A Phase 3, Double-Blind, Randomized Study To Compare The Efficacy And Safety Of Luspatercept (ACE-536) Versus Placebo For The Treatment Of Anemia Due To IPSS-R Very Low, Low, Or Intermediate Risk Myelodysplastic Syndromes In Subjects With Ring Syderoblasts Who Require Red Blood Cell Transfusions

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Anaemias nonhaemolytic and marrow depression
Study type	Interventional

Summary

ID

NL-OMON47664

Source
ToetsingOnline

Brief title
MEDALIST / ACE-536-MDS-001

Condition

- Anaemias nonhaemolytic and marrow depression

Synonym
anemia

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Celgene Corporation

Intervention

Keyword: Anemia, Blood cell transfusions, Myelodysplastic syndromes, Ring sideroblasts

Outcome measures

Primary outcome

The primary efficacy endpoint of transfusion independent response is defined as

the absence of any RBC transfusion during any consecutive 56 day period during

the Primary Phase of the Treatment Period.

Secondary outcome

The key secondary endpoint is the proportion of subjects achieving RBC-TI with

duration * 12 weeks.

Study description

Background summary

This is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in subjects with ring sideroblasts (* 15%) who require

RBC transfusions.

Study objective

The primary objective is:
* To evaluate RBC transfusion independence (RBC-TI) of luspatercept compared with placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in subjects with ring sideroblasts (* 15%) who require RBC transfusions

The secondary objectives are:
* To assess the safety and tolerability of luspatercept compared with placebo
* To evaluate the effect of luspatercept on reduction in RBC transfusions, increase in hemoglobin, duration of RBC-TI, improvement in health-related quality of life (HRQoL) (ie, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30]), increase in neutrophils, increase in platelets, decrease in serum ferritin, decrease in iron chelation therapy use, and time to RBC-TI compared with placebo
* To evaluate population pharmacokinetics and exposure-response relationships for luspatercept in MDS subjects

Study design

The study is divided into the Screening Period, a double-blind Treatment Period (Primary Phase and Extension Phase) and a Posttreatment Follow-up Period.

Eligible subjects will be randomized at a 2:1 ratio to either:
* Experimental Arm - Luspatercept (ACE-536): Starting dose of 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)
OR
* Control Arm: Placebo (volume equivalent to experimental arm) subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle).

After randomization, no crossover between the treatment arms will be permitted at any point during the study.
Best supportive care may be used in combination with study treatment in both arms when clinically indicated per investigator discretion.

Stratification will be based on the following factors:
1. RBC Transfusion burden at baseline
* * 6 RBC units/8 weeks (mean of the two consecutive 8-week periods immediately prior to randomization)
* < 6 RBC units/8 weeks (mean of the two consecutive 8-week periods immediately prior to randomization)
2. IPSS-R at baseline

* Very low, low
* Intermediate

Primary Phase of the Treatment Period: Weeks 1-24
Subjects should receive investigational product (IP) through at least the first 24 calendar weeks unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other discontinuation criteria.

MDS Disease Assessment: Week 25 Visit
The Week 25 Visit should be completed 24 calendar weeks after the date of first dose, regardless of dose delays. Because central laboratory results from bone marrow and peripheral blood samples are required as part of the MDS Disease Assessment, a 14-day window is allowed for the Week 25 Visit.

In order for subjects to remain on double-blind treatment beyond the first 24 calendar weeks, the following criteria must be confirmed upon the completion of the MDS Disease Assessment by the investigator at the Week 25 Visit:
* Evidence of clinical benefit (eg, decrease in RBC transfusion requirement compared to baseline requirement or hemoglobin increase compared to baseline) AND
* Absence of progression to acute myeloid leukemia (AML) or high/very high risk category MDS per IPSS-R based on morphological assessment of bone marrow and peripheral blood and cytogenetics.

Based on the outcome of the Week 25 Visit MDS Disease Assessment, subjects will either be discontinued from treatment with IP and enter the Posttreatment Follow-up Period or continue double-blind treatment with IP in the Extension Phase of the Treatment Period.
Refer to Protocol Section 6.2.2 for additional details related to procedures/assessments.

Extension Phase of the Treatment Period: After Week 25 Visit
Subjects who meet the criteria for remaining on double-blind treatment with IP in the Extension Phase may continue dosing on Day 1 of each 21-day treatment cycle until the subject experiences unacceptable toxicities, progression to AML or high/very high risk MDS per IPSS-R or withdraws consent, or meets any other discontinuation criteria.

MDS Disease Assessment will be repeated by the investigator at Extension Cycle 8, Day 1 and Day 1 of every eighth Extension cycle thereafter (ie, Extension Cycle 8, 16, 24+, or every 24 weeks in the event of dose delays) until the subject is discontinued from IP.

Posttreatment Follow-up Period:
All subjects discontinued from protocol-prescribed therapy for any reason will be followed for adverse event (AE)/serious adverse event (SAE) reporting for a period of 42 days after the last dose of IP, as well as for SAEs made known to

the Investigator at any time thereafter that are suspected of being related to IP.

Continuation of monitoring for progression to AML will occur in the Posttreatment Follow-up Period along with collection of information related to subsequent MDS therapies, and overall survival for at least 3 years from the date of last dose of IP unless the subject withdraws consent from the study, dies, or is lost to follow-up.

Intervention

Eligible subjects will be randomized at a 2:1 ratio to either:
* Experimental Arm - Luspatercept (ACE-536): Starting dose of 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)
OR
* Control Arm: Placebo (volume equivalent to experimental arm) subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle).

Study burden and risks

Burden
- Subcutaneous administration of study medication: every cycle
- ECG: 3x
- Blood sampling: every visit
- Bone Marrow Biopsy/Aspirate: +/- 4 x
- Questionnaires: every other cycle

See also Protocol section 5 (Table of Events) of Protocol d.d. 25Sep2015

Luspatercept may cause the following very common side effects:
- Increases in red blood cell count, hemoglobin and hematocrit is expected with treatment of ACE-536. This may result in an increase in blood pressure. Both your red blood cell count and your blood pressure will be monitored by your study doctor during the study. You may have a delay or reduction in study drug dosing to minimize this risk.
- The study drug will be given as an injection (shot) under the skin. As with any solution given this way, there may be redness, bruising, or slight swelling where the injection was given. In the healthy volunteers, bleeding and /or a darker colored skin mark at the injection site (injection site hemorrhage, injection site macule) was commonly reported. You may feel some pain when the needle is inserted or afterwards. Although it does not happen often, it is possible that people you could faint or get an infection at the place the needle is inserted.

Very common (> 10 %) reported side effects in subjects:

Infection of the nose and throat (viral upper respiratory tract infection), Headache, Fatigue, Cough, Diarrhea, Shortness of breath (dyspnoea), Increased blood pressure (hypertension), Joint pain (arthralgia), Swelling of the arms and legs (peripheral edema), Lung infection (pneumonia), Infection of the bladder (urinary tract infection).

Contacts

Public
Celgene Corporation

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US
Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject is * 18 years of age the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Documented diagnosis of MDS according to WHO 2008 classification (Appendix

B) that meets IPSS-R classification (Greenberg, 2012; Appendix D) of very low, low, or intermediate risk disease, and: Ring sideroblast * 15% of erythroid precursors in bone marrow, and < 5% blasts in bone marrow
4. Refractory or intolerant to, or ineligible for, prior ESA treatment, as defined by any one of the following:
- Refractory to prior ESA treatment - documentation of non-response or response that is no longer maintained to prior ESA-containing regimen, either as single agent or combination (eg, with G-CSF); ESA regimen must have been either:
a) recombinant human erythropoietin (rHu EPO) * 40,000 IU/wk for at least 8 doses or equivalent;
OR
b) darbepoetin alpha * 500 *g Q3W for at least 4 doses or equivalent;
- Intolerant to prior ESA treatment - documentation of discontinuation of prior ESAcontaining regimen, either as single agent or combination (eg, with G-CSF), at any time after introduction due to intolerance or an adverse event
- ESA ineligible - Low chance of response to ESA based on endogenous serum erythropoietin level > 200 U/L for subjects not previously treated with ESAs
5. If previously treated with ESAs or granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), both agents must have been discontinued * 4 weeks prior to date of randomization.
6. Requires RBC transfusions, as documented by the following criteria:
- average transfusion requirement of * 2 units/8 weeks of pRBCs confirmed for a minimum of 16 weeks immediately preceding randomization.
- no consecutive 56-day period that was RBC transfusion-free during the 16 weeks immediately preceding randomization
7. Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2
8. Females of childbearing potential (FCBP) defined as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) 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), must:
a) Have two negative pregnancy tests as verified by the Investigator prior to starting study therapy, (unless the screening pregnancy test was done within 72 hours of C1D1). She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment.
b) If sexually active, agree to use, and be able to comply with, effective contraception without interruption, 5 weeks prior to starting investigational product, during the study therapy (including dose interruptions), and for 12 weeks after discontinuation of study therapy.
9. Male subjects must practice true abstinence* (which must be reviewed prior to each IP administration or on a monthly basis [eg, in the event of dose delays]) 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 following investigational product discontinuation, even if he has undergone a successful vasectomy.

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

Exclusion criteria

1. Prior therapy with disease modifying agents or experimental agents for underlying MDS disease
2. Previously treated with either luspatercept (ACE-536) or sotatercept (ACE-011)
3. MDS associated with del 5q cytogenetic abnormality
4. Secondary MDS, ie, MDS that is known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases.
5. Known clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding
6. Prior allogeneic or autologous stem cell transplant
7. Known history of diagnosis of AML
8. Use of any of the following within 5 weeks prior to randomization:
- Anticancer cytotoxic chemotherapeutic agent or treatment
- Corticosteroid, except for subjects on a stable or decreasing dose for * 1 week prior to randomization for medical conditions other than MDS
- Iron-chelating agents, except for subjects on a stable or decreasing dose for at least 8 weeks prior to randomization
- Other RBC hematopoietic growth factors (eg, Interleukin-3)
9. Uncontrolled hypertension, defined as repeated elevations of diastolic blood pressure (DBP) * 100 mmHg despite adequate treatment.
10. Absolute neutrophil count (ANC) < 500/*L (0.5 x 10^9/L)
11. Platelet count < 50,000/*L (50 x 10^9/L)
12. Estimated glomerular filtration rate (eGFR) or creatinine clearance < 40 mL/min
13. Serum aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) * 3.0 x upper limit of normal (ULN)
14. Total bilirubin * 2.0 x ULN.
- Higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (ie, ineffective erythropoiesis).
- Subjects are excluded if there is evidence of autoimmune hemolytic anemia manifested as a corrected reticulocyte count of > 2% with either a positive Coombs* test or over 50% indirect bilirubin
15. Prior history of malignancies, other than MDS, unless the subject has been free of the disease 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)
16. Major surgery within 8 weeks prior to randomization. Subjects must have completely recovered from any previous surgery prior to randomization
17. History of stroke, deep venous thrombosis (DVT), pulmonary or arterial embolism within 6 months prior to randomization
18. Pregnant or breastfeeding females
19. Myocardial infarction, uncontrolled angina, uncontrolled heart failure, or uncontrolled cardiac arrhythmia as determined by the investigator within 6 months prior to randomization
20. Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment), known Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV) infection, and/or Hepatitis C (HCV) infection.
21. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product.
22. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
23. 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.
24. Subject has any condition or concomitant medication that confounds the ability to interpret data from the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-01-2017
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Luspatercept
Generic name:	Luspatercept

Ethics review

Approved WMO Date:	10-03-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-06-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	10-05-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-11-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-003454-41-NL
ClinicalTrials.gov	NCT02631070
CCMO	NL55975.028.16

Study results

Results posted: 03-01-2022

First publication
10-12-2021