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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

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:

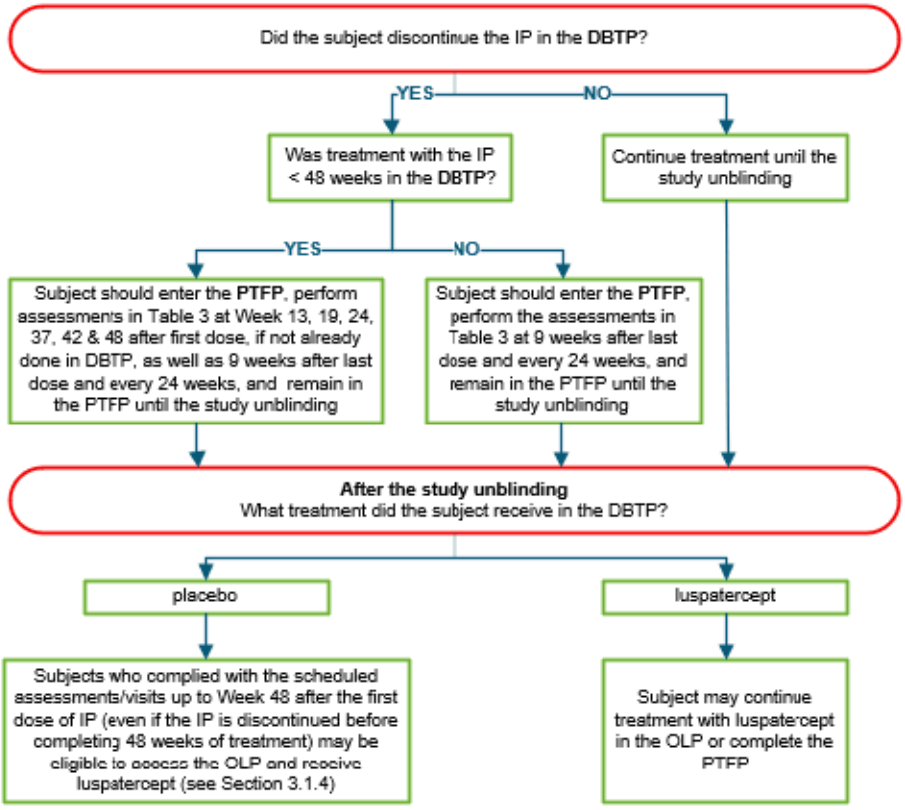
- Subjects who received placebo and have been assessed as per protocol at least up to 48 weeks after the first dose of IP (even if the IP is discontinued before complete 48 weeks of treatment), may access the Open Label Period (OLP) to receive luspatercept for a maximum 15 months before moving to the 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.

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

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	-	-

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

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.

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

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.

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.

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

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

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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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

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.

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.

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	-	-

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.

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.

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

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).

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

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

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.

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