description above for FACIT-F		X
	Mean change from baseline in the physical component summary (PCS) and mental component summary (MCS) scores of the Medical Outcomes Study 36-Item Short Form (SF-36) at Week 24 and Week 48	SF-36 is administered to subjects every other dose prior to receiving IP dose	X	X
	Proportion of subjects with improvement of iron overload at Week 24 and Week 48, as measured by: o For subjects with baseline liver iron concentration (LIC) (by magnetic resonance imaging [MRI]) ≥3 mg/g dw: ≥20% reduction in LIC, OR ≥ 33% decrease in iron chelation therapy (ICT) daily dose o For subjects with baseline LIC (by MRI) < 3 mg/g dw: no increase in LIC > 1 mg/g dw AND not starting treatment with ICT or no increase in ICT daily dose ≥ 33%, if on ICT at baseline	Baseline ICT dose is based on medical history over 24 weeks prior to randomization; ICT drug and dose collected at every visit	X	X

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Endpoint Measurement	
			Wk 24	Wk 48
Secondary Efficacy Endpoints	Mean change from baseline in serum ferritin at Week 24, Week 48 and up to last assessment	All values available in the medical history over 24 weeks prior to randomization will be entered in the Electronic case report form (eCRF)	X	X
	Mean change from baseline in LIC at Week 24, Week 48 and up to last assessment	LIC at screening, Week 24, 48 and in the OLP, as applicable	X	X
	Proportion of subjects who are transfusion-free over 24 weeks	Occurrence of transfusions is assessed at every visit	X	
	Proportion of subjects who are transfusion-free over 48 weeks	See description above		X
	Duration of the mean hemoglobin increase from baseline ≥1.0 g/dL	Time from first to last Hb measurement with increase from baseline ≥1.0 g/dL	X	X
	Mean change from baseline in the 6-minute walk test (6MWT) distance at Week 24 and Week 48	6MWT is performed every 4 doses, eg, Dose 1, 5, 9, etc. and at Week 24 & Week 48 (± 7 days) regardless of dose delay and even if the IP is discontinued	X	X
	Proportion of subjects who have an increase from baseline ≥1.5 g/dL in mean of hemoglobin values over a continuous 12-week interval from Week 13 to Week 24 in the absence of transfusions	See description above for baseline Hb	X	
	Proportion of subjects with a decrease from baseline ≥ RD in mean NTDT-PRO T/W score, over Weeks 13 to 24 and Weeks 37 to 48	NTDT-PRO is administered as a daily diary for 24 weeks and after that over the 7 days prior to receiving IP dose	X	X

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Endpoint Measurement	
			Wk 24	Wk 48
Safety and PK	Safety and tolerability, including immunogenicity	Type, frequency, severity and relationship to investigational product (IP) of adverse events; frequency of anti-drug antibodies and their effect on efficacy and safety	X	X
	Pharmacokinetics (PK)	PK parameters	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Endpoint Measurement	
			Wk 24	Wk 48
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a Phase 2, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in adults with non-transfusion dependent beta (β)-thalassemia. The study is divided into the Screening Period, Double-blind Treatment Period (DBTP), Open-label Phase (OLP) and Post-treatment Follow-up Period (PTFP). The overall study design is described in Figure 7.

It is planned to randomize approximately 150 subjects at a 2:1 ratio of luspatercept versus placebo.

3.1.1. Screening Period

Upon giving written informed consent, the subject enters the Screening Period to determine eligibility. A subject identification document (ID) number will be allocated via the Interactive Response Technology (IRT) system as detailed in Section 7.3. The Screening Period will last up to 4 weeks with an administrative window of + 3 days to allow all laboratory results to be available at site for evaluating the subject's eligibility. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study as detailed in Table 3, Table of Events.

If the subject received transfusions during the 24 weeks prior to randomization, 24 weeks of transfusion history (including units or volume transfused and pre-transfusion hemoglobin level), should be recorded in the subject's electronic case report form (eCRF). If subjects received ICT during the 24 weeks prior to randomization, 24 weeks of ICT use history (including types of ICT and doses) should be recorded in the subject's electronic case report form (eCRF).

Re-screening is allowed, and a new subject ID number will be assigned (see Section 6.1).

Subjects will be stratified at the time of randomization based on:

1. Baseline hemoglobin level:
   - ≥ 8.5 g/dL
   - < 8.5 g/dL
2. Baseline NTDT-PRO T/W score:
   - ≥ 3 points
   - < 3 points

3.1.2. Double-blind Treatment Period

Subjects will enter the Double-blind Treatment Period (DBTP) once they have completed the required assessments in the Screening Period and been randomized via the IRT system, as detailed in Section 7.3. The DBTP will begin on Dose 1 Day 1 and will end when all subjects have completed 48 weeks of treatment or have discontinued earlier. At that time, the study will be unblinded.

Subject randomization will occur via the IRT system and Dose 1 Day 1 should be scheduled within 3 days of randomization (can be on the same day as randomization).

Eligible subjects will be randomized at a ratio of 2:1, luspatercept versus placebo, at a starting dose level of 1.0 mg/kg administered by subcutaneous (SC) injection once every 3 weeks. The maximum total dose per administration is 120 mg.

Best supportive care is allowed in both the luspatercept and placebo groups. This will include RBC transfusions, iron-chelating agents, use of antibiotic therapy, antiviral and antifungal therapy, nutritional support as needed, and other medications that are not prohibited (see Section 8.2), thus minimizing the safety risk to patients. Please, also refer to Section 8.1.2 for concomitant medication for anemia, Section 8.1.3 for concomitant iron chelation therapy use and Section 8.1.4 for concomitant RBC transfusions.

Study visits and serial measurements of safety and efficacy parameters will be performed as described in Table 3, Table of Events.

After the study is unblinded, and after DMC's recommendation:

- Subjects who received placebo and have been assessed as per protocol at least up to 48 weeks after the first dose of IP (even if the IP is discontinued before complete 48 weeks of treatment), may access the Open Label Period (OLP) to receive luspatercept for a maximum 15 months before moving to the rollover protocol for longer treatment.
- Subjects receiving luspatercept may continue their treatment in the OLP for maximum 15 months before moving to the rollover protocol for longer treatment (ie, 5 years from Dose 1 in the DBTP, or until treatment discontinuation, whichever occurs later).
- Subjects who received luspatercept and discontinued the IP in the DBTP may continue and/or complete the PTFP of 5 years from first dose of IP, or 3 years from last dose (whichever occurs later), to complete the Post-treatment Follow-up Period under the rollover protocol in this study until the of End of Trial (see Section 3.3).

Subjects may be discontinued from treatment and/or the study for reasons described in Section 11.1 and Table 5. The decision to discontinue a subject from study treatment is the responsibility of the treating physician; the Sponsor will not delay or refuse it. However, prior to deciding to discontinue a subject, it is recommended that the Investigator contact the Medical Monitor of this study and provide any supporting information for review and discussion. Possible dose modifications are detailed in Section 7.2.1.

3.1.3. Open-label Phase

The start of this Open-label Phase (OLP) will be determined by the availability of primary analysis data that justify the use of luspatercept in an OLP, which will be reviewed by the independent external DMC. After review of safety and efficacy, the DMC will determine if the use of luspatercept in subjects previously randomized to receive placebo in this OLP is safe and recommended, and if subjects already on luspatercept can continue to be treated at their current dose level (best supportive care is allowed). In the OLP, subjects may receive luspatercept for maximum 15 months or discontinue.

Access to the OLP:

Subjects initially assigned to placebo in the DBTP may enter the OLP only if the DMC allows it, as outlined above, and if:

- they are still receiving placebo at the time of unblinding, or
- they discontinued the treatment before the unblinding, but they continued their participation in the PTFP until the unblinding and complied with the PTFP assessments, as detailed in Section 5 Table of Events, and they still fulfill the following selected eligibility criteria prior to Dose 1 Day 1, as per PI assessment using central lab data:
  - Inclusion criteria: numbers 8-10 (Refer to Section 4.2)
  - Exclusion criteria: numbers 1-8, 10, 12-15, 17, 18 and 20 (Refer to Section 4.3)

Subjects initially assigned to luspatercept in the DBTP can enter the OLP if they are still receiving luspatercept at the time of unblinding and may continue their treatment in the rollover protocol, after completion of the OLP. **Note:** Per Investigator's request, subjects who discontinued luspatercept in the DBTP for reasons not related to subject's safety, and are still in the PTFP at the time of unblinding, may access the OLP and be re-treated with luspatercept after consultation with Sponsor Medical Monitor and review of safety and efficacy data as long as they still fulfill the study eligibility criteria prior to Dose 1 Day 1.

Subjects who discontinue from the study before the unblinding and without completing the PTFP period are not allowed to re-enter this study and access luspatercept in the OLP.

Subjects may be discontinued from treatment and/or study as described in Section 11 and Table 5.

3.1.4. Post-treatment Follow-up Period

Subjects who discontinue treatment with the IP in the DBTP or OLP, regardless of reason, will enter the PTFP and may continue or complete the long-term follow-up of 5 years from first dose of IP, or 3 years from last dose (whichever occurs later), under the rollover protocol until the End of Trial (see Section 3.3). Specific assessments and visits to be performed during this period are defined in Table 3, Table of Events. After the unblinding, and after DMC's recommendation:

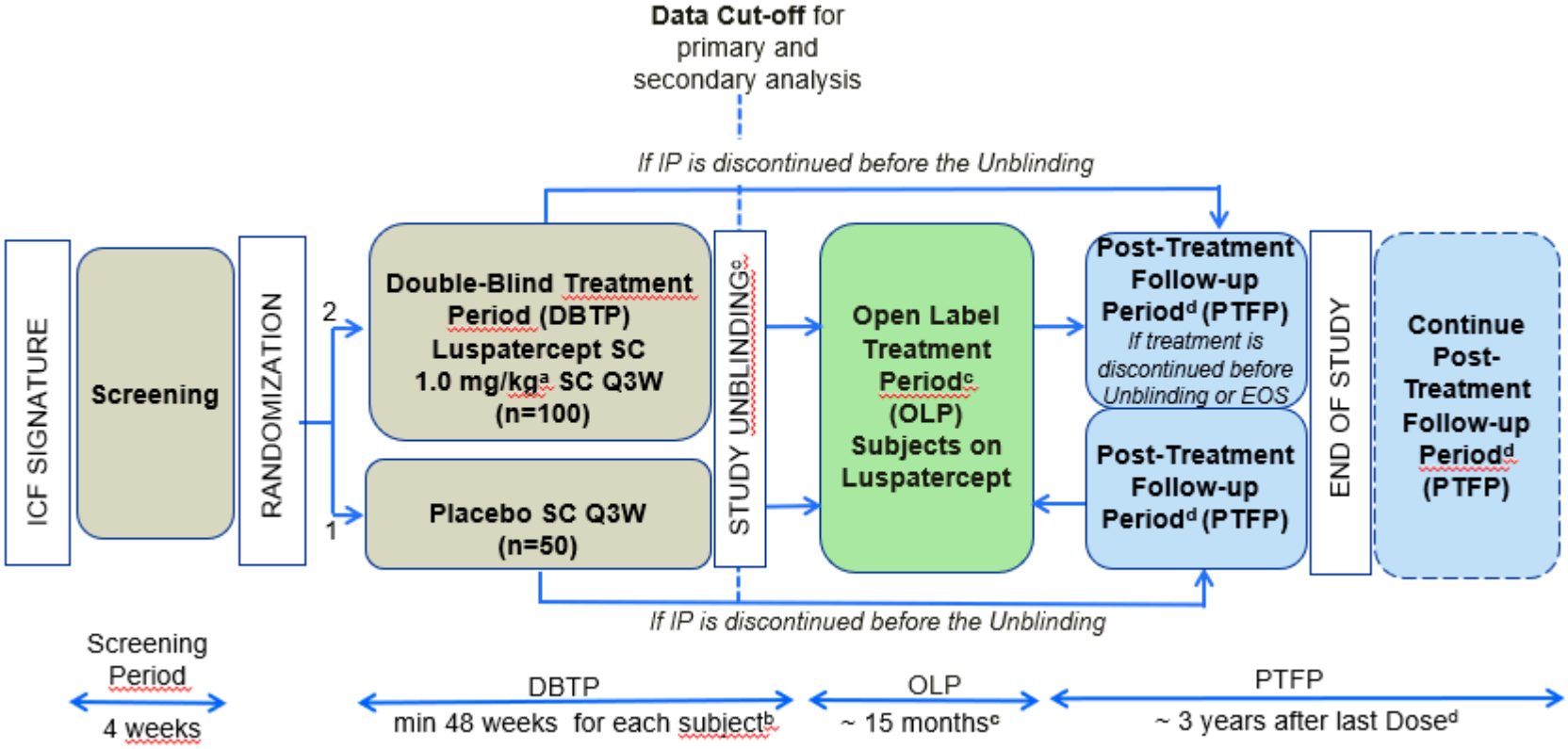
- Subjects who received placebo and have been assessed as per protocol at least up to 48 weeks after the first dose of IP (even if the IP is discontinued before completing 48 weeks of treatment), may stop the PTFP and access the OLP to receive luspatercept, if eligible.
- Subjects who received luspatercept and discontinued the IP in the DBTP or OLP may complete the PTFP and continue or complete the long-term follow-up of 5 years from first dose of IP, or 3 years from last dose (whichever occurs later), to complete the Post-treatment Follow-up Period under the rollover protocol until the End of Trial (see Section 3.3). Note: only the visit at 9 weeks after last dose may be performed in this study before moving to the rollover study.

3.1.5. Committees

The conduct of this trial will be overseen by an independent external Data Monitoring Committee (DMC) and by a steering committee (SC). During the DBTP, the DMC will review unblinded data, while the SC will not have access to unblinded data. Refer to Section 9.10.3 and Section 9.10.4 for additional information. Further details will be provided in the DMC and SC charters.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 7: Overall Study Design



EOS: end of study; EOT: end of trial; ICF: informed consent form; IP: investigational product; Q3W: every 3 weeks; SC: Subcutaneous.

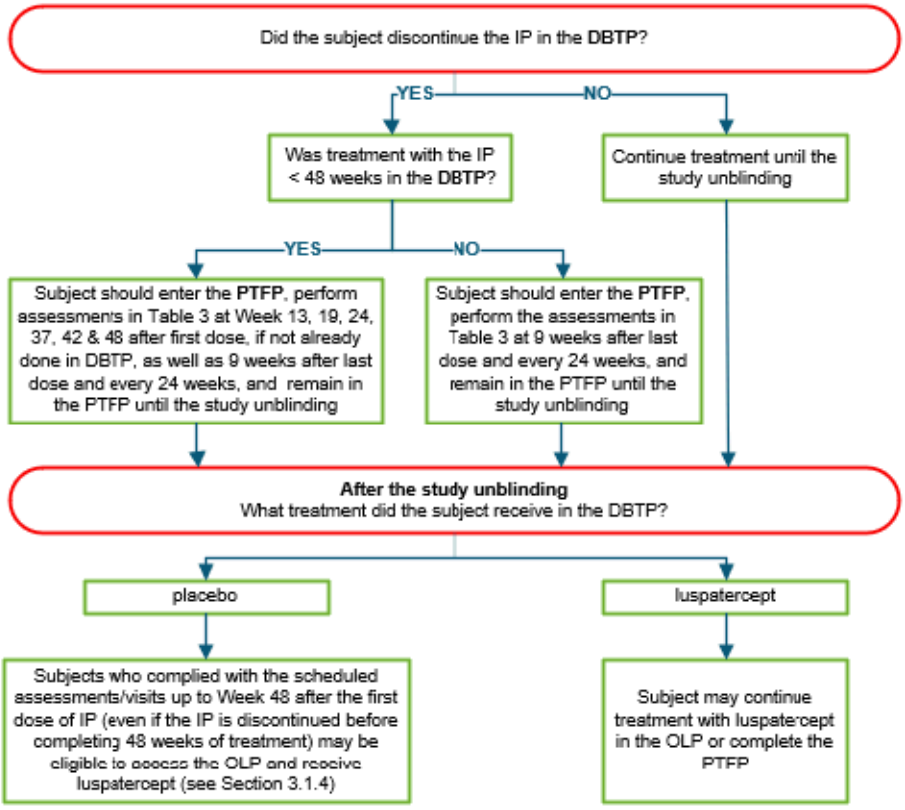
[a] Dose may be titrated up to a maximum of 1.25 mg/kg.

[b] Double-blind Treatment Period (DBTP) will end after last subject enrolled has completed 48 weeks of treatment or discontinued earlier, or when the study is unblinded.

[c] The study will be unblinded 48 weeks after last subject has received the first dose of IP. At that time, subjects still benefitting from luspatercept treatment as well as subjects who received placebo and have been assessed as per protocol up to 48 weeks after the first dose of IP (even if they have discontinued the IP before completing 48 weeks of treatment), may access the OLP to receive luspatercept for maximum 15 months on the basis of DMC recommendation after unblinded data review, and can continue treatment in the rollover protocol after EOT up to 5 years of Dose 1, or treatment discontinuation, whichever occurs later.

[d] Subjects in the DBTP who have discontinued luspatercept before the unblinding will continue the PTFP until the End of Trial (EOT) and may continue the PTFP in the rollover study up 5 years from first dose of IP, or 3 years from last dose (whichever occurs later), may complete the Post-treatment Follow-up Period under the rollover protocol. Subjects in the DBTP who have discontinued the placebo before the unblinding will continue the PTFP until the unblinding and may access the OLP, after DMC's recommendation.

Figure 8: Subjects Study Periods Flowchart



DBTP: double-blind treatment period; IP: investigational product; OLP: open-label phase; PTFP: post-treatment follow-up period.

3.2. Study Duration for Subjects

Study participation for each individual subject will be approximately 4 weeks in the Screening Period, at least 48 weeks in the DBTP, maximum 15 months in the OLP and 5 years from first dose of IP, or 3 years from last dose (whichever occurs later) in Post-treatment Follow-up Period until the End of Trial (Section 3.3)

End of Treatment for each individual subject is defined as the date of the last IP dose in the DBTP or OLP, whichever occurs later.

End of Study for each individual subject should occur after the study is unblinded (ie, 48 weeks after last subject has received the first dose of IP), and the OLP or the PTFP have been completed, as appropriate, or at the End of Trial as defined in Section 3.3, whichever occurs later.

3.3. End of Trial

The End of Trial is defined as the date all subjects complete the OLP (if allowed to access the OLP as defined in Section 3.1.3), or discontinue earlier, or, the date of receipt of the last data

point from the last subject that is required for primary, secondary, and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

The Sponsor may end the trial when all key endpoints and objectives of the study have been analyzed, and the availability of a rollover protocol exists into which any subjects remaining on study may be consented and continue to receive access to luspatercept, if not yet commercially available, and/or complete the PTFP.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 150 subjects diagnosed with non-transfusion dependent β-thalassemia (including Hemoglobin E/ β-thalassemia, excluding Hemoglobin S/β-thalassemia and Hemoglobin H) will be randomized.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subjects must be ≥ 18 years of age at the time of signing the informed consent document (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule (eg, not scheduled to receive hematopoietic stem cell transplantation) and other protocol requirements.
4. Subject must have documented diagnosis of β-thalassemia or hemoglobin E/ β-thalassemia. Concomitant alpha globin mutation and/or duplication are allowed.
5. Subject must be non-transfusion dependent, defined as 0 to 5 units of RBCs received during the 24-week period prior to randomization. Note: 1 unit defined for this entry criterion as approximately 200 to 350 mL of transfused packed RBCs.
6. Subject must not be on a regular transfusion program and must be RBC transfusion-free for at least ≥ 8 weeks prior to randomization
7. Subject must have mean baseline hemoglobin ≤ 10 g/dL, based on a minimum of 2 measurements ≥ 1 week apart within 4 weeks prior to randomization; hemoglobin values within 21 days post-transfusion will be excluded.
8. Subject must have performance status: Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1.
9. A female of childbearing potential (FCBP) for this study is defined as a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). A FCBP participating in the study must:
    a. Have 2 negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact.
    b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented). If a FCBP engages in sexual activity that may result in a pregnancy, she must agree to use, and be able to comply

with, effective contraception** without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 12 weeks (approximately 5 times the mean terminal half-life of luspatercept based on multiple-dose pharmacokinetics [PK] data) after discontinuation of study therapy.

10. Male subjects must:

    a. Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential** while participating in the study, during dose interruptions and for at least 12 weeks (approximately 5 times the mean terminal half-life of luspatercept based on multiple-dose PK data) following IP discontinuation, even if he has undergone a successful vasectomy

* True abstinence is acceptable when it is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.]

** Agreement to use highly effective methods of contraception that alone or in combination resulting in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly throughout the course of the study. Such methods include: Combined (estrogen and progestogen containing) hormonal contraception: Oral; Intravaginal; Transdermal; Progestogen-only hormonal contraception associated with inhibition of ovulation: Oral; Injectable hormonal contraception; Implantable hormonal contraception; Placement of an intrauterine device (IUD); Placement of an intrauterine hormone-releasing system (IUS); Bilateral tubal occlusion; Vasectomized partner; Sexual Abstinence.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. Subject has a diagnosis of hemoglobin S/β-thalassemia or alpha (α)-thalassemia (eg, Hemoglobin H).
5. Subject has active hepatitis C (HCV) infection as demonstrated by a positive HCV-RNA test of sufficient sensitivity, or active infectious hepatitis B as demonstrated by the presence of hepatitis B surface antigen (HBsAG) and/or hepatitis B virus DNA (HBV-DNA) positive, or known positive human immunodeficiency virus (HIV).

   Note: Subjects receiving antiviral therapies should have 2 negative HCV-RNA test 3 months apart before ICF signature, ie, one test at the end of the anti-viral therapy and second test 3 months following the first test.
6. Subject had deep vein thrombosis (DVT) or stroke requiring medical intervention ≤ 24 weeks prior to randomization.
7. Subjects on chronic anticoagulant therapy are excluded, unless they stopped the treatment at least 28 days prior to randomization. Anticoagulant therapies for prophylaxis and for

surgery or high-risk procedures as well as low molecular weight (LMW) heparin for superficial vein thrombosis (SVT) and chronic aspirin are allowed before and during the study.

8. Subject has received treatment with another investigational drug or device ≤ 28 days prior to randomization.
9. Subject had prior exposure to sotatercept (ACE-011) or luspatercept (ACE-536).
10. Subject has platelet count > 1000 x 10^9/L.
11. Subjects on iron chelation therapy (ICT) at the time of ICF signature must have initiated the treatment with ICT at least 24 weeks before the predicted randomization date. ICT can be initiated at any time during treatment and should be used according to the label.
12. Subject had Hydroxyurea and ESA treatment ≤ 24 weeks prior to randomization, and no prior gene therapy.
13. Subject is pregnant or a lactating female.
14. Subject has uncontrolled hypertension. Controlled hypertension for this protocol is considered ≤ Grade 1 according to National Cancer Institute Common Terminology for Adverse Events (NCI CTCAE) version 4.0 (current active minor version).
15. Subject has major organ damage, including:
    a. Liver disease with alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN) or history/evidence of cirrhosis, as well as presence of liver solid masses/tumor detected by ultrasound at screening.
    b. 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 (MI) within 6 months of randomization.
    c. Severe lung disease, including pulmonary fibrosis or pulmonary hypertension, ie, ≥ G3 NCI CTCAE version 4.0 (current active minor version).
    d. Estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 (per Modification of Diet in Renal Disease [MDRD] formula).
16. Subject has received chronic systemic glucocorticoids ≤ 12 weeks prior to randomization (physiologic replacement therapy for adrenal insufficiency is allowed).
17. Subject had major surgery ≤ 12 weeks prior to randomization (subjects must have completely recovered from any previous surgery prior to randomization).
18. Subject has history of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (see Investigator Brochure).
19. Subject has received immunosuppressants ≤ 28 days prior to randomization.
20. Subject has history or current malignancies (solid tumors and hematological malignancies) unless the subject has been free of the disease (including completion of any active or adjuvant treatment for prior malignancy) for ≥ 5 years. However, subjects with the following history/concurrent conditions are allowed:

- Basal or squamous cell carcinoma of the skin
- Carcinoma in situ of the cervix
- Carcinoma in situ of the breast
- Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system)

5. TABLE OF EVENTS

Table 3: Table of Events

Assessments	Ref.	Screening Period	Double-blind Treatment Period (DBTP) (Luspatercept or Placebo)						Open-label Period (OLP) (Luspatercept)		Post-treatment Follow-up Period (PTFP)			
		From Week -4 to Day -1	Week 1 Dose 1	From Dose 2 up to Unblinding					Week -1 (Placebo subj. from PTFP)[16]	From Week N Dose 1 (subj. allowed in the OLP)[17]	Subjects who did not complete 48 weeks in DBTP[9]	All subjects regardless of treatment duration with IP[10]		End of Study[11]
		(+3 days)	Day 1 (+3 days)	Day 1 (±3 days)	Dose 6 Day 8 (±3 days)	Dose 6 Day 15 (±3 days)	Weeks[14] 13, 19, 37, 42 (± 7 days)	Weeks[14] 24 & 48 (± 7 days)	Week -1 (- 5 days)	Day 1 (+5 days)	Weeks[9] 13, 19, 24, 37, 42 & 48 after first dose, if not already done in DBTP (±7 days)	9 wks after last dose (±7 days)	Every 24 wks[10] (±7 days)	At any time or End of Trial[11]
Informed consent	6.1	X	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	6.1	X	-	-	-	-	-	-	X[16]	-	-	-	-	-
Demographics	6.1	X	-	-	-	-	-	-	-	-	-	-	-	-
Medical history	6.1	X	-	-	-	-	-	-	-	-	-	-	-	-
β-thalassemia comorbidities assessment for NTDT severity score system	6.1 6.2 6.4	X	-	-	-	-	-	X	-	-	Wks 24 & 48	-	-	-
β-thalassemia genotype (only if not already available; central or local lab)	6.1	X	-	-	-	-	-	-	-	-	-	-	-	-
Hepatitis B & C[12] (local or central lab) if not done within 10 weeks of ICF signature	6.1	X	-	-	-	-	-	X	-	-	-	-	-	-
Iron Chelation Therapy (history starting from at least 24 weeks prior to Dose 1 Day 1 in DBTP)	6.1 to 6.4	X	Record on ongoing basis, until 9 weeks after last dose[18]											

Table 3: Table of Events (Continued)

Assessments	Ref.	Screening Period	Double-blind Treatment Period (DBTP) (Luspatercept or Placebo)						Open-label Period (OLP) (Luspatercept)		Post-treatment Follow-up Period (PTFP)			
		From Week -4 to Day -1	Week 1 Dose 1	From Dose 2 up to Unblinding					Week -1 (Placebo subj. from PTFP)[16]	From Week N Dose 1 (subj. allowed in the OLP)[17]	Subjects who did not complete 48 weeks in DBTP[9]	All subjects regardless of treatment duration with IP[10]		End of Study[11]
		(+3 days)	Day 1 (+3 days)	Day 1 (±3 days)	Dose 6 Day 8 (±3 days)	Dose 6 Day 15 (±3 days)	Weeks[14] 13, 19, 37, 42 (± 7 days)	Weeks[14] 24 & 48 (± 7 days)	Week -1 (- 5 days)	Day 1 (+5 days)	Weeks [9]13, 19, 24, 37, 42 & 48 after first dose, if not already done in DBTP (±7 days)	9 wks after last dose (±7 days)	Every 24 wks[10] (±7 days)	At any time or End of Trial[11]
Prior / Concomitant / Post treatment (disease specific)/ Medications / Therapies	6.1 to 6.4	X	Record on ongoing basis, until 9 weeks after last dose[18]											
Prior/ Concomitant / Post treatment procedures (eg, surgery, radiation therapy).	6.1 to 6.4	X	Record on ongoing basis, until 9 weeks after last dose[18]											
Transfusion assessment (history starting from at least 24 weeks prior to Dose 1 Day 1 in DBTP and OLTP)	6.1 to 6.4	X	Record on ongoing basis, until 9 weeks after last dose[18]											
Adverse events	6.1 to 6.4	Starting after informed consent signature, on ongoing basis until 9 weeks after last dose, only related SAEs to be reported until End of Study												
Malignancy and premalignancy reporting (Section 10.5.3)[13]	6.1 to 6.4	Continuous reporting occurrence of any case regardless of causality, starting after informed consent signature											X[13]	X[13]
Vital signs[1]	6.1 to 6.4	X	X	X (every dose)	-	-	-	-	-	X	-	X	-	-
Height (at Screening only) and weight	6.1 to 6.4	X	X	X (every dose)	-	-	-	-	-	X	-	X	-	-

Table 3: Table of Events (Continued)

Assessments	Ref.	Screening Period	Double-blind Treatment Period (DBTP) (Luspatercept or Placebo)						Open-label Period (OLP) (Luspatercept)		Post-treatment Follow-up Period (PTFP)			
		From Week -4 to Day -1	Week 1 Dose 1	From Dose 2 up to Unblinding					Week -1 (Placebo subj. from PTFP)[16]	From Week N Dose 1 (subj. allowed in the OLP)[17]	Subjects who did not complete 48 weeks in DBTP[9]	All subjects regardless of treatment duration with IP[10]		End of Study[11]
		(+3 days)	Day 1 (+3 days)	Day 1 (±3 days)	Dose 6 Day 8 (±3 days)	Dose 6 Day 15 (±3 days)	Weeks[14] 13, 19, 37, 42 (± 7 days)	Weeks[14] 24 & 48 (± 7 days)	Week -1 (- 5 days)	Day 1 (+5 days)	Weeks[9] 13, 19, 24, 37, 42 & 48 after first dose, if not already done in DBTP (±7 days)	9 wks after last dose (±7 days)	Every 24 wks[10] (±7 days)	At any time or End of Trial[11]
ECOG performance status	6.1 6.3	X	-	-	-	-	-	-	X	-	-	-	-	-
12-Lead electrocardiogram (local reading)	6.1 to 6.4	X	-	-	X	-	-	-	X	-	-	X	-	-
Echocardiography or MRI (same technique to be used throughout the study): to assess LVEF and TRV	6.1 to 6.4	X, if not done within 8 weeks of ICF signature	-	-	-	-	-	X	X	Wk 144 (± 7 days) if applicable	Wks 24 & 48	-	-	-
Pregnancy testing[2]	6.1 to 6.4	X	X	X (every dose)	-	-	-	-	X (serum, central lab)	X (local lab)	-	X	-	-
Menstrual status	6.1 to 6.4	X	-	X	-	-	-	-	-	X	-	X	-	-
Hematology[3] (by central lab Screening, predose Hb value by both local and central lab in DBTP, OLP and PTFP)	6.1 to 6.4	X (at Wk -4 and Wk -3 or Wk -2)	X	X (every dose)	X	X	X	X	X (central lab)	X (local lab and central lab)	X	X	-	-

Table 3: Table of Events (Continued)

Assessments	Ref.	Screening Period	Double-blind Treatment Period (DBTP) (Luspatercept or Placebo)					Open-label Period (OLP) (Luspatercept)		Post-treatment Follow-up Period (PTFP)			
		From Week -4 to Day -1	Week 1 Dose 1	From Dose 2 up to Unblinding				Week -1 (Placebo subj. from PTFP)[16]	From Week N Dose 1 (subj. allowed in the OLP)[17]	Subjects who did not complete 48 weeks in DBTP[9]	All subjects regardless of treatment duration with IP[10]		End of Study[11]
		(+3 days)	Day 1 (+3 days)	Day 1 (±3 days)	Dose 6 Day 8 (±3 days)	Dose 6 Day 15 (±3 days)	Weeks[14] 13, 19, 37, 42 (± 7 days)	Weeks[14] 24, 48 & 120 (± 7 days)	Week -1 (- 5 days)	Day 1 (+5 days)	Weeks[9] 13, 19, 24, 37, 42 & 48 after first dose, if not already done in DBTP (±7 days)	9 wks after last dose (±7 days)	Every 24 wks[10] (±7 days)	At any time or End of Trial[11]
Serum Chemistry Panel 1[4] (predose, by central lab up to Week 48/Dose 17)	6.1 to 6.2	X	X	X (every dose up to Dose 17)	-	-	-	-	-	-	-	-	-	-
Serum chemistry panel 2[4] (predose, by central lab in the DBTP and OLP)	6.1 to 6.4	-	-	X (every 4 doses after Wk 48/ Dose 17)	-	-	-	-	X	X (every 4 doses; central lab)	-	X (central)	-	-
Urinalysis[8] by central lab in the DBTP and local lab in the OLP; Local lab at Screening only if central lab results are not available on time	6.1 to 6.4	X	X	X (every 4 doses from Dose 1: at Dose 5, 9, 13 etc.)	-	-	-	-	X (local lab)	X (every 4 doses from Dose 1: at Dose 5, 9, 13 etc: local lab)	-	X (central)	-	-

Table 3: Table of Events (Continued)

Assessments	Ref.	Screening Period	Double-blind Treatment Period (DBTP) (Luspatercept or Placebo)						Open-label Period (OLP) (Luspatercept)		Post-treatment Follow-up Period (PTFP)			
		From Week -4 to Day -1	Week 1 Dose 1	From Dose 2 up to Unblinding					Week -1 (Placebo subj. from PTFP)[16]	From Week N Dose 1 (subj. allowed in the OLP)[17]	Subjects who did not complete 48 weeks in DBTP[9]	All subjects regardless of treatment duration with IP[10]		End of Study[11]
		(+3 days)	Day 1 (+3 days)	Day 1 (±3 days)	Dose 6 Day 8 (±3 days)	Dose 6 Day 15 (±3 days)	Weeks[14] 13, 19, 37, 42 (± 7 days)	Weeks[14] 24, 48 & 120 (± 7 days)	Week -1 (- 5 days)	Day 1 (+5 days)	Weeks[9] 13, 19, 24, 37, 42 & 48 after first dose, if not already done in DBTP (±7 days)	9 wks after last dose (±7 days)	Every 24 wks[10] (±7 days)	At any time or End of Trial[11]
Serum erythropoietin (EPO), predose, by central lab	6.2 to 6.4	-	X	X (every 4 doses from Dose 1: at Dose 5, 9, 13 etc.)	-	-	-	-	-	X (every 4 doses from Dose 1: at Dose 5, 9, 13 etc.)	-	X only in DBTP	-	-
PK (predose on dosing day; serum collection; by central lab)	6.5	-	X	X (Dose 2, 4, and 6, 8, 12, 16 and every 6 doses: at Dose 22, 28, 34 etc.)	X	X	-	-	-	-	-	-	-	-
Anti-drug antibody (ADA)[5] up to maximum 2 years from Dose 1 Day 1; by central lab	6.6	-	X	X (Dose 2, 4 and 6; 8, 12, 16 and every 6 doses: at Dose 22, 28, 34 etc.)	-	-	-	-	-	X (if positive in DBTP, every 6 doses)[5]	-	-	X[5]	-

Table 3: Table of Events (Continued)

Assessments	Ref.	Screening Period	Double-blind Treatment Period (DBTP) (Luspatercept or Placebo)						Open-label Period (OLP) (Luspatercept)		Post-treatment Follow-up Period (PTFP)			
		From Week -4 to Day -1	Week 1 Dose 1	From Dose 2 up to Unblinding					Week -1 (Placebo subj. from PTFP)[16]	From Week N Dose 1 (subj. allowed in the OLP)[17]	Subjects who did not complete 48 weeks in DBTP[9]	All subjects regardless of treatment duration with IP[10]		End of Study[11]
		(+3 days)	Day 1 (+3 days)	Day 1 (±3 days)	Dose 6 Day 8 (±3 days)	Dose 6 Day 15 (±3 days)	Weeks[14] 13, 19, 37, 42 (± 7 days)	Weeks[14] 24 & 48 (± 7 days)	Week -1 (- 5 days)	Day 1 (+5 days)	Weeks[9] 13, 19, 24, 37, 42 & 48 after first dose, if not already done in DBTP (±7 days)	9 wks after last dose (±7 days)	Every 24 wks[10] (±7 days)	At any time or End of Trial[11]
MRI for LIC (mg/g dw) by T2* or R2[6] as per clinical site's practice	6, 6.1 to 6.4	X, if not done within 12 weeks of ICF signature	-	-	-	-	-	X	X	Wk 144 (± 7 days), if applicable	Wks 24 & 48	-	-	-
MRI for extramedullary masses[6] – only subjects with medical history of masses	6, 6.1 to 6.4	X	-	-	-	-	-	Wk 48	X	Wk 144 (± 7 days), if applicable	Wk 48	-	-	-
MRI of spleen, if not splenectomized: MRI is the preferred technique for measuring the spleen size[6]	6, 6.1 to 6.4	X	-	-	-	-	-	X	X	Wk 144 (± 7 days), if applicable	Wks 24 & 48	-	-	-
Abdominal ultrasound for liver	6, 6.1, 6.3	X	-	-	-	-	-	-	X	-	-	-	-	-
DXA scan[7] – total hip, lumbar spine (read locally)	6, 6.1 to 6.4	X, if not done within 20 weeks of ICF signature	-	-	-	-	-	Wk 48	X	Wk 144 (± 7 days), if applicable	Wk 48	-	-	-

Table 3: Table of Events (Continued)

Assessments	Ref.	Screening Period	Double-blind Treatment Period (DBTP) (Luspatercept or Placebo)						Open-label Period (OLP) (Luspatercept)		Post-treatment Follow-up Period (PTFP)			
		From Week -4 to Day -1	Week 1 Dose 1	From Dose 2 up to Unblinding					Week -1 (Placebo subj. from PTFP)[16]	From Week N Dose 1 (subj. allowed in the OLP)[17]	Subjects who did not complete 48 weeks in DBTP[9]	All subjects regardless of treatment duration with IP[10]		End of Study[11]
		(+3 days)	Day 1 (+3 days)	Day 1 (±3 days)	Dose 6 Day 8 (±3 days)	Dose 6 Day 15 (±3 days)	Weeks[14] 13, 19, 37, 42 (± 7 days)	Weeks[14] 24, 48 & 120 (± 7 days)	Week -1 (- 5 days)	Day 1 (+5 days)	Weeks[9] 13, 19, 24, 37, 42 & 48 after first dose, if not already done in DBTP (±7 days)	9 wks after last dose (±7 days)	Every 24 wks[10] (±7 days)	At any time or End of Trial[11]
6MWT	6.1 to 6.4	X (at wk -4 and between wk -3 and -2)	-	X (every 4 doses, eg, Dose 1, 5, 9, etc.)	-	-	-	X	X	Wk 144 (± 7 days), if applicable	Wks 24 & 48	X	-	-
QoL questionnaire (NTDT PRO with additional PGI-S item), to be completed as daily diary in the evening	6.1 to 6.3, 6.8	X (daily over 7 days before Dose 1 Day 1)	X	X (daily up to wk 24 and thereafter over 7 days prior to dosing, at every other dose eg, Dose 9, 11, 13, etc.)	-	-	-	-	X (daily over 7 days before Dose 1 Day 1)	X (7 days prior to dosing, at every other dose eg, Dose 9, 11, 13, etc.)	X (over 7 days prior to Wks 13, 24, 37 & 48)	X	-	-
QoL questionnaires (SF-36v2, FACIT-F and PGI-C) to be completed before knowing the Hb test result on dosing visits	6.1 to 6.3, 6.8	X	X	X (every other dose from Dose 3 and: Dose 5, 7, 9, etc.)	-	-	-	-	X	X (every other dose from Dose 3, 5, 7, 9, etc.)	Wks 13, 24, 37 & 48	X	-	-

Table 3: Table of Events (Continued)

Assessments	Ref.	Screening Period	Double-blind Treatment Period (DBTP) (Luspatercept or Placebo)					Open-label Period (OLP) (Luspatercept)		Post-treatment Follow-up Period (PTFP)			
		From Week -4 to Day -1	Week 1 Dose 1	From Dose 2 up to Unblinding				Week -1 (Placebo subj. from PTFP)[16]	From Week N Dose 1 (subj. allowed in the OLP)[17]	Subjects who did not complete 48 weeks in DBTP [9]	All subjects regardless of treatment duration with IP[10]		End of Study [11]
		(+3 days)	Day 1 (+3 days)	Day 1 (±3 days)	Dose 6 Day 8 (±3 days)	Dose 6 Day 15 (±3 days)	Weeks[14] 13, 19, 37, 42 (± 7 days)	Weeks[1][4] 24 & 48 (± 7 days)	Week -1 (- 5 days)	Day 1 (+5 days)	Weeks [9]13, 19, 24, 37, 42 & 48 after first dose, if not already done in DBTP (±7 days)	9 wks after last dose (±7 days)	Every 24 wks[10] (±7 days)	At any time or End of Trial [11]
Healthcare Resource Utilization (HRU)	6.8	Record on ongoing basis, until 9 weeks after last dose [18]											
Serum ferritin (by central lab; also enter in the eCRF all values available in the medical history over 24 weeks prior to Dose 1 Day 1 in DBTP/OLP)	6.1 to 6.4	X	X	X (every dose)	-	-	-	-	X (central)	X (every 4 doses by central)	Wks 24 & 48	X	-	-
Leg ulcer evaluation (if applicable)	6.1 to 6.4	X	Record on ongoing basis, until 9 weeks after last dose[18]											
Serum GDF11 and other related biomarkers (by central lab; predose sample on dosing days)	6.7	-	X	X (Dose 6, 8, and 16)	X	X	-	-	-	X (every 4 doses)	-	X[15]	-	-
Hemoglobin fractions (by central lab; predose sample on dosing days)	6.7	X	-	X (every dose)	X	X	-	-	-	X (every 4 doses)	-	X	-	-
Administer luspatercept / placebo every 21 days and perform drug accountability	6.2 to 6.3, 7.5	-	X	X	-	-	-	-	-	X	-	-	-	-

ADA = anti-drug (ACE-536) antibody; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BMD = bone mineral density; BUN = blood urea nitrogen; DBP = diastolic blood pressure; DBTP = Double-blind Treatment Period; dw = dry weight; DXA = dual-energy x-ray absorptiometry; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EPO= Serum erythropoietin; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; GDF = growth differentiation factor; Hb = hemoglobin; HBsAG = Hepatitis B surface antigen; Hct = hematocrit; Hem = Hematology laboratory assessments; HRU = Health Resource Utilization; ICF = Informed consent form; IP= investigational product; lab = laboratory; LDH = lactic dehydrogenase; LIC= liver iron concentration; LVEF = left ventricular ejection fraction; MCH = Mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; 6MWT = 6 minute walk test; NTDT-PRO= Non-transfusion dependent β-thalassemia-patient reported outcome; OLP = Open-label Phase; PGI-C= Patient Global Impression of Change; PGI-S= Patient Global Impression of Severity; PK = Pharmacokinetic; PTFP = Post-treatment Follow-up Period; QOL = quality of life; RBC = red blood cell; RDW = red blood cell distribution width; Ref. = Section Reference; SAE = serious adverse event; SBP = systolic blood pressure; SF-36v2 = Medical Outcomes Study 36-Item Short Form; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase; Subj. = subjects; TRV = Tricuspid Regurgitant Velocity; WBC = white blood cell; Wk = week/Week; Wks = weeks.

[1] Vital signs (including heart rate, seated blood pressure [DBP and SBP], and temperature) 2 separate seated blood pressure measurements obtained predose and 10 minutes apart.

[2] Two pregnancy tests are required during screening for all female subjects of childbearing potential. One test is in serum (beta human chorionic gonadotropin (β-hCG) test with a minimum sensitivity of 25 mIU/mL must be performed within 4 weeks prior Dose 1 Day 1) and the second test can be either in urine or serum within 72 hours of Dose 1 Day 1. During DBTP and OLP, urine or serum pregnancy tests are allowed.

[3] Hematology assessment includes RBC count, Hb, Hct, MCV, MCH, MCHC, RDW, WBC count (corrected by erythroblast count) and differential count, absolute neutrophil count (ANC), and absolute lymphocytes count, platelet (all preceding parameters assessed by Central and Local Lab), and reticulocyte absolute values and circulating erythroblasts (nucleated RBC) counts (by Local Lab). On dosing days, hemoglobin levels and WBC count (corrected by erythroblast count) should be measured at predose locally and centrally in the DBTP to ensure the drug administration criteria are met and the modification rules are followed (Section 7.2). **Note:** Hb must be measured by central or local lab in the wk 13, 19, 24, 37, 42, and 48 (± 7 days) of DBTP regardless of dose delay and even if the IP is discontinued. Laboratory evaluations may be repeated more frequently if clinically indicated. If the dose is delayed, all planned Day 1 assessments should be performed as detailed in the Table of Events, Table 3, regardless of the dose delays, and appropriate samples sent to the central laboratory. Lab assessments causing the dose delay can be repeated locally until restarting the IP (See Section 6.2.1 for further details).

[4] Serum chemistry panel 1 (calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, creatinine clearance, microalbumin, total protein, alkaline phosphatase, bilirubin [total, non conjugated], AST/SGOT, ALT/SGPT, LDH and uric acid) performed by central laboratory up to Dose 17, included. After Dose 17, serum chemistry panel 2 (creatinine, creatinine clearance, alkaline phosphatase, bilirubin [total, non conjugated] AST/SGOT, ALT/SGPT) will be performed every 4 doses by central lab in the DBTP and OLP, In the DBTP, local laboratory results are accepted at screening only if central lab results are not available in timely manner to allow eligibility assessment. Laboratory evaluations can be repeated more frequently, if clinically indicated. If the dose is delayed, all planned Day 1 assessments should be performed as detailed in the Table of Events, Table 3, and appropriate samples sent to the central laboratory, regardless of the dose delays. Lab assessments causing the dose delay can be repeated locally until restarting the IP (See Section 6.2.1 for further details).

[5] For ADA test, additional blood draws are not needed if a time-matched PK sample will be collected up to maximum 2 years from Dose 1 Day 1 (central lab). The test will be performed using the serum collected for PK samples. In PTFP, ADA samples will be collected every 24 weeks until reaching 2 years from Dose 1 Day 1 of DBTP. After the unblinding, only ADA positive subjects will continue testing for up to 2 years from Dose 1 Day 1 of DBTP, if not already achieved the 2 years of testing. For subjects on placebo in the DBTP, ADA will be tested every 6 doses for up to 2 years from Dose 1 Day 1 of DBTP if ADA positive in the OLP, continue testing in PTFP every 24 weeks up to maximum 2 years from Dose 1 Day 1 of OLP.

[6] MRI for LIC, extramedullary masses, and spleen should be performed using one MRI acquisition, if possible. MRI for extramedullary masses will be performed at baseline and at Week 48 only to subjects with medical history of masses. MRI of spleen, if not splenectomized: MRI is the preferred technique (same MRI acquisition of LIC, if possible) for measuring the spleen size. Alternatively, ultrasound can be used. Same technique to be used throughout the study.

[7] DXA scan of the lumbar spine, total hip for bone mineral density (BMD).

[8] Urinalysis: microalbumin, creatinine, microalbumin/creatinine ratio (morning void; central lab in the DBTP, and local lab in the OLP). In the DBTP, local lab at Screening is accepted only if central lab results are not available on time for eligibility evaluation.

[9] Subjects who did not complete 48 weeks in DBTP should perform visits at: 9 weeks after last dose and every 24 weeks after last dose up to End of Study, as all subjects regardless of treatment duration with IP, in addition they should perform visits at Weeks 13, 19, 24, 37, 42, and 48 after first dose, if not already done in the DBTP.

[10] Regardless of treatment duration with IP, all subjects should perform a visit at 9 weeks after last dose in the DBTP or OLP, and **visits** every 24 weeks at least 5 years from first dose of IP, or 3 years from last dose (whichever occurs later). After the study is unblinded, subjects who discontinue luspatercept in the DBTP may continue the PTFP in the OLP and subsequently in the rollover study.
[11] End of Study visit should occur after the study is unblinded (ie, 48 weeks after last subject received the first dose of IP), and, at the End of Trial as defined in Section 3.3, whichever occurs later. Or, at the time a subject discontinues from the study.
[12] Hepatitis B and C: perform HCV-RNA and HBsAG and/or HBV-DNA by central lab; local lab results are accepted only if central lab results are not available on time for eligibility evaluation.
[13] Subjects are required to see the Investigator at least every 24 weeks to assess for malignancy and premalignancy, as per standard of care.
[14] Visits at Weeks 13, 19, 24 37, 42 and 48 in DBTP should occur only if a dosing visit is not scheduled within ± 7 days of those respective weeks. Week 120 visit might be performed in the DBTP or in the OLP, if applicable (see footnote 17).
[15] Serum GDF11 and other related biomarkers sample collection at 9 weeks after last dose to be performed only if not performed at Dose 16, and not performed within the last 12 weeks.
[16] Subjects on placebo who discontinued the treatment, but have been assessed as per protocol up to 48 weeks after the first dose of IP, and continued their participation in the PTFP until the time of unblinding, refer to Section 3.1.4, will perform Week -1 visit to re-assess some Inclusion/Exclusion criteria as per Section 3.1.3. Eligibility review/confirmation of selected Inclusion/Exclusion criteria will be performed by the Investigator using local lab data that will be reported in the eCRFs. Note: Week -1 assessments in the OLP can be performed up to pre-Dose 1 Day 1, if needed.
[17] All subjects on luspatercept treatment at the time of unblinding, as well as subjects on placebo in the DBTP or in the PTFP at the time of unblinding, if eligible as per Section 3.1.3, can be treated with luspatercept in the OLP starting from Dose 1 Week N (N = number of weeks in the DBTP since Dose 1 Week 1).
[18] For early discontinuation subjects, these parameters to be reported up to 48 weeks Post Dose 1 Day 1 or Week 9 post last dose whichever is the later date.

6. PROCEDURES

All protocol required assessments are listed in Section 5, Table 3 with an "X" indicating at which visits the assessments are to be performed. All data obtained from these assessments must be recorded in the subject's source documentation.

Dosing visits during the DBTP must occur within ± 3 days of the scheduled day, except for Dose 1 Day 1 which must occur within 3 days of the randomization via IRT.

For assessments to be performed at certain weeks of the study periods (eg, magnetic resonance imaging [MRI] scans at Week 24 and Week 48), the site can apply a flexibility window as indicated in Table of Events, Table 3, to match the diagnostic assessment with the closest dosing visit.

During the PTFP, visits must occur within ± 7 days of the scheduled day.

Local and central laboratory assessments are specified in the Table of Events, Table 3, and in sections below (Sections 6.1, 6.2, 6.2.1, 6.3). Moreover, local laboratory assessments are allowed in the following circumstances: when timely results are needed for randomization (with the exception of Hb levels), study treatment dosing decisions, assessments between clinic visits, and AE. Local laboratory data should be recorded in the eCRF if relevant to dose administration, modification, AE, or when no central laboratory results were obtained.

Procedures to be performed during each study period are detailed in the sections below and in the Table of Events, Table 3.

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 4 weeks (+ 3 days administrative window to allow all laboratory results to be available) of randomization via IRT. Two visits should occur at Week -4 and at Week -3 or Week -2 of the screening period, respectively. Hemoglobin levels and other laboratory results assessed by central laboratory must be available on time for evaluating the subject's eligibility (refer to Table of Events, Table 3 for further information). Dose 1 Day 1 should be scheduled within 3 days of randomization via IRT (it can be on the same day as randomization).

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary, or subjects can be rescreened (see Section 6.1.1).

The following will be performed at Screening as specified in the Table of Events (Table 3), after informed consent has been obtained:

- Assessment of inclusion/exclusion criteria for study eligibility
- Demographics (date of birth, sex, race, and ethnicity [if allowed by local regulations])

- Complete medical history: specific information regarding all diagnosed relevant medical conditions (occurring prior to screening) should be recorded including any additional details, as needed.
- β-thalassemia comorbidities assessment for NTDT severity score system
- β-thalassemia genotype (ie, beta and alpha globin mutations should be assessed only if not already available)
- Hepatitis B and hepatitis C (HCV-RNA and HBsAG and/or HBV-DNA) should be done only if not done already within 10 weeks before ICF signature)
- Type of iron chelating therapy and period of treatment should be recorded in the related eCRF, at least 24 weeks of history before Dose 1 Day 1 in DBTP.
- Prior medications/therapies: including those taken ≤ 28 days before screening, such as surgery, radiation, systemic or any other therapy for the subject's disease. Prior ESA history (24 weeks prior to randomization) should also be recorded.
- Prior procedures (including all procedures occurring ≤ 28 days before Screening)
- Transfusion assessment – record RBC transfusion history (≥ 24 weeks of history prior to Dose 1 Day 1 in DBTP), including Hb levels prior to each transfusion, the number of units and/or volumes transfused, the dates of transfusion. If available, the hematocrit (Hct) of the transfused unit should be collected, as well as the age when subject started regular transfusion. These retrospective data will be recorded in the subject's electronic case report form (eCRF).
- Adverse event assessment is starting after informed consent signature – record in the eCRF all AEs regardless of causality on an ongoing basis until 9 weeks after last dose (refer to Section 10 for additional information)
- Malignancy and premalignancy reporting from ICF signature up to End of Study - continuous reporting the occurrence of any case regardless of causality (refer to Section 10.5.3 for additional information). Subjects are required to see the Investigator at least every 24 weeks to assess for malignancy and premalignancy, as per standard of care.
- Vital signs (including seated blood pressure to assess diastolic blood pressure [DBP] and systolic blood pressure [SBP], temperature, and heart rate). Two separate measurements 10 minutes apart of seated blood pressure must be obtained at predose.
- Height (only at Screening) and weight
- Eastern Cooperative Oncology Group (ECOG) performance status (Appendix B)
- 12-lead electrocardiogram (ECG) – read locally
- Echocardiography or MRI for left ventricular ejection fraction (LVEF) and tricuspid valve regurgitation velocity (TRV), if not done within 8 weeks of ICF signature
- Pregnancy testing is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test (which must be negative) with a minimum sensitivity of 25 mIU/mL must be performed within 4 weeks prior Dose 1

Day 1. A second pregnancy test is required this can be a urine or serum test within 72 hours prior to Dose 1 Day 1.

- For female subjects: menstrual status
- Hematology assessment includes: RBC count, Hb, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW), white blood cell (WBC) count (corrected by erythroblast count) and differential count, absolute neutrophil count (ANC), and absolute lymphocytes count, platelets, (all previously listed assessments by central and local laboratory) absolute reticulocyte, and circulating erythroblasts (nucleated RBC) counts (by local laboratory) – 2 Hb measurements are required, by central laboratory at ≥ 1-week intervals at Week -4 and at Week -3 or Week -2.
- Serum chemistry panel 1 (calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, creatinine clearance, microalbumin, total protein, alkaline phosphatase, bilirubin [total, non conjugated], aspartate aminotransferase/serum glutamic oxaloacetic transaminase [AST/SGOT], alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT], lactic dehydrogenase [LDH], and uric acid) - central laboratory assessment should be performed within 4 weeks prior to Dose 1 Day 1 (Local laboratory results are accepted at screening only if central laboratory results are not available in timely manner to allow eligibility assessment).
- Urinalysis: microalbumin, creatinine, microalbumin/creatinine ratio (morning void) - central laboratory assessment should be performed within 4 weeks prior to Dose 1 Day 1). Local laboratory results at Screening are accepted only if central laboratory results are not available in timely manner to allow eligibility assessment.
- MRI for LIC (mg/g dw) by T2* or R2, as per site's practice (to be performed during Screening, only if subject has not had MRI performed within 12 weeks prior to signing ICF)
- MRI for extramedullary masses - only for subjects who have history of masses at baseline
- MRI of spleen, if not splenectomized - MRI is the preferred technique (same MRI acquisition of LIC, if possible), the longest longitudinal dimension and width should be used. Alternatively, ultrasound can be used. Same technique to be used throughout the study
- Abdominal ultrasound for liver (only at screening)
- Bone imaging dual-energy x-ray absorptiometry [DXA] scan - total hip, lumbar spine (read locally) (DXA to be performed during Screening, only if not performed within 20 weeks prior to signing ICF)
- 6MWT (6-minute walk test) at Week -4 and between Week -3 and Week -2
- QoL questionnaire (NTDT - PRO with additional Patient Global Impression of Severity [PGI-S] item for validation), to be completed as a daily diary over 7 days before Dose 1 Day 1 in the evening

- QoL questionnaires (SF-36 v2, FACIT-F, and Patient Global Impression of Change [PGI-C])
- Healthcare Resource Utilization (HRU)
- Serum ferritin: central laboratory assessment should be performed within 4 weeks prior to Dose 1 Day 1, also enter in the eCRF all values available in the medical history over 24 weeks prior to Dose 1 Day 1 in DBTP.
- Leg Ulcer evaluation (if applicable)
- Hemoglobin fractions by central laboratory

6.1.1. Rescreening

If a subject fails screening and the Investigator wishes to rescreen this subject, a new subject number will be assigned by IRT. All screening assessments performed until the subject is declared to be a screen fail (at least 4 weeks after the ICF signature) can be entered in the eCRF pages under the new subject ID, if these are within the validity windows indicated below:

- Urine (except urine pregnancy test), blood tests, ECGs, abdominal ultrasound for liver and MRI for spleen, if not splenectomized, MRI for extramedullary masses (only for subjects who have history of masses at baseline), QoL questionnaires and vital signs must all be performed within 4 weeks (+ 3 days) of randomization. If outside this 4-week window (+ 3 days), assessments must be repeated.
- MRIs for LIC must be performed within 16 weeks of randomization. If outside the 16-week window (+ 3 days flexibility window), the MRIs must be repeated.
- DXA must be performed within 24 weeks of randomization. If outside the 24-week window (+ 3 days flexibility window), the DXA must be repeated.
- Echocardiography or MRI for LVEF and TRV must be performed within 12 weeks of actual Dose 1 Day 1 date. If outside the 12-week window (+ 3 days flexibility window), assessment must be repeated.
- Abnormal assessments that caused ineligibility of the subject during the initial screening must always be repeated.

6.2. Double-blind Treatment Period

Subjects will begin the DBTP upon acknowledgement of eligibility by the Sponsor and will start the treatment with luspatercept or placebo within at least 4 weeks of signing the informed consent form (ICF). An administrative window of + 3 days is permitted on the Screening Period (refer to Table of Events, Table 3 for further information). Dose 1 Day 1 should be scheduled within 3 days of randomization via IRT (it can be on the same day as randomization). If screening assessments are performed within 72 hours of Dose 1 Day 1, safety laboratory assessments do not need to be repeated at Dose 1 Day 1, except hematology and blood chemistry assessments.

Subjects will receive their first subcutaneous (SC) dose of luspatercept or placebo on Day 1 of each dosing cycle.

Treatment is administered every 21 days, and will occur as described in Section 7.2 and as reflected in the Table of Events, Table 3.

The following evaluations will be performed at the frequency specified in the Table of Events, Table 3. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- β-thalassemia comorbidities assessment for NTDT severity score system
- Iron chelating therapies: record on ongoing basis (as detailed in Section 6.1).
- [redacted]
- Concomitant procedures - record on an ongoing basis.
- Transfusion assessment - record transfusions on ongoing basis and include subject's Hb levels prior to each transfusion, the number of units transfused, the date(s) of transfusion(s). If available, record in the eCRF: the volume transfused in mL of each transfusion and Hct of the transfused units.
- Adverse event assessment - record all AEs regardless of causality on an ongoing basis until 9 weeks after last dose, only related SAEs to be reported until End of Study (refer to Section 10 for additional information)
- Malignancy and premalignancy reporting from ICF signature up to End of Study - continuous reporting the occurrence of any case regardless of causality (refer to Section 10.5.3 for additional information). Subjects are required to see the Investigator at least every 24 weeks to assess for malignancy and premalignancy, as per standard of care.
- Vital signs (as detailed in Section 6.1)
- Weight
- 12-lead electrocardiogram (ECG) – read locally
- Echocardiography or MRI for left ventricular ejection fraction (LVEF) and tricuspid regurgitant velocity (TRV)
- Female subjects of childbearing potential: Urine or serum medically supervised pregnancy test with a minimum sensitivity of 25 mIU/mL for FCBP at Day 1 of each dose
- For female subjects: menstrual status
- Hematology assessments (as detailed in Section 6.1): predose by local and central laboratory; in case of AE, local and/or central laboratory to be used, if the dose is delayed refer to Section 6.2.1. **Note:** at Weeks 13, 19, 24, 37, 42, and 48 (± 7 days) hemoglobin should be measured by central or local laboratory regardless of dose delay and even if the IP is discontinued (see PTFP, Section 6.3).
- Serum chemistry panel 1 (as detailed in Section 6.1): predose by central lab up to Dose 17, included. After Dose 17, serum chemistry panel 2 (creatinine, creatinine clearance, alkaline phosphatase, bilirubin [total, non conjugated] AST/SGOT, ALT/SGPT) will be performed every 4 doses. In case of AE, local and/or central

laboratory to be used. If the dose is delayed, the assessments are performed centrally and locally on the planned dosing visit when the dose is not given (refer to Section 6.2.1 for further details).

- Urinalysis: microalbumin, creatinine, microalbumin/creatinine ratio (as detailed in Section 6.1)
- Serum erythropoietin: predose, analyzed by central laboratory
- Pharmacokinetic (PK) sampling: predose, if at the dosing day; serum sample collection; analyzed by central laboratory (refer to Section 6.5)
- Anti-drug antibody (ADA) sampling: analyzed by central laboratory (additional blood draws might not be needed if a time-matched PK sample is also collected)
- MRI for LIC (mg/g dw) by T2* or R2, as per site's practice
- MRI for extramedullary masses - only for subjects who have history of masses at baseline
- MRI for spleen, if not splenectomized - MRI is the preferred technique (same MRI acquisition of LIC, if possible), the longest longitudinal dimension and width should be used. Alternatively, ultrasound can be used. Same technique to be used throughout the study
- Bone imaging DXA scan - total hip, lumbar spine (read locally)
- 6MWT (6-minute walk test)
- QoL Questionnaire (NTDT - PRO with PGI-S for validation): to be completed by the subjects as daily diary up to Week 24 and thereafter over 7 days prior to dosing, every other dose
- QoL Questionnaires (SF-36 v2, FACIT-F, and PGI-C): to be completed by the subjects before knowing the Hb test result on dosing visits indicated in the Table of Events, Table 3
- HRU
- Serum ferritin
- Leg ulcer evaluation (if applicable)
- GDF11 and other related biomarkers (sampling): central laboratory assessment
- Hemoglobin fractions by central laboratory
- Administration of luspatercept/placebo on Day 1 of each dose cycle

6.2.1. Dose Delays in Double-blind Treatment Period

In case of dose delay (refer to Dose Delay, Dose Reduction, and Discontinuation Guidelines, Section 7.2.1.2), the clinical assessments and procedures to be performed include, but are not limited to:

- All planned Day 1 assessments should be performed as detailed in the Table of Events, Table 3, and Section 6.2.1, and appropriate samples sent to the central laboratory, regardless of the reason for the dose delay.
- If dose delay is due to increased hemoglobin level (refer to Table 5, Dose Delay, Dose Reduction and Discontinuation Guidelines, Section 7.2.1.2), perform hematology on Day 1 of dose delay by central and local laboratory and then at least weekly by local laboratory until the subject meets either the treatment administration criteria or treatment discontinuation criteria, as detailed in Sections 7.2.1.2, and 11.1.
- If dose delay is due to AE, laboratory or vital signs abnormality (refer to Table 5, Dose Delay, Dose Reduction and Discontinuation Guidelines, Section 7.2.1.2), repeat any clinically indicated assessment by local laboratory at a frequency decided by the Investigator until the subject meets either the treatment administration criteria or treatment discontinuation criteria, as detailed in Section 7.2.1.3 and 11.1.
- PK/ADA samples should be performed on Day 1 of dose delay and before next dose.
- At the time of IP administration following a dose delay, perform the scheduled dosing visit assessments as detailed in the Table of Events, Table 3 and Section 6.2.1, regardless of the duration of the dose delays.

6.3. Open Label Period

The assessments and procedures that will be performed during the Open Label Treatment Period are outlined in the Table of Events (see Table 3). An administrative window of ± 5 days is permitted.

Subjects who received placebo and are in PTFP at the time of unblinding will perform the following assessments and procedures on **Week -1 of the OLP** before accessing the OLP:

- Assessment of eligibility: Inclusion criteria numbers 8-10 and exclusion criteria numbers 1-8, 10, 12-15, 17, 18 and 20 must be met at Dose 1 Day 1 of the OLP
- Prior medications/therapies: at least 24 weeks prior to Dose 1 Day 1 of luspatercept
- Prior procedures: at least 24 weeks prior to Dose 1 Day 1 of luspatercept
- Transfusion assessment: at least 24 weeks RBC transfusion history prior to Dose 1 Day 1 of the Open-label Phase of luspatercept including subject's Hb levels prior to each transfusion, the number of units transfused, the date(s) of transfusion(s). If available, record in the eCRF: the volume transfused in mL of each transfusion and Hct of the transfused units.
- Adverse event assessment — starting after informed consent, record on an ongoing basis until 9 weeks after last dose as detailed in Section 6.1. and Section 10.

- Leg ulcer evaluation (if applicable), record on ongoing basis, until 9 weeks after last dose
- Malignancy and Pre-Malignancy Reporting (refer to Section 6.1 and Section 10.5.3 for additional information)
- HRU
- ECOG performance status (Appendix B)
- 12-Lead Electrocardiogram – read locally
- Females: Serum medically supervised pregnancy test with a minimum sensitivity of 25 mIU/mL for FCBP at Day 1 Dose 1 of luspatercept
- Hematology (as detailed in Section 6.1): predose by central and local lab
- Serum chemistry panel 2 (as detailed in Section 6.1): predose by central lab
- Urinalysis (as detailed in Section 6.1): by local lab microalbumin, creatinine, microalbumin/creatinine
- Serum ferritin by central lab and enter in the eCRF all values available in the medical history over 24 weeks prior to Dose 1 Day 1 in OLP
- Hepatitis B and hepatitis C (HCV-RNA and HBsAG and/or HBV-DNA) should be done only if not done already within 10 weeks before ICF signature)
- Echocardiography or MRI (same technique to be used throughout the study): to assess LVEF and TRV
- MRI for LIC (mg/g dw) (as detailed in Section 6.1)
- MRI for extramedullary masses
- MRI or abdominal ultrasound for spleen measurement (as detailed in Section 6.1)
- Bone imaging DXA scan (as detailed in Section 6.1)
- Abdominal ultrasound for liver: to be performed up to 4 weeks before Dose 1 in the OLP
- 6MWT (6-minute walk test)
- QoL questionnaire (NTDT - PRO with additional Patient Global Impression of Severity [PGI-S] item for validation) to be completed as a daily diary over 7 days before Dose 1 Day 1 in the evening
- QOL questionnaires (SF-36 v2, FACIT-F, and Patient Global Impression of Change [PGI-C])

All subjects, ie, subjects who are continuing the treatment with luspatercept after the unblinding of the study, and subjects who are starting the treatment with luspatercept after received placebo in DBTP, will perform the following assessments and procedures, according to Table 3:

- Iron chelating therapies: record on an ongoing basis, until 9 weeks after last dose (as detailed in Section 6.1)
- Concomitant medications/therapies: such as surgery, radiation, systemic or any other therapy for the subject's disease - record on ongoing basis, until 9 weeks after last dose
- Concomitant procedures - record on ongoing basis, until 9 weeks after last dose
- Transfusion assessment - record on an ongoing basis, until 9 weeks after last dose (as detailed in Section 6.1)
- Adverse event assessment — starting after informed consent, record on an ongoing basis until 9 weeks after last dose as detailed in Section 6.1 and Section 10.
- Leg ulcer evaluation (if applicable), record on ongoing basis, until 9 weeks after last dose
- Malignancy and Pre-Malignancy Reporting (refer to Section 6.1 and Section 10.5.3 for additional information)
- Vital signs (as detailed in Section 6.1)
- Weight
- Female subjects of childbearing potential: Urine or serum medically supervised pregnancy test with a minimum sensitivity of 25 mIU/mL for FCBP at Day 1 of each dose
- Female subjects of childbearing potential: menstrual status
- Hematology (as detailed in Section 6.1)
- ADA (if applicable) – refer to Section 6.6
- HRU
- Serum chemistry panel 2 (as detailed in Section 6.1): predose by central lab
- Urinalysis (as detailed in Section 6.1): by local lab microalbumin, creatinine, microalbumin/creatinine.
- Serum ferritin by central lab (as detailed in Section 6.2)
- Serum erythropoietin (EPO): predose by central lab (as detailed in Section 6.2)
- Serum GDF11 and other related biomarkers (by central lab; predose sample on dosing days) (as detailed in Section 6.7)
- Hemoglobin fractions (by central lab; predose sample on dosing days) (as detailed in Section 6.7)
- Administration of luspatercept on Day 1 of each dosing cycle
- QoL Questionnaire (NTDT-PRO with PGI-S for validation): to be completed by the subjects 7 days prior to dosing, every other dose

- QoL Questionnaires (SF-36 v2, FACIT-F, and PGI-C): to be completed by the subjects before knowing the Hb test result on dosing visits indicated in Table 3
- Only at Week 144 post first dose, if applicable, ie, for subjects who entered the OLP prior to reaching Week 144 in the DBTP:
    - Echocardiography or MRI (same technique to be used throughout the study): to assess LVEF and TRV
    - MRI for LIC (mg/g dw) (as detailed in Section 6.1) - only at Week 144 post first dose, if applicable
    - MRI for extramedullary masses - only at Week 144 post first dose, if applicable, only subjects with medical history of masses
    - MRI or abdominal ultrasound for spleen measurement (as detailed in Section 6.1) - only at Week 144 post first dose, if applicable
    - Bone imaging DXA scan (as detailed in Section 6.1) - only at Week 144 post first dose, if applicable
    - 6MWT (6-minute walk test)- only at Week 144 post first dose, if applicable

6.3.1. Dose Delays in Open Label Treatment Period

In case of dose delay as described in Table 5, Dose Delay, Dose Reduction and Discontinuation Guidelines, the clinical assessments and procedures to be performed include, but are not limited to:

- All planned Day 1 assessments should be performed as detailed in the Table of Events, Table 3, and Section 6.3.
- If dose delay is due to increased hemoglobin level (refer to Table 5, Dose Delay, Dose Reduction and Discontinuation Guidelines), perform hematology on Day 1 of dose delay and then at least weekly by local laboratory until the subject meets either the treatment administration criteria or treatment discontinuation criteria, as detailed in Sections 7.2.1.2, 7.2.1.3 and 11.1.
- If dose delay is due to an AE, laboratory or vital signs abnormality (refer to Table 5, Dose Delay, Dose Reduction and Discontinuation Guidelines), repeat any clinically indicated assessment by local laboratory at a frequency decided by the Investigator until the subject meets either the treatment administration criteria or treatment discontinuation criteria, as detailed in Section 7.2.1.3 and 11.1.

  At the time of IP administration following a dose delay, perform the scheduled dosing visit assessments as detailed in the Table 3, and Section 6.3, regardless of the duration of the dose delays.

6.4. Post-treatment Follow-Up Period

All subjects who discontinue the IP before the study is unblinded will move to the PTFP to be followed until the unblinding. After the study is unblinded, subjects who discontinue luspatercept

in the DBTP may continue 5 years from first dose of IP, or 3 years from last dose (whichever occurs later), to complete the Post-treatment Follow-up Period under the rollover protocol.

All subjects who discontinue luspatercept after the study is unblinded, during the OLP, will move to the PTFP to be followed until the End of Trial (see Section 3.3) and may continue 5 years from first dose of IP, or 3 years from last dose (whichever occurs later), to complete the Post-treatment Follow-up Period under the rollover protocol

An administrative window of ± 7 days is permitted for visits.

In particular, subjects who discontinue the IP before completing 48 weeks in DBTP should perform the following visits: at 9 weeks after last dose, Weeks 13, 19, 24, 37, 42, 48 after first dose, if not already performed these visits at these time-points during the DBTP, and every 24 weeks up to at least 5 years from first dose of IP, or 3 years from last dose (whichever occurs later)(see Table 3 and below for specific assessments to be performed at each visit).

All subjects regardless of treatment duration with IP should perform the following visits: at 9 weeks after last dose and every 24 weeks up to at least 5 years from first dose of IP, or 3 years from last dose (whichever occurs later)(see Table 3 and below for specific assessments to be performed at each visit).

All subjects in PTFP, regardless of treatment duration with IP, will perform the following assessments at the above indicated visits as outlined in the Table of Events (see Table 3), which includes but not limited to:

- Iron chelating therapies - record on ongoing basis, until 9 weeks after last dose (as detailed in Section 6.2)
- Post-treatment medications/therapies: such as surgery, radiation, systemic or any other therapy for the subject's disease - record on ongoing basis, until 9 weeks after last dose
- Post-treatment procedures - record on ongoing basis, until 9 weeks after last dose
- Transfusion assessment - record on ongoing basis, until 9 weeks after last dose (as detailed in Section 6.2)
- Adverse event assessment - record on an ongoing basis all AEs until 9 weeks after last dose, related SAEs to be reported until End of Study (refer to Section 10 for additional details)
- Malignancy and premalignancy reporting from ICF signature up to End of Study - continuous reporting the occurrence of any case regardless of causality (refer to Section 10.5.3 for additional information). Subjects are required to see the Investigator at least every 24 weeks to assess for malignancy and premalignancy, as per standard of care.
- Leg ulcer (if applicable) record on ongoing basis, until 9 weeks after last dose
- Vital signs (as detailed in Section 6.1)
- Weight
- 12-Lead Electrocardiogram – read locally

- Female subjects of childbearing potential: Urine or serum medically supervised pregnancy test with a minimum sensitivity of 25 mIU/mL for FCBP
- Female subjects of childbearing potential: menstrual status
- Hematology (as detailed in Section 6.1): use local and central laboratory
- Serum chemistry (as detailed in Section 6.1): use central laboratory
- Urinalysis (as detailed in Section 6.1): use local laboratory
- Serum erythropoietin only in DBTP
- ADA - refer to Section 6.6
- 6MWT (6-minute walk test)
- QoL Questionnaire (NTDT – PRO with PGI-S): only at 9 weeks after last dose in the DBTP
- QoL Questionnaire (SF-36v2,FACIT-F and PGI-C): only at 9 weeks after last dose in the DBTP
- HRU
- Serum Ferritin
- GDF 11 and other related biomarkers analyzed by central laboratory at 9 weeks after last dose in the DBTP and if not performed at Dose 16 and not performed within the last 12 weeks.
- Hemoglobin fractions analyzed by central laboratory at 9 weeks after last dose in the DBTP

Subjects who discontinue the IP within 48 weeks of the first dose in the DBTP, in addition to the above assessments, will also perform the following assessments as indicated in Table 3), Table of Events:

- β-thalassemia comorbidities assessment for NTDT severity score system
- Echocardiography or MRI for left ventricular ejection fraction (LVEF) and tricuspid regurgitant velocity (TRV)
- Hematology: Hb must be measured by central or local laboratory at week 13, 19, 24, 37, 42 and 48 (± 7 days) after first dose of IP, if not already done in the DBTP at these timepoints.
- MRI for LIC (mg/g dw) by T2* or R2, as per site's practice
- MRI for extramedullary masses - only for subjects who have history of masses at baseline
- MRI for spleen, if not splenectomized - MRI is the preferred technique (same MRI acquisition of LIC, if possible), the longest longitudinal dimension and width should be used. Alternatively, ultrasound can be used. Same technique to be used throughout the study
- Bone imaging DXA scan - total hip, lumbar spine (read locally)

- 6MWT
- QoL Questionnaire (NTDT – PRO, SF-36v2, and FACIT-F) at Weeks 13, 24, 37, and 48 after first dose in the DBTP

End of Study visit should occur after the study is unblinded (ie, 48 weeks after last subject has received the first dose of IP), and at the End of Trial as defined in Section 3.3, whichever occurs later. The End of study visit will occur at the time a subject discontinues from the study or transitions to rollover protocol. The following assessments will be performed, as outlined in the Table of Events (see Table 3):

- Iron chelating therapies - record on an ongoing basis up to End of Study (as detailed in Section 6.1.1).
- Post-treatment medications/therapies - such as surgery, radiation, systemic or any other therapy for the subject's disease - record on an ongoing basis up to End of Study.
- Post-treatment procedures - record on an ongoing basis up to End of Study.
- Transfusion assessment - as detailed in Section 6.1.1.
- Adverse event assessment - refer to Section 10 for additional details
- Malignancy and premalignancy reporting from ICF signature up to End of Study - continuous reporting the occurrence of any case regardless of causality (refer to Section 10.5.3 for additional information). Subjects are required to see the Investigator to assess for malignancy and premalignancy, as per standard of care.
- HRU
- Leg ulcers

6.5. Pharmacokinetics

Blood samples will be collected to analyze luspatercept concentrations in serum in all subjects. At each PK time point, approximately 3 mL of blood will be collected, and serum prepared as described in the study reference guide. Blood samples for PK will be taken at the following visits during the study (also see Table 3):

- DBTP: Doses 1 to 16: at predose (Dose 1 Day 1, must be collected before the first dose), Dose 2 Day 1, Dose 4 Day 1, Dose 6 Day 1, Dose 6 Day 8, Dose 6 Day 15, Dose 8 Day 1, Dose 12 Day 1, Dose 16 Day 1, and every 6 doses (at Dose 22, 28, 34, etc.)

6.6. Anti-Luspatercept Antibody

Blood samples will be collected for assessment of anti-drug antibodies (ADAs) against luspatercept in serum in all subjects. At each ADA time point, approximately 3 mL blood will be collected, and serum prepared as described in the study reference guide. However, during the first year of treatment, an additional blood draw is not needed for the ADA test, as the ADA test will be conducted utilizing the PK samples obtained at the same visit. Blood samples for ADA will be taken at the following visits during the study (also see Table 3):

- DBTP: Doses 1 to 16: at predose (Dose 1 Day 1, must be collected before the first dose), Dose 2 Day 1, Dose 4 Day 1, Dose 6 Day 1, Dose 8 Day 1, Dose 12 Day 1, Dose 16 Day 1 and every 6 doses (at Dose 22, 28, 34 etc.) up to maximum 2 years from Dose 1 Day 1)
- OLP: for subjects continuing treatment with luspatercept, only if positive in the DBTP, perform the ADA every 6 doses up to 2 years from Dose 1 Day 1 of the DBTP.
- PTFP: every 24 weeks until the unblinding. After the unblinding, if ADA positive in the DBTP, continue testing every 24 weeks up to maximum 2 years from Dose 1 Day 1 of DBTP. After the unblinding, only ADA positive subjects will continue testing for up to 2 years from Dose 1 Day 1 of DBTP, if not already achieved the 2 years of testing. For subjects on placebo in the DBTP, if ADA positive in the OLP, continue testing every 24 weeks up to maximum 2 years from Dose 1 Day 1 of OLP.

ADA sampling per Investigator's or Sponsor's discretion is allowed and should be recorded as an unscheduled visit.

Detailed procedures of ADA sample collection, processing, and shipping are provided in the study reference guide.

[redacted]

6.8. Quality of Life

- NTDT PRO – The NTDT-PRO V2.1 is a six-item PRO instrument to assess the severity of anemia-related symptoms associated with NTD β-thalassemia. It was designed as a daily electronic diary (eDiary) with recall of β-thalassemia related symptoms during the past 24 hours. The six items assess presence and severity of each symptom using a numerical rating scale (NRS) ranging from 0 (no) to 10 (extreme). These six items are:
  - Tiredness (lack of energy) when not doing physical activity
  - Tiredness (lack of energy) when doing physical activity
  - Weakness (lack of strength) when not doing physical activity
  - Weakness (lack of strength) when doing physical activity
  - Shortness of breath when not doing physical activity
  - Shortness of breath when doing physical activity

There are two domain scores. Tiredness/Weakness (T/W) domain score and Shortness of Breath (SoB). Furthermore, one Patient Global Impression of Severity item (PGI-S) was administered as an addition to the measure at the same timepoints to be later used as an anchor for supporting evidence in determining the minimum clinical important difference (MCID). The item assesses the overall severity of Thalassemia symptoms in the past 24 hours on an 11-point numerical rating scale (anchors of 0 - no symptoms and 10 - very severe symptoms).

Subjects will be asked to complete this disease specific quality of life questionnaire in the evening as daily diary over a 7 days period prior to Dose 1 Day 1 in the DBTP and daily up to Week 24. After that, subjects will complete this questionnaire over a 7-day period prior to dosing, every other dose. If the IP is discontinued in the DBTP, the subjects will compete the questionnaire over a 7-day period prior to Weeks 13, 24, 37, and 48 after first dose, and at 9 weeks after last dose, as detailed in Table 3. In the OLP, subjects will complete disease specific quality of life questionnaire daily up to Week 24 and thereafter over 7 days prior to dosing, at every other dose as detailed in Table 3.

- SF-36 v2 – The SF-36 version 2 is a 36-item generic PRO questionnaire used to assess patient-reported HR-QoL outcomes. The SF-36 yields scores for eight domains of health: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH) as well as physical component summary (PCS) and mental component summary (MCS) scores. The SF-36 is scored such that higher scores reflect a better health state. For this study, a 7-day recall period is used.

  Subjects will be asked to complete this quality of life questionnaire at Screening and every other dose (at Dose 1 Day 1, Dose 3 Day 1, Dose 5 Day 1 and thereafter) in the DBTP and at 9 weeks after last dose, as detailed in Table 3. The questionnaire must be always completed by the subjects before knowing the predose Hb test result. In the OLP, subjects will complete this quality of life questionnaire every other dose as detailed in Table 3.

- FACIT-F – The FACIT-Fatigue, is a multidimensional, self-report quality of life instrument. It consists of 27 core items, the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire, which assesses patient function in 4 domains: Physical, Social/Family, Emotional, and Functional well-being, which is further supplemented by a 13-item measure designed to capture cancer-related fatigue, the Fatigue subscale (FS). The items are measured on a response scale with five options (0 = not at all to 4 = very much) and has a 7-day recall period.

  Subjects will be asked to complete this quality of life questionnaire at Screening and every other dose (at Dose 1 Day 1, Dose 3 Day 1, Dose 5 Day 1, and thereafter) in the DBTP and at 9 weeks after last dose, as detailed in Table 3. In the OLP, subjects will complete this quality of life questionnaire every other dose as detailed in Table 3. The questionnaire must be always completed by the subjects before knowing the predose Hb test result.

- Patient Global Impression of Change (PGI-C) – The PGI-C is a seven-point single-item measure assessing patient global impression of change in thalassemia symptoms since the start of the study. The response options are: (1) a great deal better; (2) much better; (3) a little better; (4) no change; (5) a little worse; (6) much worse; and (7) a great deal worse. Subjects will be asked to complete this quality of life questionnaire at Screening and every other dose (at Dose 1 Day 1, Dose 3 Day 1, Dose 5 Day 1 and thereafter) in the DBTP and at 9 weeks after last dose, as detailed in Table 3. The questionnaire must be always completed by the subjects before knowing the predose Hb test result. In the OLP, subjects will complete this quality of life questionnaire every other dose as detailed in Table 3.
- Healthcare resource utilization (HRU) will be assessed on an ongoing basis at every visit until 9 weeks after last dose. The economic objective of this assessment is to characterize medical resource utilization among subjects treated with luspatercept as compared to subjects receiving placebo treatment. To facilitate this aim, medical HRU data will be collected. In addition, the number of transfusion events will be evaluated, as these relate directly to hours or days devoted to receiving RBC transfusions that can impact patients' quality of life.

6.9. Screen Failures

For all subjects classified as screen failures, the following information should be captured in the subject's source documents and appropriate eCRF page(s): the date ICF was signed, demographics, the reason subject did not qualify for the study, and the Investigator's signature for the eCRF pages. The adverse events experienced by screen failure subjects will be collected from the date of signing consent to the day the subject is confirmed as screen failure. Relevant information will also be recorded on the Screening Log.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

Luspatercept will be provided by the Sponsor. Luspatercept for injection is formulated as a sterile, preservative-free, lyophilized cake/powder. Luspatercept for injection is available in 25 mg and 75 mg vials, and when reconstituted, each consists of 50 mg/mL luspatercept in a 10 mM citrate buffer-based solution (10 mM citrate, pH 6.5, 9% sucrose, 0.02% polysorbate 80).

The recommended storage condition for luspatercept for Injection (25 mg/vial and 75 mg/vial; lyophilized powder formulation) is 2°C to 8°C. Reconstituted luspatercept in its original container closure system may be held for up to < 10 hours at 2°C to 8°C, however it should be administered at room temperature. It is recommended that the reconstituted luspatercept for injection be used immediately. If not used immediately, the total in-use time of the reconstituted luspatercept for injection, from reconstitution to administration, must not exceed 10 hours.

Samples of luspatercept drug product, held at the recommended storage condition, have been shown to be stable through the labeled shelf-life.

Placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection) administered as a SC injection. Designated individuals will prepare the placebo syringes to match the active syringe. All staff except unblinded pharmacists and designated personnel will be blinded. The manufacturer's directions for placebo storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the placebo.

7.2. Treatment Administration and Schedule

Luspatercept or placebo will be administered as a SC injection to subjects by the study staff at the clinical site and administration will be documented in the subject's source record. Subcutaneous injections will be given in the upper arm, thigh, and/or abdomen. Calculated doses requiring reconstituted volume greater than 1.2 mL should be divided into two separate similar volume injections across 2 separate body sites using the same anatomical location but on the opposite sites of the body (example left thigh and right thigh). The maximum volume per SC injection should not exceed 1.2 mL. The injection sites can be rotated according to Investigator's judgment, and the injections can be given in the following order as needed, for example: 1) right upper arm, 2) left upper arm, 3) right upper thigh, 4) left upper thigh.

In the DBTP, subjects will be assigned to be administered treatment as per one of the following regimens:

- Luspatercept starting dose level 1.0 mg/kg SC every 21 days
- Placebo SC every 21 days

In the OLP, subjects previously randomized to receive placebo will be assigned to be administered luspatercept starting dose level 1.0 mg/kg SC every 21 days and subjects previously randomized to luspatercept will continue on their last assigned dose.

Treatment Administration Criteria:

On dosing days, the following criteria must be met to allow the administration of the IP at the same dose level:

1. Predose Hb, measured on the dosing day (or, the day before dosing) by local laboratory is < 11.5 g/dL (if predose Hb is ≥ 11.5 g/dL, check if subject was transfused within 21 days prior to current dose and review the pre-transfusion Hb, if this is < 11.5 g/dL, the subject can be dosed, otherwise, the dose should be delayed. If the first dose of IP (ie, Dose 1) should be administered, the dose should be delayed until Hb is < 11.5 g/dL, if subsequent doses should be administered (ie, Dose 2, Dose 3, etc.), the dose should be delayed until Hb is ≤ 11.0). Refer to Table 5, Dose Delay, Dose Reduction and Discontinuation Guidelines.
2. Increase of Hb < 2.0 g/dL compared to the Hb level on Day 1 of previous dose
3. Absence of related adverse event ≥ Grade 2 according to NCI CTCAE criteria (Appendix C) on dosing day
4. Predose WBC count (corrected by erythroblast count) < 3 x baseline and absence of leukocytosis Grade 3 according to NCI CTCAE on dosing day.
5. Leukopenia, neutropenia and/or thrombocytopenia should be < Grade 3, as per NCI CTCAE criteria
6. No decrease of > 2 g/dL Hb from baseline (uninfluenced by transfusion) or subject becomes regularly transfused in combination with an unexplained shift from baseline (worsening) of ≥ 2 Grades leukopenia, neutropenia or thrombocytopenia.

Refer to Table 5 for dose modifications and dose delays guidelines.

IMPORTANT REMINDERS:

The above treatment administration criteria numbers 2, 3, and 4 should not be applied on Dose 1 Day 1 (except for the absence of leukocytosis) for the DBTP.

Hemoglobin not influenced by a transfusion, defined as Hb ≥ 21 days post-transfusion, should be considered to allow IP dose administration. If a transfusion occurred within 21 days prior to dosing, and predose Hb is ≥ 11.5 g/dL, the pre-transfusion Hb may be considered for dosing purposes.

If IP dose is delayed due to Hb level not meeting the above dose administration criteria, the Hb level should be retested on a weekly basis or at a frequency decided by the Investigator.

Subjects must have Hb and WBC count assessed and results available prior to each IP administration, therefore, local laboratory results can be used. However, in the DBTP central laboratory result will be used, when available, to confirm Investigator's decision, therefore, blood samples will be also collected and shipped to the central laboratory, as detailed in the Table of Events, Table 3.

During the DBTP; local laboratory assessments are only allowed if specified in the Table of Events, Table 3, and Section 6 as well as in the following circumstances: eg, randomization, when timely results are needed (blood samples will be also collected and shipped to the central laboratory if required in the Table of Events, Table 3, and Section 6), study treatment dosing

decisions, dose delays, assessments between clinic visits and AE. Local laboratory data should be collected in the eCRF if relevant to dose administration, modification and AE, or when no central laboratory results were obtained.

Subjects must have blood pressure assessed prior to each IP administration. Blood pressure values should be confirmed by means of 2 readings obtained approximately 10 minutes apart with the patient seated for approximately 10 minutes prior to initial reading.

Refer to Table 5 for guidelines on dose modifications and dose delays.

7.2.1. Dose Modifications: Dose Titration, Dose Reduction and Dose Delay

7.2.1.1. Dose Titration

Subjects may be dose-escalated up to 1.25 mg/kg during the DBTP and OLP. The dose escalation criteria are defined as follows:

- Dose escalation may be performed if at a constant dose level, the increase of mean hemoglobin (uninfluenced by transfusions, ie, > 21 days post-transfusion) over 2 cycles (6 weeks) is < 1.0 g/dL, compared to the baseline hemoglobin value (mean of 2 values 1 week apart within 4 weeks of randomization);
- Dose escalation may be performed if at a constant dose level, the increase of mean hemoglobin (uninfluenced by transfusions, ie, > 21 days post-transfusion) over 2 cycles (6 weeks) is ≥ 1.0, but < 2.0 g/dL compared to the baseline hemoglobin value (mean of 2 values 1 week apart within 4 weeks of randomization).

Starting dose with dose reductions and escalations are presented in Table 4.

Note: Subjects who have been dose-reduced due to any related AE ≥ Grade 3, as indicated in Table 5, should not be dose-escalated during the DBTP. Although, following Investigator's requests, the Sponsor may allow dose increase to the next higher dose level, after safety and efficacy data review.

Table 4: Starting Dose Level with Dose Titrations

3rd Dose Reduction (~ 25 %)	2nd Dose Reduction (~ 25 %)	1st Dose Reduction (~ 25 %)	Starting Dose Level	1st Dose Increase
0.45 mg/kg	0.6 mg/kg	0.8 mg/kg	1.0 mg/kg	1.25 mg/kg

7.2.1.2. Dose Delay and Dose Reduction

Dose delay of IP from the planned dosing schedule may occur due to increased hemoglobin or adverse events considered related to luspatercept. Table 5 provides guidelines for dose modifications and dose delay. However, dose delay might occur at Investigator's discretion for AEs regardless of causality, or for other reasons.

Hemoglobin not influenced by a transfusion (ie, Hb ≥ 21 days post-transfusion) should be considered for dose administration, dose delays, and discontinuation actions. Subjects can experience a dose reduction based on the change in mean Hb level (Hb not influenced by a transfusion) with respect to the last dose, as well as related adverse events, as detailed in Table 5.

If a subject is experiencing a dose delay due to Hb increase, Hb measurement should occur every week.

If dose delay is longer than 15 weeks from the last dose administered, including cases of elective surgery/hospitalization, the treatment should be discontinued. Assessments to be performed during the dose delay period are detailed in Section 6.

Celgene or its authorized representative should be notified of dose modification or interruption within 24 hours.

Dose reduction and dose delay guidelines are detailed in Table 5. Treatment discontinuation criteria are detailed in Section 11.1.

Table 5: Dose Delay, Dose Reduction, and Treatment Discontinuation Guidelines

Event at the Day of Dosing	Action
Any related AE = Grade 2[a]	Dose delay[b] until resolved to < Grade 1 or baseline
Any related AE ≥ Grade 3[a]	Dose delay[b] until resolved to < Grade 1 or baseline, and then reduce dose to the next lower dose level indicated in Table 4
> 2 dose reductions due to related AE[a]	Discontinue treatment[d]
ΔHb ≥ 2.0 g/dL compared to the Hb on Day 1 of the previous dose[c]	Reduce dose to the next lower dose level indicated in Table 4
Hb ≥ 11.5 g/dL[c]	Dose delay[c] until Hb ≤ 11.0 g/dL
Decrease of > 2 g/dL Hb from baseline Hb (uninfluenced by transfusion)[c] or subject becomes regularly transfused in combination with an unexplained shift from baseline (worsening) of ≥ 2 grades leukopenia, neutropenia or thrombocytopenia[g].	Dose delay[c] and repeat WBC, neutrophils and platelets weekly for two consecutive weeks. If WBC, neutrophils and platelets are resolved to ≤ Grade 1 or baseline, continue with dosing at the same dose level. If WBC, neutrophils and platelets are Grade 2 and above baseline, then continue with dose delay until resolution to ≤ Grade 1 and evaluate for alternative explanations of cytopenia as per standard clinical practice. If shift (worsening) of ≥ 2 grades is maintained for ≥ 14 days, or thrombocytopenia does not improve to Grade < 2 within 14 days, and no alternative explanation is identified, then perform bone marrow assessment: If hematologic malignancy is confirmed, discontinue treatment[d] If hematologic malignancy is not confirmed, then discuss future dosing with medical monitor.
WBC count[e] ≥ 2X baseline in the absence of an associated condition (eg, infection or concomitant corticosteroid use)	Subject can be dosed, repeat WBC count weekly: If repeat WBC remains ≥ 2 X above baseline, Investigator should assess the cause of increase to exclude malignancy as per standard clinical practice If hematologic malignancy is confirmed, discontinue treatment[d]

Table 5: Dose Delay, Dose Reduction, and Treatment Discontinuation Guidelines (Continued)

Event at the Day of Dosing	Action
WBC count[e] ≥ 3X baseline	Dose delay[b] until WBC count < 3 X baseline, repeat WBC count weekly: Investigator should assess the cause of increase per standard clinical practice to exclude malignancy If hematologic malignancy is confirmed, discontinue treatment[d]
Grade ≥ 3 leukopenia, neutropenia and/or thrombocytopenia[h]	Dose delay[c] and, repeat assessment weekly for two consecutive weeks Investigator should assess the cause of cytopenia per standard clinical practice to exclude hematologic malignancy. If WBC, neutrophils and platelets resolved to ≤ Grade 1, continue with dosing at the same dose level. If WBC, neutrophils and platelets ≥ Grade 2 and above baseline sustained for ≥ 14 days perform bone marrow assessment. If hematologic malignancy is confirmed, discontinue treatment[d] If hematological malignancy is not confirmed, then discuss future dosing with a medical monitor.
Grade 3 leukocytosis[f]	Discontinue treatment[d]

AE: adverse event; Hb: hemoglobin; WBC: white blood cell.
[a] Possibly, probably, or definitely related.
[b] If dose delay is > 15 consecutive weeks, treatment should be discontinued.
[c] Based on the predose Hb value not influenced by transfusion (ie, > 21 days post-transfusion); Hb should be rechecked weekly during dose delay.
[d] Additional treatment discontinuation criteria are in Section 11.1.
[e] Central lab corrected WBC values should be used in DBPT and OLP for confirming the Investigator's decision, which may be based on local results. Baseline = highest WBC value between Screening WBC and Dose 1 Day 1.
[f] Grade 3 leukocytosis (WBC > 100,000/mm^3) should be confirmed by central lab values.
[g] Per CTCAE: Grade 1 leukopenia: < LLN – 3000/mm^3; Grade 1 neutropenia: < LLN – 1500/mm^3; Grade 1 thrombocytopenia :< LLN – 75,000/mm^3; Grade 2 Leukopenia: <3000 – 2000 / mm^3; Grade 2 Neutropenia: < 1500 – 1000 / mm3; Grade 2 Thrombocytopenia :< 75,000 – 50,000 / mm^3.
[h] Per CTCAE: Grade 3 leukopenia: < 2000 - 1000/mm^3, neutropenia: < 1000 - 500/mm^3 and thrombocytopenia: < 50,000 – 25,000/mm^3.

7.2.1.3. Overdose

Overdose, as defined for this protocol, refers to luspatercept dosing only. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of luspatercept assigned to a given patient, regardless of any associated adverse events or sequelae.

SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF. See Section 10.1 for the reporting of adverse events associated with overdose.

7.3. Method of Treatment Assignment

The treatment assignment (randomization) will occur at the end of the Screening Period, once all the required screening procedures have been completed and all required data have been submitted to the Sponsor or its authorized representative. Upon receiving acknowledgment of subjects' eligibility from the Sponsor or its authorized representative, subject can be assigned for treatment using IRT. This study will utilize the IRT for randomization.

Designated research personnel at each investigational site will be assigned password protected, coded identification numbers which allows them to access the IRT to enroll subjects. For drug assignment at each dose start and in the event of any dose reduction, dose escalation site staff must contact IRT to record the new dose level and obtain the new study treatment assignment.

The relationship of the randomization number to the subject ID number will be described by a randomization algorithm. The randomization algorithm will be employed by the IRT system to assign a subject to a treatment based on the prespecified rules, such as double-blind study, stratified randomization with randomization ratio active versus placebo on a 2:1; subjects will be placed into the appropriate stratum per the responses/data entered/collected for questions collecting stratification and based on the combination of these data points, the IRT will place the subject in the next available slot within the appropriate stratum for that subject. The IRT will be utilized to ensure an equal weight central randomization based on block randomization method according to stratification factors defined in Section 3.1, Design of Study. The randomization number corresponds to a particular treatment arm within a stratum. The randomization number, by itself, will not unblind a user to the subject's treatment. The randomization number should be coupled with all the unblinded code information, in order the subject to become unblinded.

7.4. Packaging and Labeling

The label(s) for luspatercept will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.4.1. Blinding

For this trial, all subjects, study site staff, and Celgene Corporation representatives with the exception of designated individuals (eg, the pharmacist at the investigational site), will remain blinded to all treatment assignments until all subjects enrolled in the study have completed 48 weeks of double-blind treatment or discontinue before reaching 48 weeks of double-blind treatment, whichever is the earlier date, or at the time the study is unblinded (per DMC recommendation) and the data base is locked.

The designated site individual (for example the pharmacist) at the investigational site will use a syringe (that exactly matches the syringe used for reconstituted luspatercept) and sterile normal saline (0.9% sodium chloride for injection) to prepare a matching placebo. Thus, the designated site individual at the investigational site will be unblinded and will give Investigators and their staff luspatercept and placebo in a blinded manner.

Randomization, drug dispensing, dose reduction/escalation, and drug discontinuation will be accomplished by an IRT system. Authorized site personnel must contact the IRT for randomization, study drug assignment at the beginning of each cycle, to register dose reductions or escalations, and treatment discontinuation. Confirmation of each call will be sent to the investigational site and Celgene.

For emergency unblinding, refer to Section 12.2.

7.5. Investigational Product Accountability and Disposal

Accountability for study drug that is administrated during the course of the study is the responsibility of the Investigator or designee. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secure and temperature-controlled location. The investigational site must maintain accurate records demonstrating dates and amounts of study drug received, to whom it was administered (subject-by-subject accounting), and accounts of any luspatercept accidentally or deliberately destroyed or returned. Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF and source documents. Unless otherwise notified, all vials of study drug, both used and unused, must be saved for drug accountability. The used vials may be discarded, per the institution's standard practice, after drug accountability has been completed by the monitor. The Investigator must return all unused vials of study drug to the Sponsor at the end of the study, or the study drug may be destroyed at the clinical site with the permission of the Sponsor. For either scenario, the outcome must be documented on the drug accountability log. The Sponsor will provide direction for the outcome of all unused vials.

Celgene (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6. Investigational Product Compliance

Study drug will be administered as a SC injection at the clinical site by the study staff. Monitoring for patient compliance with the treatment regimen is therefore unnecessary.

Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF and source documents.

The Investigator or designee is responsible for accounting for all IP that is administered during the course of the study.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

The proposed Phase 2 study is a double-blind, randomized, placebo- controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in adult NTDT subjects. The study populations, study endpoints, and statistical plan are discussed below.

9.2. Study Population Definitions

Study populations to be analyzed are defined as follows:

Intent-to-treat (ITT): The ITT population will consist of all randomized subjects regardless of whether or not the subject received IP.

Per Protocol Set (PPS): Subjects in the ITT who have taken at least 1 dose of IP and do not have major protocol deviations (details will be specified in the SAP prior to database [DB] lock). The PPS population might be used in addition to ITT population to analyze primary and secondary endpoints as detailed in the SAP.

Safety: The safety population will consist of all subjects who were randomized and received at least 1 dose of IP. Subjects will be included in the treatment group corresponding to the IP they actually received.

QoL Evaluable Population: The QoL evaluable population consists of all subjects in the ITT population who completed the health-related QoL assessment at baseline (screening) and at least one postbaseline assessment visit.

Statistical methods to handle missing data will be described in the SAP. The SAP will also describe detailed rules for data handling and analysis (eg, time windows, visit-by-visit analysis, endpoint analysis, protocol deviations).

9.3. Sample Size and Power Considerations

Based on the assumption of a targeted primary endpoint response rates at least 50% in the luspatercept group and 10% for the placebo group, and 2:1 randomization, a total sample size of 150 (100 in the luspatercept group, 50 in the placebo group) will have at least 99% power to detect the difference between the 2 groups with a 2-sided alpha of 0.05 and assumed 10% drop-out rate.

For NTDT-PRO T/W domain scores, assume the mean change from baseline scores at Week 24 are 1.2 and 0.5 for luspatercept and placebo group, respectively, with a common standard deviation of 1.2, the statistical power will be 91%.

Randomization and Stratification

Subjects will be randomized to receive luspatercept or placebo at a 2:1 ratio. Randomization will be accomplished by an IRT to ensure timely registration and randomization. A stratified block randomization schedule will be implemented. Randomization will be stratified by:

Baseline hemoglobin level

- ≥ 8.5 g/dL
- < 8.5 g/dL

Baseline NTDT-PRO T/W score

- ≥ 3 points
- < 3 points

9.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations by dose cohort. Prior transfusion history will be summarized. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulator Activities (MedDRA) system organ class and preferred term. Beta-thalassemia diagnoses as well as RBC transfusion burden will be summarized using frequency tabulations.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

Primary analysis will be done after ALL subjects completed 48 weeks or discontinued earlier. Then at the end of the OLP phase, updated safety and efficacy analysis will be done.

9.6.1. Primary Efficacy Analysis

The primary efficacy endpoint of this study is erythroid response, defined as an increase from baseline ≥1.0 g/dL in mean of hemoglobin values over a continuous 12-week interval from Weeks 13 to 24 in the absence of transfusions.

The Hb values within 21 days following a transfusion may be influenced by the transfusion and will be excluded from this analysis. Baseline Hb is the average of 2 or more Hb measurements at least 1 week apart within 4 weeks before Dose 1. For discontinued subjects who do not complete 24 weeks of the Double-blind Treatment Period, Hb data will continue to be collected (see Table 3).

The primary efficacy analysis will be performed on the ITT population. Cochran-Mantel-Haenszel (CMH) test will be performed with randomization stratification factor(s) in the model to compare the treatment and placebo groups at 2-sided 0.05 level; the corresponding 95% confidence interval for odds ratio will also be provided.

For a subject, if the Hb average over Weeks 13-24 interval cannot be calculated due to missing data, the closest Hb 12-week average will be used.

Sensitivity analysis: If a subject has less than 3 Hb measurements from Week 13 (-7 days) to Week 24 (+7 days), he/she will be considered as non-evaluable. Similar approach will be followed for Hb secondary endpoints over Weeks 37 to 48.

9.6.2. Key Secondary Efficacy Analysis

The analyses of key secondary efficacy endpoints will be performed on the ITT population. The three key secondary endpoints are as follows:

1) Mean change from baseline in NTDT-PRO Tiredness and Weakness (T/W) domain score over a continuous 12-week interval from Week 13 to Week 24.

2) Mean change from baseline in mean of hemoglobin values over a continuous 12-week interval from Week 13 to Week 24 in the absence of transfusions.

3) Proportion of subjects who have an increase from baseline ≥1.0 g/dL in mean of hemoglobin values over a continuous 12-week interval from Week 37 to Week 48 in the absence of transfusions.

To control the overall Type 1 error rate for three key secondary endpoints, the testing procedure will be implemented strictly in order: after the result from the primary efficacy analysis in the ITT population shows statistical significance, the key secondary endpoint 1 will be tested next. The key secondary endpoint 2 will be tested only if the test results for both primary endpoint and the key secondary endpoint 1 are significant. The key secondary endpoint 3 will be tested only if the test results for primary endpoint and the key secondary endpoints 1 and 2 are all significant. The details of the multiplicity control will be specified in the SAP.

9.6.2.1. NTDT-PRO (T/W Domain) Mean Change Between Weeks 13 to 24

Mean NTDT-PRO (T/W domain) change from baseline over a 12-week window between Weeks 13 to 24 will be analyzed using analysis of covariance (ANCOVA) method with treatment group and randomization stratification factor(s) in the model score as covariates.

9.6.2.2. Hemoglobin Mean Change Between Weeks 13 to 24

Mean Hemoglobin change from baseline over 12-week window between Weeks 13 to 24 during the treatment period will be analyzed using ANCOVA method with treatment group and randomization stratification factor(s) in the model value as covariates.

9.6.2.3. Hemoglobin Response Between Weeks 37 to 48

Hemoglobin responder between Weeks 37 to 48, defined as an increase from baseline ≥ 1.0 g/dL in mean of hemoglobin values over a continuous 12-week interval from Weeks 37 to 48 in the absence of transfusions.

The CMH test will be performed with randomization stratification factor(s) in the model to compare the luspatercept and placebo groups at 2-sided 0.05 level; the corresponding 95% confidence interval for odds ratio will also be calculated.

Analysis similar to the primary analysis will be performed.

9.6.3. Secondary Efficacy Analysis

9.6.3.1. FACIT-F Fatigue Subscale: Mean Change from Baseline between Weeks 13 to 24 and Weeks 37 to 48

Mean FACIT-F Fatigue subscale change from baseline over a 12-week window between Weeks 13 to 24 will be analyzed using ANCOVA method with treatment group, randomization stratification factor(s) in the model and baseline FACIT-F Fatigue subscale score as covariates.

Mean change from baseline for Weeks 37 to 48 will be analyzed similarly.

9.6.3.2. NTDT-PRO SoB Domain: Mean Change from Baseline between Weeks 13 to 24 and Weeks 37 to 48

Mean NTDT-PRO SoB Domain from baseline over a 12-week window between Weeks 13 to 24 will be analyzed using ANCOVA method with treatment group, randomization stratification factor(s) in the model and baseline NTDT-PRO SoB scores covariates. Similar analysis will be performed for Weeks 37 to 48.

9.6.3.3. Hemoglobin Mean Change Between Weeks 37 to 48

Mean Hemoglobin change from baseline over 12-week window between Weeks 37 to 48 during the treatment period will be analyzed using ANCOVA method with treatment group, randomization stratification factor(s) in the model as covariates.

9.6.3.4. NTDT-PRO (T/W Domain) Mean Change Between Weeks 37 to 48

Mean NTDT-PRO (T/W domain) change from baseline over a 12-week window between Weeks 37 to 48 will be analyzed using analysis of covariance (ANCOVA) method with treatment group, randomization stratification factor(s) in the model as covariates.

9.6.3.5. Definition of NTDT-PRO Minimum Clinical Important Difference (MCID) and Responder Definition (RD)Thresholds

The minimum clinical important difference (MCID) is the amount of difference in a PRO measure between treatment groups in a clinical trial that will be interpreted as a treatment benefit. The responder definition (RD) threshold is the individual subject score change over a predetermined time period that will be interpreted as a treatment benefit. In case of MCID and RDRD thresholds for the NTDT-PRO will be primarily determined with longitudinal anchor-based methods prior to database lock and unblinding using data collected over a 12-week window between Weeks 13 to 24. Distribution-based methods will also be used as additional supporting evidence. Anchors to be considered include the PGI-C, PGI-S, SF-36v2 Vitality and Physical Functioning scales, and FACIT-F score. PGI-S is included as an extra item administered at the end of each NTDT-PRO assessment (see Section 6.8).

After the database lock and unblinding, statistical analysis will be performed for unblinded data. Proportion of subjects with a decrease from baseline ≥ RD in mean NTDT-PRO T/W score, over Weeks 13 to 24 and Weeks 37 to 48 in the luspatercept group will be compared with the placebo group. The CMH test will be used with baseline NTDT-PRO T/W category ≥ 3 versus < 3 as the stratum to compare the response rates between the 2 groups. The corresponding 95% confidence interval for odds ratio will also be provided.

9.6.3.6. FACIT-F Fatigue Subscale: Response at Weeks 13 to 24 and Weeks 37 to 48

Proportion of subjects with an increase from baseline ≥ 3 in mean FACIT-F Fatigue subscale (FS) score, over Weeks 13 to 24 and Weeks 37 to 48 in the luspatercept group will be compared with the placebo group. The CMH test will be used with baseline FACIT-F Fatigue subscale category ≥ 37 versus < 37 as the stratum to compare the response rates between the 2 groups. The corresponding 95% confidence interval for odds ratio will also be provided.

Similar analysis will be performed for Weeks 37 to 48.

9.6.3.7. SF-36 v2: Mean Change from Baseline at Week 24 and Week 48

The SF-36 Version 2.0 (acute condition with 1-week recall period) is a self-administered instrument consisting of 8 multi-item scales that assess 8 health domains: Physical functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social functioning, Role-Emotional, and Mental Health. Two overall summary scores (Physical Component and Mental Component) can also be obtained.

Summary statistics for the PCS and MCS norm-based scores, as well as change from baseline in these scores, will be assessed at Weeks 12, 24, 36, and 48. Scoring for the SF-36 and methods to address missing values will be accomplished according to directions provided by the instrument developers.

A mixed effect repeated measure model will be used with subjects as the random effect. The model includes the change from baseline scores up to Week 24 and 48 as the outcome, and treatment group assignment, time, baseline scores, randomization stratification factor(s), time-by-baseline score, and time-by-treatment group assignment in the model. If any of the interaction terms are not significant, it will be excluded from the final model.

9.6.3.8. LIC / ICT: Responder Analysis at Week 24 and Week 48

There are 3 scheduled LIC measurements for each subject: baseline, Weeks 24 and 48. For subjects who discontinued before 48 weeks the LIC and ICT data may be collected in the PTFP.

ICT daily dosing data will be collected during the study.

At Week 24 or Week 48, a LIC/ICT responder will be defined as one of the following:

- Baseline LIC (by MRI) ≥3 mg/g dw: ≥20% reduction in LIC, OR, ≥33% decrease in ICT daily dose
- Baseline LIC < 3 mg/g dw: no increase in LIC > 1 mg/g dw AND not starting treatment with ICT or no increase in ICT daily dose ≥ 33%, if on ICT at baseline

CMH test will be performed with baseline ICT use (Yes, No) and randomization stratification factor(s) as the strata adjusted to compare the luspatercept and placebo groups at 2-sided 0.05 level; the corresponding 95% confidence interval for odds ratio will also be calculated.

9.6.3.9. Serum Ferritin: Mean Change from Baseline at Week 24 and Week 48

Serum ferritin change from baseline at Week 24 will be analyzed using ANCOVA method with treatment group and randomization stratification factor(s) in the model and baseline Serum ferritin as the covariate.

If the normality assumption is significantly deviated, the nonparametric Wilcoxon rank-sum test will be used instead.

Mean change at week 48 will be analyzed similarly.

9.6.3.10. Liver Iron Concentration: Mean Change from Baseline at Weeks 24 and 48

LIC mean change from baseline will be analyzed using ANCOVA method with treatment group and randomization stratification factor(s) in the model and baseline Liver Iron Concentration as the covariate.

LIC mean change from Baseline at Week 48 will be analyzed similarly.

9.6.3.11. Transfusion Free for 24 and 48 weeks

Proportion of subjects who receive no RBC transfusions from Week 1 to Week 24 will be compared between the 2 treatment groups using CMH test with randomization stratification factor(s) adjusted.

Similarly, proportion of subjects who receive no RBC transfusion from Week 1 to Week 48 will be compared between the 2 treatment groups using CMH test with stratification factor(s) adjusted.

9.6.3.12. Duration of Mean Hemoglobin Increase from Baseline ≥1.0 g/dL

Descriptive statistics will be generated for the duration of mean hemoglobin increase for each treatment group. Kaplan-Meier method will be used for censored subjects. No statistical test will be performed to compare the 2 groups.

The duration will start from the first day of the first rolling 12-week window that achieves mean Hb increase from baseline ≥1.0 g/dL. It will end with the last day of the last consecutive rolling 12-week window that maintains mean Hb increase from baseline ≥1.0 g/dL.

9.6.3.13. 6MWT: Mean Change at Week 24 and 48

Mean changes from baseline at Weeks 24 and 48 will be analyzed using ANCOVA method with treatment group and randomization stratification factor(s) in the model and baseline 6MWT value as the covariate. In addition, subgroup of subjects with baseline 6MWT ≤ 450 meter will be performed.

Mean changes from baseline at Week 48 will be analyzed similarly.

9.6.3.14. Proportion of Mean Hemoglobin Increase From Baseline ≥1.5 g/dL at Week 13 to 24

Similar to the primary efficacy analysis, the proportion of subjects who have an increase from baseline ≥1.5 g/dL in mean of hemoglobin values over a continuous 12-week interval from Week 13 to Week 24 will be performed on the ITT population. Cochran-Mantel-Haenszel (CMH) test will be performed with randomization stratification factor(s) in the model to compare the treatment and placebo groups at 2-sided 0.05 level.

9.7. Safety Analysis

All safety analyses will be performed on the safety population. Full details will be included in the SAP. Planned data presentations and analyses include the following:

- Adverse events will be coded using MedDRA. Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent adverse events will be summarized by system organ class and preferred term. Treatment-emergent adverse events leading to death or to discontinuation from treatment, TEAEs classified as NCI CTCAE (version 4.0) all grades or grade 3/4 TEAEs, related to investigational product, and serious TEAEs will be summarized separately.
- Clinical laboratory results will be summarized descriptively by treatment group. Clinically significant hematologic and non-hematologic laboratory abnormalities will be listed and summarized according to the NCI CTCAE by treatment group.
- Physical examination data and vital sign measurements, including body weight, will be listed for each subject at each visit. Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by treatment group.

9.8. Interim Analysis

No Interim analysis is planned.

9.9. Timing of Analyses

9.9.1. Primary Clinical Study Report

Clinical study report (CSR) will include safety and efficacy parameters with a cut-off date at the time when all subjects enrolled in the DBTP have completed 48 weeks in the study or discontinued earlier (ie, at the time of the unblinding of the study, whichever occurs later). Thus, the primary and secondary analysis will be conducted after all required information is available for these endpoints (ie, after all subjects have completed 48 weeks in the study or discontinued earlier). With this cut-off date and upon the data base lock the study will be unblinded.

9.9.2. Final Clinical Study Report

The final CSR will include efficacy and safety data at the time of the End of the Trial (EOT definition in Section 3.3).

The final analyses will be conducted on efficacy and safety endpoints as applicable after Week 48.

9.10. Other Topics

9.10.1. Pharmacokinetic Analysis

Population PK analysis will be performed using nonlinear mixed effect modeling. Concentration data obtained from this study and other studies will be combined to develop a population PK model that describes the PK exposure data and the associated variability. Subject-specific factors (demographics, baseline characteristics, markers for organ function, anti-luspatercept antibodies,

etc.) will be explored as covariates for their potential to influence luspatercept PK parameters. Empiric individual Bayesian estimates of PK parameters will be generated using the final population PK model. With these individual parameter estimates and appropriate measures of luspatercept exposure (AUC, maximum concentration of drug [C_{max}], or other exposure metrics of interest) will be computed for each subject.

The relationship between serum luspatercept exposure and the selected efficacy/safety endpoints or biomarkers of interest will be explored as appropriate.

[redacted]

9.10.3. Data Monitoring Committee (DMC)

The independent DMC will be comprised of experts in the β-thalassemia not involved in ACE-536- B-THAL-002 protocol, an Independent Cardiologist, an Independent Statistician, and may include additional ad hoc members. Representatives of Sponsor will be attending the blinded part of the DMC meetings. The Sponsor will not have access to the unblinded data.

During the course of the study, the DMC will review unblinded safety data regularly, or ad-hoc, as well as safety and efficacy data in accordance with the guidelines for the preplanned analyses. An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, to the DMC members for each scheduled or ad-hoc meeting.

The DMC responsibilities, authorities, and procedures will be detailed in the DMC charter, which will be endorsed by the DMC prior to the first data review meeting.

Operational details for the DMC will be detailed in the DMC charter.

9.10.4. Scientific Steering Committee (SSC)

A Scientific Steering Committee (SSC) will be established by charter for this study. The SSC will be comprised of study Investigators, Sponsor representatives, and may include additional ad hoc members. The SSC will review blinded data. The SSC will serve in an advisory capacity to the Sponsor. The SSC will advise and recommend to the Sponsor:

- Changes to the protocol or conduct of the study based upon emerging clinical or scientific data from this and/or other studies.

- Procedures to ensure the safety of subjects and integrity of study data.
- Procedures to meet the overall goals and objectives of the study.

The SSC responsibilities, authorities, and procedures will be detailed in the SSC charter, which will be endorsed by the SSC prior to the first data review meeting.

Operational details for the SSC will be detailed in a separate SSC charter.

Note: The SSC is separate from the DMC.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject 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 subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF. (See Section 7.2.1.3 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for luspatercept overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs regardless of causality will be recorded by the Investigator from the time the subject signs informed consent until 9 weeks after the last dose of IP as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. In addition, SAEs that are suspected to be related to the IP as well as new malignancies or premalignancies regardless of causality (see Section 10.5.3) will be recorded by the Investigator until at least 5 years from first dose of IP, or 3 years from last dose (whichever occurs later) in this study or rollover study. Information will be collected at scheduled visits (see Table of Events, Table 3, and Section 6.3 for additional information. AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusions as a routine treatment of the studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2. Severity/ Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic

interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not

a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

10.4.1. Females of Childbearing Potential:

Females of childbearing potential (FCBPs) are advised to avoid becoming pregnant during study and for 12 weeks after the last dose of IP. Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 9 weeks of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Males are advised to use a latex condom during any sexual contact with FCBP prior to starting investigational product and continue for 12 weeks following the last dose of IP, even if he has undergone a successful vasectomy.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 9 weeks after the last dose of IP in the DBTP and/or OLP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.5.2. Thromboembolic Events

The occurrence of a thromboembolic event will be monitored as an event of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report the occurrence of thromboembolic events as SAEs to Celgene Drug Safety within 24 hours, regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICF through 9 weeks post last dose. Beyond 9 weeks post last-dose period, only related thromboembolic events should be reported.

10.5.3. Malignancy and Premalignancy Reporting

The occurrence of a new malignancy or premalignant lesion will be monitored as an event of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report the development of any new malignancy or premalignant lesion as a serious adverse event, regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICF up to and including 5 years from first dose of IP, or 3 years from last dose (whichever occurs later).

Events of new malignancy, premalignant lesions (excluding benign tumors or benign neoplasia) are to be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and subject's source documents. Documentation of the diagnosed malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, x-rays, CT scans, etc.).

Malignancies or cancerous tumors are lesions capable of invading into adjacent tissues, and may be capable of spreading to distant tissues. A benign tumor has none of those properties.

Malignancy or cancer is characterized by anaplasia, invasiveness, and metastasis.

Premalignant or precancerous lesions refer to a state of disordered morphology of cells that is associated with an increased risk of cancer. If left untreated, these conditions may lead to cancer. Such conditions are usually either dysplasia or benign neoplasia (and the dividing line between those is sometimes blurry). Sometimes the term "precancer" is used to describe carcinoma in situ, which is a noninvasive cancer that has not progressed to an aggressive, invasive stage. Not all carcinoma in situ will progress to invasive disease.

Premalignant lesions are morphologically atypical tissue which appears abnormal under microscopic examination, and in which cancer is more likely to occur than in its apparently normal counterpart.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to luspatercept based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

In addition, any report of hematologic malignancy regardless of causality in the luspatercept arm will be reported to the Regulatory Authorities in an expedited manner, if requested.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse Event(s):
  - Any serious AE assessed as related to luspatercept
  - Any AE ≥ Grade 3 assessed to be related to luspatercept if the event causes a treatment delay for > 15 consecutive weeks
  - Grade 3 leukocytosis
  - If a subject experiences > 2 dose reductions due to related AE
- Diagnosis of any new malignancy
- Withdrawal of consent - An indication that a study participant has removed itself from the study treatment
- Death
- Lost to follow-up - the loss or lack of continuation of a subject to follow-up
- Pregnancy
- If dose is delayed for more than 15 weeks due to AEs, and including case of elective surgery/hospitalization
- Undergo splenectomy
- Other: Different than the one(s) previously specified or mentioned

The reason for discontinuation of treatment should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

The following events **are** considered sufficient reasons for discontinuing a subject from the study and perform the End of Study assessments:

- Screen failure
- Completed study per protocol
- Withdrawal of consent - An indication that a study participant has removed itself from the study
- Death

- Lost to follow-up - The loss or lack of continuation of a subject to follow-up
- Other: Different than the one(s) previously specified or mentioned

The reason for End of Study should be recorded in the eCRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products (Emergency Unblinding)

The blind must not be broken during the course of the study **unless** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the IRT.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

The Sponsor may consider closing this trial when data supporting key endpoints and objectives of the study have been analyzed. In the case where there are subjects still being administered the investigational product, and it is the opinion of the investigator(s) that these subjects continue to receive benefit from treatment, the subjects may transition to a rollover protocol (ACE-536-LTFU-001) to allow these subjects continued access to luspatercept following their participation in this study (ACE-536-B-THAL-002) until the drug is commercially available and reimbursable.

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.*

14.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene appropriate SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the subject. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect,

seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. [redacted]

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

18. APPENDICES

Appendix A: Table of Abbreviations

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BMD	Bone mineral density
BP	Bodily Pain
BSC	Best supportive care
BUN	Blood urea nitrogen
CD-ROM	Compact disc, read-only-memory
C_{max}	Maximum plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DB	Database
DBP	Diastolic blood pressure
DBTP	Double-blind Treatment Period
DMC	Data Monitoring Committee
DO_2	Delivery of Oxygen
DNA	Deoxyribonucleic Acid
DVT	Deep vein thrombosis
dw	Dry weight
DXA	Dual-energy x-ray absorptiometry
EC	Ethics Committee
ECD	Extracellular domain

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDiary	Electronic diary
EPO	Erythropoietin
eCRF	Electronic case report form
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMH	Extramedullary hematopoietic
EOT	End of Trial
ESA	Erythropoiesis stimulating agent
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-G	Functional Assessment of Cancer Therapy - General
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FS	Fatigue subscale
GCP	Good Clinical Practice
GH	General Health
GLP	Good Laboratory Practice
Hb	Hemoglobin
HbA	Adult Hemoglobin
HbE	Hemoglobin E
HbF	Fetal hemoglobin
HbH	Hemoglobin H
HBsAG	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR-QoL	Health-related quality of life

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
HRU	Health resource utilization
HSCT	Hematopoietic stem cell transplantation
HU	Hydroxyurea
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICT	Iron chelation therapy
ID	Identification document
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Integrated Response Technology
ITT	intent-to-treat (subjects)
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LDH	Lactic dehydrogenase
LIC	Liver iron concentration
LMW	Low Molecular Weight
LLN	Low Limit of Normal
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular hemoglobin
MCID	Minimum clinical important difference
MCS	Mental component summary
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental Health
6MWT	6-minute walk test
MRI	Magnetic resonance imaging

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
mRNA	Messenger Ribonucleic Acid
NCI	National Cancer Institute
NRS	Numeric Rating Scale
NTDT	Non-transfusion dependent β-thalassemia
NTDT-PRO	Non-transfusion dependent β-thalassemia-patient reported outcome
PCS	Physical component summary
PF	Physical Functioning
PGI-C	Patient Global Impression of Change
PGI- S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PPS	Per protocol set
PQC	Product Quality Complaint
PRO	Patient reported outcome
PTFP	Post-treatment Follow-up Period
QoL	Quality of life
Q3W	Every 3 weeks
RBC	Red blood cell
RD	Responder Definition
RDW	Red blood cell distribution width
RE	Role Emotional
ROS	Reactive oxygen species
RP	Role-Physical
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SF	Social Functioning
SF-36	Medical Outcomes Study 36-Item Short Form
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
SoB	Shortness of breath (domain of NTDT-PRO)
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
SVT	Superficial Vein Thrombosis
TDT	Transfusion-dependent β-thalassemia
TGF-β	Transforming growth factor-β
TI	Thalassemia Intermedia
TRV	Tricuspid valve regurgitation velocity
T/W	Tiredness and weakness (domain of NTDT-PRO)
ULN	Upper limit of normal
TEAE	Treatment-emergent adverse events
TEE	Thromboembolic Event
VT	Vitality
WBC	White blood cell (count)

Appendix B: ECOG Performance Status Scale

The Eastern Cooperative Oncology Group (ECOG) Performance Status scale [redacted] is used to assess a patient's quality of life in an evaluation by a health professional of the daily activities and how the activities are affected by the disease of the patient.

Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix C: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

Currently active minor version of NCI CTCAE, Version 4.0:

Appendix D: New York Heart Association - Classification of Heart Failure

New York Heart Association - Classification of Heart Failure

Class	Symptoms
Class 1	No limitation of activities. No symptoms from ordinary activities
Class 2	Mild limitation of activity. Comfortable with rest or mild exertion
Class 3	Marked limitation of activity and be comfortable only at rest
Class 4	Complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

[redacted]

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