An Efficacy and Safety Study of Luspatercept (ACE-536) Versus Placebo in Subjects With Myeloproliferative Neoplasm-Associated Myelofibrosis on Concomitant JAK2 Inhibitor Therapy and Who Require Red Blood Cell Transfusions (INDEPENDENCE)

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Main Information

Primary registry identifying number
LBCTR2023075332

Protocol number
ACE-536-MF-002

MOH registration number

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

Primary sponsor
Celgene Corporation, a wholly-owned subsidiary of Bristol Myers Squibb company

Primary sponsor: Country of origin
New Jersey, United States of America

Date of registration in primary registry
06/09/2023

Date of registration in national regulatory agency

Public title
An Efficacy and Safety Study of Luspatercept (ACE-536) Versus Placebo in Subjects With Myeloproliferative Neoplasm-Associated Myelofibrosis on Concomitant JAK2 Inhibitor Therapy and Who Require Red Blood Cell Transfusions (INDEPENDENCE)

Acronym
N/A

Scientific title
A phase 3, double-blind, randomized study to compare the efficacy and safety of Luspatercept (ACE-536) versus placebo in subjects with Myeloproliferative Neoplasm-Associated Myelofibrosis on concomitant JAK2 inhibitor therapy and who require red blood cell transfusions

Acronym
N/A

Brief summary of the study: English
This is a Phase 3, global, double-blind, randomized, multicenter study. The primary objective is to evaluate the efficacy of Luspatercept compared with placebo for the treatment of anemia in subjects with MPN-associated MF with concomitant JAK2 inhibitor therapy and who require RBC transfusions.

Brief summary of the study: Arabic
دراسة في المرحلة 3، عالمية، مزدوجة التعمية، عشوائية التوزيع، لمقارنة فعالية عقار لوسباتيرسيبت ACE-536 وسلامته مقابل الدواء الوهمي لدى المشاركين المصابين بالتليف النقوي المرتبط بالورم النقوي ويحتاجون إلى عمليات نقل خلايا الدم الحمراء JAK2 التكاثري الذين يتلقون علاجًا مصاحبًا بمثبط.

Health conditions/problem studied: Specify

Myeloproliferative Neoplasm-associated Myelofibrosis with concomitant JAK2 inhibitor therapy requiring red blood cell transfusions.

Interventions: Specify

The study is divided into Screening Period, a Treatment Phase (consisting of a Blinded Core Treatment Period, a Day 169 Response Assessment, a Blinded Extension Treatment Period, and an Open-label Extension Treatment Period), and a Post treatment Follow-up Period.

Subjects satisfying the eligibility criteria will be randomized by a central randomization procedure using IRT at a 2:1 ratio to either:
- Experimental Arm: Luspatercept (ACE-536, also known as BMS-986346) + BSC; luspatercept starting dose of 1.33 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle).
or
- Control Arm: Placebo + BSC; placebo starting dose with volume equivalent to experimental arm subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle).

During the Treatment Phase, the starting dose can be titrated (increased) up to a maximum of 1.75 mg/kg, provided that the subject meets the appropriate criteria.

Key inclusion and exclusion criteria: Inclusion criteria

1. Subject is ≥ 18 years of age at the time of signing the ICF.
2. Subject has a diagnosis of PMF according to the 2016 World Health Organization (WHO) criteria (APPENDIX C) or diagnosis of post-ET or post-PV MF according to the IWG-MRT 2007 criteria (APPENDIX D), confirmed by the most recent local pathology report.
3. Subject is requiring RBC transfusions as defined as:
a. Average RBC-transfusion frequency: 4 to 12 RBC units/12 weeks immediately up to randomization. There must be no interval > 6 weeks (42 days) without ≥ 1 RBC transfusion.
b. RBC transfusions are scored in determining eligibility when given for treatment of:
- Symptomatic (ie, fatigue or shortness of breath) anemia with a pretransfusion Hgb ≤ 9.5 g/dL or
- Asymptomatic anemia with a pretransfusion Hgb ≤ 7 g/dL
c. RBC transfusions given for worsening of anemia due to bleeding or infections are not scored in determining eligibility.
4. Subjects on continuous (eg, absent of dose interruptions lasting ≥ 2 consecutive weeks) JAK2 inhibitor therapy as approved in the country of the study site for the treatment for MPNassociated MF as part of their standard-of-care therapy for at least 32 weeks, on stable daily dose for at least 16 weeks immediately up to the date of randomization and anticipated to be on a stable daily dose of that JAK2 inhibitor for at least 24 weeks after randomization.
5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
6. 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 (eg, has had menses at any time in the preceding 24 consecutive months). Females of childbearing potential (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 IP.
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, 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 IP based on multiple-dose PK data) after discontinuation of study therapy.
7. Male subjects must:
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 IP based on multiple-dose PK data) following IP discontinuation, even if he has undergone a successful vasectomy.
8. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
9. Subject is willing and able to adhere to the study visit schedule and other protocol requirements including the use of the electronic patient reported outcomes device.

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

90

Key inclusion and exclusion criteria: Exclusion criteria

1. Subject with anemia from cause other than MPN-associated MF or JAK2 inhibitor therapy (eg, iron deficiency, vitamin B12 and/or folate deficiencies, autoimmune or hemolytic anemia, infection, or any type of known clinically significant bleeding or sequestration).
2. Subject use of hydroxyurea, immunomodulatory compounds such as pomalidomide, thalidomide, ESAs, androgenic steroids or other drugs with potential effects on hematopoiesis ≤ 8 weeks immediately up to the date of randomization.
a. Systemic corticosteroids are permitted for nonhematological conditions providing the subject is receiving a constant dose equivalent to ≤ 10 mg prednisone for the 4 weeks immediately up to randomization.
b. Iron chelation therapy (ICT) is permitted providing the subject is receiving a stable dose for the 8 weeks immediately up to randomization.
3. Subject with any of the following laboratory abnormalities at screening:
a. Neutrophils: < 1 x 109/L
b. White blood count (WBC): > 100 x 109/L

c. Platelets: the lowest allowable level as approved for the concomitant JAK2 inhibitor but not < 25 x 109/L or > 1000 x 109/L
d. Peripheral blood myeloblasts: > 5%
e. Estimated glomerular filtration rate: < 30 mL/min/1.73 m2 (via the 4-variable modification of diet in renal disease [MDRD] formula) or nephrotic subjects (eg, urine albumin-to creatinine ratio > 3500 mg/g)
f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT): > 3.0 x upper limit of normal (ULN)
g. Direct bilirubin: ≥ 2 x ULN Higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (eg, ineffective erythropoiesis)
4. Subject with uncontrolled hypertension, defined as repeated elevations of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, that is not resolved at the time of randomization.
5. Subject with prior history of malignancies, other than disease under study, unless the subject has been free of the disease for ≥ 3 years. However, subject with the following history/concurrent conditions is allowed:
a. Basal or squamous cell carcinoma of the skin
b. Carcinoma in situ of the cervix
c. Carcinoma in situ of the breast
d. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system)
6. Subject with prior hematopoietic cell transplant or subject anticipated to receive a hematopoietic cell transplant during the 24 weeks from the date of randomization.
7. Subject with stroke, myocardial infarction, deep venous thrombosis, pulmonary or arterial embolism within 6 months immediately up to the date of randomization.
8. Subject with major surgery within 2 months up to the date of randomization. Subject must have completely recovered from any previous surgery immediately up to the date of randomization.
9. Subject with a major bleeding event (defined as symptomatic bleeding in a critical area or organ and/or bleeding causing a decrease in Hgb of ≥ 2 g/dL or leading to transfusion of ≥ 2 units of packed red cells) in the last 6 months prior to the date of randomization.
10. Subject with inadequately controlled heart disease and/or have a known left ventricular ejection fraction < 35%.
11. Subject with 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).
a. History of active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 4 weeks prior to screening, unless the subject has adequately recovered from coronavirus disease 2019 (COVID-19) symptoms and related complications as per Investigator's discretion and following a discussion with the Medical Monitor. Use of a live COVID-19 vaccine is prohibited within 4 weeks prior to randomization.
12. Subject with known human immunodeficiency virus (HIV), evidence of active Hepatitis B (HepB) as demonstrated by the presence of Hepatitis B surface antigen (HBsAg) and/or positive for Hepatitis B virus DNA (HBVDNA-positive), and/or evidence of active Hepatitis C (HepC) as demonstrated by a positive Hepatitis C virus RNA (HCV-RNA) test of sufficient sensitivity.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Therapy

Trial scope: Specify scope

N/A

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

Yes, Worldwide

IMP has market authorization: Specify

USA, EU, Canada, Saudi, Qatar, Australia, UAE, Oman, Hong Kong, Singapore and China,

Name of IMP

Luspatercept

Year of authorization

2019

Month of authorization

11

Type of IMP

Immunological

Pharmaceutical class

Luspatercept is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor type IIB
(ActRIIB) linked to the Immunoglobulin G1 (IgG1) Fc domain (Figure 1A). The ActRIIB receptor and its ligands are members of the transforming growth factor-β (TGF-β) superfamily, a group of proteins involved in the development, differentiation, and/or maturation of various tissues.

Therapeutic indication

Treatment of anemia associated with myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) in subjects who are on concomitant Janus kinase 2 (JAK2) inhibitor therapy and who require red blood cell (RBC) transfusions.

Therapeutic benefit

Luspatercept acts as a ligand trap for growth differentiation factor 11 (GDF11) and other TGF-β superfamily ligands to suppress Smad2/3 signaling. During normal erythropoiesis, GDF11 appears to inhibit differentiation and maintain the survival of immature erythroid progenitors, but its expression is decreased as cells mature, and thus its effect is transient.

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

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

Samples with DNA**

Biospecimen description

Additional and optional research may be performed using leftover samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

Target sample size

309

Actual enrollment target size

Date of first enrollment: Type

Actual

Date of first enrollment: Date

25/02/2021

Date of study closure: Type

Actual

Date of study closure: Date

04/08/2025

Recruitment status

Recruiting

Recruitment status: Specify

Date of completion

23/05/2024

IPD sharing statement plan

No

IPD sharing statement description

N/A

Additional data URL

https://clinicaltrials.gov/ct2/show/NCT04717414

Admin comments

Trial status

Approved

Secondary Identifying Numbers

No Numbers

Sources of Monetary or Material Support

Name
Celgene Corporation, a wholly-owned subsidiary of Bristol Myers Squibb company

Secondary Sponsors

No Sponsors

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
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Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
American University of Beirut Medical Center	Dr. Ali Taher	Professor of Medicine, Hematology & Oncology	Pending
Hammoud Hospital University Medical Center	Dr. Fadi Farhat	Doctor of Medicine, Hematology/Oncology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Hammoud Hospital University Medical Center	05/04/2023	Ibrahim Omeis	iomeis@hammoudhospital.org	009617721021

Countries of Recruitment

Name
Lebanon
Austria
Belgium
Czech Republic
France
Germany
Greece
Ireland
Italy
Poland
Spain
United States of America
Australia
Canada
China
Japan
United Kingdom
Hungary
Romania

Health Conditions or Problems Studied

Condition	Code	Keyword
Myeloproliferative Neoplasm-Associated Myelofibrosis	Neoplasm of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue, unspecified (D47.9)	Myelofibrosis

Interventions

Intervention	Description	Keyword
ACE-536	Every 3 weeks (Q3W):1.33 mg/kg or Placebo	Treatment Phase

Primary Outcomes

Name	Time Points	Measure
Red blood cell-transfusion independence (RBC-TI) ≥ 12 weeks (RBC-TI 12)	Up to 24 weeks	Proportion of subjects who become RBC-transfusion free over any consecutive 12-week period starting within the first 24 weeks

Key Secondary Outcomes

Name	Time Points	Measure
Red blood cell-transfusion independence ≥ 16 weeks (RBC-TI 16)	Up to 24 weeks	Proportion of subjects who become RBC-transfusion free over any consecutive 16-week period
Duration of Red blood cell-transfusion independence (RBC-TI 12)	Up to end of treatment, approximately 3 years	Maximum duration of RBC-TI response
Reduction of transfusion burden by ≥ 50% and by ≥ 4 units/12 weeks from baseline over any consecutive 12-week period	Up to 24 weeks	Proportion of subjects who reduce their transfusion burden by ≥ 50% and by ≥ 4 units/12 weeks from baseline over any consecutive 12-week period
Duration of reduction in transfusion burden	Up to end of treatment, approximately 3 years	Maximum duration of when RBC-transfusion dependent subjects who reduce their transfusion burden by ≥ 50% and by ≥ 4 units/12 weeks from baseline over any consecutive 12 week period
Red blood cell-transfusion independence ≥ 12 weeks in the treatment period (RBC-TI 12/TP)	Up to end of treatment, approximately 3 years	Proportion of subjects who become RBC-transfusion free over any consecutive 12-week period
Red blood cell-transfusion independence ≥ 16 weeks in the treatment period (RBC-TI 16/TP)	Up to end of treatment, approximately 3 years	Proportion of subjects who become RBC-transfusion free over any consecutive 16-week period
Change in RBC transfusion burden	Up to 24 weeks	Mean change in transfusion burden (RBC units) from baseline
Cumulative duration of RBC-transfusion independence	Up to end of treatment, approximately 3 years	Cumulative response duration for subjects achieving multiple episodes of RBC-TI 12
Mean Hgb increase ≥ 1 g/dL from baseline over any consecutive 12-week period in absence of RBC transfusions	Up to end of treatment, approximately 3 years	Proportion of subjects achieving a mean Hgb increase ≥ 1 g/dL from baseline over any consecutive 12-week period in absence of RBC transfusions
Change in serum ferritin from baseline	Up to end of treatment, approximately 3 years	Change in serum ferritin
Incidence of Adverse Events (AEs)	From screening up to 42 days post last dose	Number of participants with adverse events
Transformation to blast phase: Number of subjects who transform into AML	Up to approximately 5 years	AML = acute myeloid leukemia
Frequency of Antidrug antibodies (ADA)	From randomization and up to including 48 weeks post first dose	Will be collected for assessment of anti-drug antibodies (ADA) against Luspatercept in serum in all subjects
Pharmacokinetics - Area Under the Concentration-Time Curve (AUC)	From randomization and up to including 48 weeks post first dose	Measures of Luspatercept exposure area under the curve
Pharmacokinetics - Maximum plasma concentration of drug (Cmax)	From randomization and up to including 48 weeks post first dose	Maximum plasma concentration of drug

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