SAMENVATTING ACE-MDS-536-001

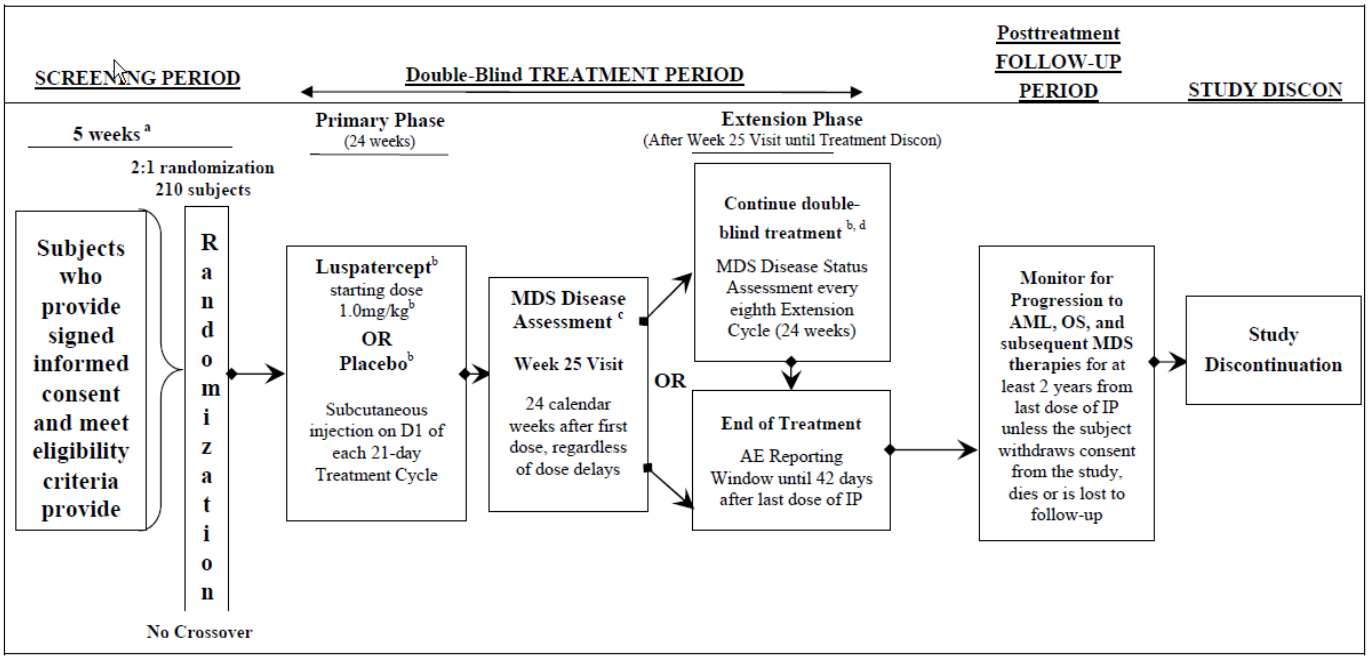
TITEL

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 Sideroblasts Who Require Red Blood Cell Transfusions

INDICATIE

Treatment of anemia due to very low, low, or intermediate risk myelodysplastic syndromes (MDS) according to the revised International Prognostic Scoring System (IPSS-R) in subjects with ring sideroblasts who require red blood cell (RBC) transfusions

SCHEMA



INCLUSION CRITERIA

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

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
   - < 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   - Refractory to prior ESA treatment - documentation of non-response or response that is no longer maintained to prior ESA-containing regimen, either as single agent or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:

- recombinant human erythropoietin (rHu EPO) ≥ 40,000 IU/wk for at least 8 doses or equivalent;
  OR
- darbepoetin alpha ≥ 500 μg 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, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), must have been discontinued ≥ 6 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 (Appendix G)
8. Females of childbearing potential (FCBP) must:

- 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 treatment. This applies even if the subject practices true abstinence* from heterosexual contact.
- Either commit to true abstinence* from heterosexual contact (which must be reviewed prior to each IP administration or on a monthly basis [eg, in the event of dose delays] and source documented) or 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

The presence of any of the following will exclude a subject from enrollment:
1. Prior therapy with disease modifying agents (eg, immune-modulatory drug [IMiDs such as lenalidomide], hypomethylating agents, or immunosuppressive therapy [IST]) 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

- iron deficiency to be determined by a bone marrow aspirate stain for iron, calculated transferrin saturation (iron/total iron binding capacity) ≤ 20%, or serum ferritin ≤ 15 μg/L

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/μL (0.5 x 109/L)
11. Platelet count < 50,000/μL (50 x 109/L)
12. Estimated glomerular filtration rate (eGRF) 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 (see Investigator Brochure).
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.