A Phase 3B, open-label, single-arm, rollover study to evaluate long-term safety in subjects who have participated in other luspatercept (ACE-536) clinical trials

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Main Information

Primary registry identifying number
LBCTR2019100218

Protocol number
ACE-536-LTFU-001

MOH registration number
43106/2019

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
01/11/2019

Primary sponsor
Celgene Corporation

Primary sponsor: Country of origin
USA

Date of registration in primary registry
02/12/2019

Date of registration in national regulatory agency
01/11/2019

Public title
A Phase 3B, open-label, single-arm, rollover study to evaluate long-term safety in subjects who have participated in other luspatercept (ACE-536) clinical trials

Acronym

Scientific title
A Phase 3B, open-label, single-arm, rollover study to evaluate long-term safety in subjects who have participated in other luspatercept (ACE-536) clinical trials

Acronym

Brief summary of the study: English

This is a Phase 3b, open-label, single-arm, rollover study for subjects who have participated in other luspatercept (ACE-536) clinical trials.
The primary objective is to evaluate the long-term safety (including progression to acute myeloid leukemia (AML) and/or other malignancies/pre-malignancies) of luspatercept in subjects who have participated in other luspatercept clinical trials. Another objective is to follow subjects for overall survival.

Brief summary of the study: Arabic

ب ، الدراسة المفتوحة ذات الذراع الواحد ، والانتقال إلى الأشخاص الذين شاركوا في تجارب سريرية أخرى3دراسة مرحلة (ACE-536).
و / أو الأورام الخبيثة الأخرى / ما) (AML)الهدف الأساسي هو تقييم السلامة طويلة الأجل (بما في ذلك التقدم إلى سرطان الدم النخاعي الحاد
الأخرى. هدف آخر هو luspatercept في الموضوعات الذين شاركوا في التجارب السريرية luspatercept قبل الأورام الخبيثة) من
متابعة الموضوعات للبقاء على قيد الحياة بشكل عام

Health conditions/problem studied: Specify

Prior participation on a clinical trial of luspatercept (ACE-536) in protocols eligible for participation in this study ACE-536-LTFU-001 with the following medical conditions:
- Myelodysplastic Syndrome (MDS)
- Beta (β)-thalassemia (THAL)

- Myelofibrosis (MF)
In Lebanon, only patients with beta (β)-thalassemia (THAL) have participated in previuos clinical trial of luspatercept (ACE-536).

Interventions: Specify

Starting as soon as Day 1 of Dose 1 of the rollover protocol, and assessed by the investigator prior to every subsequent treatment dose, subjects may have the dose level increased in a stepwise manner:
 beyond the starting dose from last dose of luspatercept from the parent protocol up to the defined maximum treatment dose.
 beyond the starting dose of 1.0 mg/kg in case of subjects crossing over to luspatercept from placebo arm of the parent protocol up to the defined maximum treatment dose.

Key inclusion and exclusion criteria: Inclusion criteria

Subjects must meet ALL the following criteria to be enrolled in this study:

1. Subject is ≥ 18 years at the time of signing the informed consent form (ICF).

2. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.

3. Subject has been participating in a luspatercept trial and continues to fulfill all the requirements of the parent protocol and the subject has been either:
a. Assigned to luspatercept treatment, continues to receive clinical benefit in the opinion of the investigator and should continue to receive luspatercept treatment, OR
b. Assigned to placebo arm in the parent protocol (at the time of unblinding or in follow-up) and should cross over to luspatercept treatment, OR
c. Assigned to the Follow-up Phase of the parent protocol, previously treated with luspatercept or placebo in the parent protocol who shall continue into Long-term Post-treatment Follow-up Phase in the rollover study until the follow-up commitments are met (unless requirements are met as per parent protocol to crossover to luspatercept treatment).

4. Subject understands and voluntarily signs an informed consent document prior to any study-related assessments or procedures being conducted.

5. Subject demonstrates compliance, as assessed by the investigator, with the parent study protocol requirements.

6. Applies to on treatment subjects only- females of childbearing potential (FCBP) defined as a sexually mature woman 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) and must:
a. Have two negative pregnancy tests as verified by the investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. 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) or agree to use, and be able to comply with highly effective, contraception without interruption, 35 days prior to starting investigational product (IP), during the study therapy (including dose interruptions), and for 84 days after discontinuation of study therapy.

7. Applies to on treatment subjects only- 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 84 days following investigational product discontinuation even if he has undergone a successful vasectomy.

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

65

Key inclusion and exclusion criteria: Exclusion criteria

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

1. Applies to on treatment subjects only- Concomitant use of any medications/procedures that are prohibited in the parent luspatercept protocol.

2. Subject has met one or more criteria for study treatment discontinuation as stipulated in the parent luspatercept protocol.

3. First luspatercept transition visit into rollover study > 21 days after end of study (EOS) visit (last dose/visit in case of no EOS visit) of the parent luspatercept study with the exception of those subjects already in the Post-treatment Follow up Phase from the parent study. Note- Subject with current dose delays from the parent protocol during the Transition Phase, will continue in the rollover protocol regardless of the delay.

4. Applies to on treatment subjects only- Pregnant or breastfeeding females.

5. Subject has any significant medical condition, laboratory abnormality, psychiatric illness, or is considered vulnerable by local regulations (eg, imprisoned or institutionalized) that would prevent the subject from participating in the study.

6. 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.

7. Subject has any condition that confounds the ability to interpret data from the study.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Safety

Trial scope: Specify scope

N/A

Study design: Allocation

N/A: Single arm study

Study design: Masking

Open (masking not used)

Study design: Control

N/A

Study phase

3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Single

Study design: Specify assignment

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

Luspatercept (ACE-536)

Year of authorization

Month of authorization

Type of IMP

Others

Pharmaceutical class

Luspatercept is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor IIB (ActRIIB) linked to the human immunoglobulin G1 fragment crystallizable (IgG1 Fc) domain. Luspatercept is a homodimeric protein comprised of 2 disulfide-linked polypeptide chains, each with 335 amino acids. Each polypeptide chain contains 3 sites for N-linked glycosylation (total of 6N- linked glycosylation sites per molecule). Peptide mapping and oligosaccharide analysis of luspatercept confirms the presence of highly branched N-linked glycans, typical of a recombinant protein produced in Chinese hamster ovary cells.

Therapeutic indication

Myelodysplastic Syndrome (MDS);
Beta (β)-thalassemia (THAL);
Myelofibrosis (MF);
Only patients with beta (β)-thalassemia (THAL) are applicable in Lebanon

Therapeutic benefit

Luspatercept acts as a ligand trap for Growth Differentiation Factor 11 (GDF11) and other TGF-β family ligands to suppress Smad2/3 signaling. In nonclinical experiments, luspatercept has been shown to bind with high affinity to some TGF-β ligands (eg, GDF11, GDF8, BMP6, and activin B) but substantially less, or not at all, to others (eg, BMP9 and activin A). The mechanism of action of luspatercept is independent from that of erythropoietin. While erythropoietin stimulates proliferation and differentiation of early erythroid progenitors, luspatercept promotes stimulation of the later, maturation phase of erythroblast differentiation and maturation in the bone marrow.

Study model

N/A

Study model: Explain model

Study model: Specify model
N/A

N/A

Time perspective
N/A

Time perspective: Explain time perspective
N/A

Time perspective: Specify perspective
N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention
None retained

Biospecimen description
Not applicable

Target sample size
742

Actual enrollment target size

Date of first enrollment: Type
Anticipated

Date of first enrollment: Date
01/11/2019

Date of study closure: Type
Anticipated

Date of study closure: Date
30/06/2027

Recruitment status
Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan
Yes

IPD sharing statement description
Patients' full identity will not be on any of the study documents or samples collected and kept by the sponsor for their studies. The partial date of birth will only be collected. Only a unique participant number for the study will link the data or samples to the patients. These data may contain your gender and race, as well as any medical and scientific data required by the study.

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
Food and Drug Administration	IND 112562

Sources of Monetary or Material Support

Name
Celgene Corporation

Secondary Sponsors

Name
Not applicable

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Aziz Zoghbi	MCT-CRO, Berytech Technology and Health, 5th Floor, Damascus Road, Beirut, Lebanon	Lebanon	009611612500	zog_az@mct-cro.com	Regional Manager
Scientific	Ali Taher	Chronic Care Center, Hazmieh, Lebanon	Lebanon	009613755669	ataher@aub.edu.lb	PI

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Chronic Care Center	Dr. Ali Taher	Professor of Medicine, Hematology & Oncology	NA
American university of Beirut	Dr. Ali Taher	Professor of Medicine, Hematology & Oncology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Chronic Care Center	30/09/2019	Michele Abi saad	cccmas@chroniccare.org.lb	05 455 103

Countries of Recruitment

Name
Lebanon
Bulgaria
Greece
Italy
Thailand
United Kingdom
United States of America
Belgium
Malaysia
Turkey
Australia
France
Germany
Canada
Netherlands
Spain
Sweden
Tunisia
Taiwan

Health Conditions or Problems Studied

Condition	Code	Keyword
Thalassemia	Thalassaemia (D56)	Thalassemia

Interventions

Intervention	Description	Keyword
ACE-536	every 3 weeks (Q3W):1.0 mg/kg or same dose as last dose of parent protocol in case IP dose modifications occurred	Treatment Phase

Primary Outcomes

Name	Time Points	Measure
Adverse events (AEs)	Enrollment to 42 days post last dose	Type, frequency, severity of AEs, relationship of treatment emergent adverse events to luspatercept
Development of other malignancies/pre-malignancies	Enrollment to Long-term Post-treatment Follow-up	Number and percentage of subjects developing other malignancies/premalignancies
Progression to high/very high risk myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) (MDS and myelofibrosis [MF] only). Not applicable for Lebanon patient population consists of B-Thal patients only.	Number and percentage of subjects progressing to high/very high risk MDS or AML	Enrollment to LTPTFU

Key Secondary Outcomes

Name	Time Points	Measure
Overall survival	Enrollment to Long-term Post-treatment Follow-up	Time from date of randomization until death from any cause

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files