# 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)

**18/07/2025 01:20:38**

## 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 |
|---|---|---|---|---|---|---|
| Public | Eliane Nasr | MCT-CRO, Berytech Technology and Health, 5th Floor, Damascus Road, Beirut | Lebanon | 0096181115830 | Eliane.nasr@mct-cro.com | Country Manager |
| Scientific | Ali Taher | American University of Beirut Medical Center, Cairo Street, Hamra, Beirut | Lebanon | 009613755669 | ataher@aub.edu.lb | PI |
| Scientific | Fadi Farhat | Hammoud Hospital University Medical Center, Ghassan Hammoud Street, Saida | Lebanon | 009613753155 | drfadi.trials@gmail.com | PI |

## 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**