INDEPENDENCE: Enrolling phase 3 trial to study the efficacy and safety of luspatercept versus placebo in patients with myelofibrosis on Janus kinase 2 inhibitor therapy requiring red blood cell transfusions

MPN-346

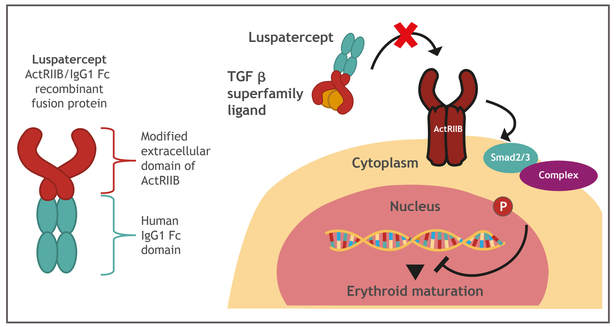
Jean-Jacques Kiladjian,[1] Claire Harrison,[2] Ruben A. Mesa,[3] Haifa K. Al-Ali,[4] John Mascarenhas,[5] Fabian Sanabria,[6] Julie Vienne Bürki,[6] Bourras-Rezki Bengoudifa,[6] Francesco Passamonti[7]

[1]Hôpital Saint-Louis et Université Paris Diderot, Paris, France; [2]Guy's and St Thomas' NHS Foundation Trust, London, UK; [3]Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC, USA; [4]Universitätsklinikum Halle (Saale), Halle, Germany; [5]Icahn School of Medicine, Mount Sinai, New York, NY, USA; [6]Bristol Myers Squibb, Boudry, Switzerland; [7]Università di Milano Statale, Policlinico di Milano, Ospedale Maggiore, Fondazione I.R.C.C.S. Ca Granda; Milano, Italy

Introduction

- Myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) is a clonal myeloid neoplasm characterized by defective bone marrow (BM) function, BM fibrosis, ineffective erythropoiesis, and increased risk of progression to acute myeloid leukemia[1]
  - Nearly 40% of patients with MF present with anemia at diagnosis, and eventually all patients with MF develop anemia[2,3]
  - Transfusion-dependent MF-associated anemia is associated with poor survival, and available treatment options are limited[2,4]
- Mutations in the Janus kinase 2 (*JAK2*) gene are present in approximately 60%–65% of patients with primary MF, while calreticulin (*CALR*) or thrombopoietin receptor (*MPL*) mutations are present in 20%–25% and 5% of patients respectively; around 10% of patients with primary MF have no detectable mutations in *JAK2*, *CALR*, or *MPL*[5,6]
- Mutations in the *JAK2*, *CALR*, and *MPL* genes lead to constitutively activated JAK2/signal transducer and activator of transcription signaling pathway and subsequent clonal expansion[7]
- Luspatercept is a first-in-class erythroid maturation agent that binds to select transforming growth factor beta (TGF β) superfamily ligands to diminish small mothers against decapentaplegic (Smad) 2/3 signaling and enhance late-stage erythropoiesis[8] (**Figure 1**)

Figure 1. Luspatercept structure and proposed mechanism of action



ActRIIB, activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; P, phosphate.

- Luspatercept is approved in both the EU and the US for treatment of anemia in patients with β-thalassemia who require red blood cell (RBC) transfusions (RBCTs) and in patients with lower-risk myelodysplastic syndromes with ring sideroblasts who did not respond to erythropoiesis-stimulating agent (ESA) treatment and require RBCTs[9,10]
- In a preliminary analysis of a phase 2 trial (NCT03194542), 26.3% of RBCT-dependent, ruxolitinib-treated patients with MF-associated anemia achieved ≥ 12 weeks of RBCT independence (RCB-TI) with luspatercept within the first 24 weeks of treatment[11]
- The INDEPENDENCE trial (NCT04717414) is a phase 3, double-blind, randomized trial evaluating the efficacy and safety of luspatercept compared with placebo in patients with MPN-associated MF and anemia on concomitant JAK2 inhibitor therapy and who require RBCTs
- Here, we report the study design, patient eligibility criteria, and study endpoints of the currently enrolling phase 3 INDEPENDENCE trial

Methods

Study design

- Approximately 309 eligible patients receiving concomitant JAK2 inhibitor therapy and who require RBCTs will be randomized 2:1 to either luspatercept or placebo, administered subcutaneously (SC) every 3 weeks
  - The starting dose of luspatercept is 1.33 mg/kg with titration allowed up to 1.75 mg/kg; dose reduction is allowed during the treatment phase
- Randomization stratification factors include:
  - RBCT burden at baseline
    - 4–5 RBC units/12 weeks before randomization
    - 6–12 RBC units/12 weeks before randomization
  - Dynamic International Prognostic Scoring System score at baseline
    - Intermediate-1/Intermediate-2
    - High risk
- Best supportive care (BSC) is allowed
- Patients who reach the end of week 24 of treatment will undergo a response assessment evaluation (day 169) to confirm whether they had clinical benefit and to assess their eligibility to continue treatment in the blinded extension phase (**Figure 2**)
- Clinical benefit is defined as:
  - RBC-TI for any consecutive ≥ 12-week period during the first 24 weeks of treatment
  - A reduction in RBCT burden by ≥ 50% and by ≥ 4 RBC units for ≥ 12 weeks immediately up to study day 169, or an incomplete duration of response (defined as being RBCT free for ≥ 4 weeks immediately up to study day 169)

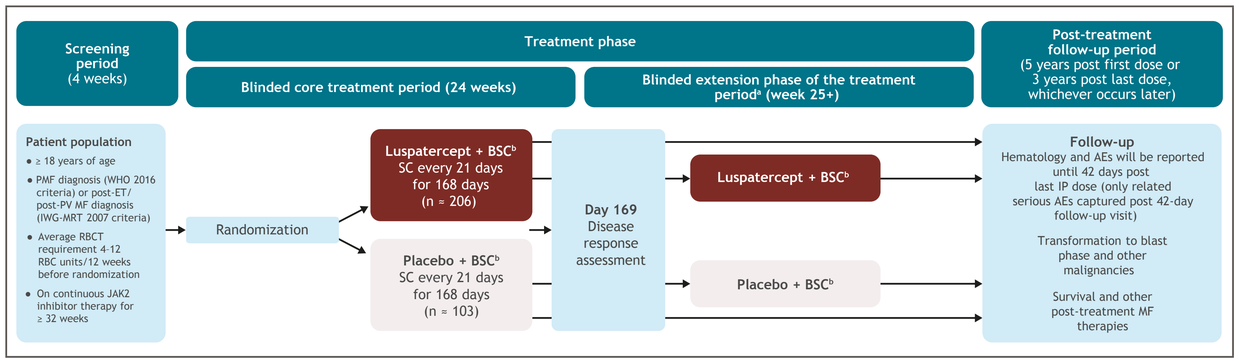
Key patient inclusion criteria

- ≥ 18 years of age at the time of providing written informed consent
- Diagnosis of primary MF (PMF) (per WHO 2016 criteria), post-essential thrombocythemia (ET) MF, or post-polycythemia vera (PV) MF (per International Working Group for Myelofibrosis Reasarch and Treatment [IWG-MRT] 2007 criteria)
- Requirement of regular RBCTs (4–12 RBC units/12 weeks prior to randomization)
- Concomitant JAK2 therapy for ≥ 32 weeks (stable daily dose for ≥ 16 weeks) before randomization
- Eastern Cooperative Oncology Group performance score ≤ 2

Key patient exclusion criteria

- Anemia due to causes other than MPN-associated MF or JAK2 therapy
- Prior use of hydroxyurea, immunomodulatory compounds (eg, pomalidomide, thalidomide), ESAs, androgenic steroids, or other drugs influencing hematopoiesis ≤ 8 weeks prior to randomization
- Uncontrolled hypertension, heart disease, or systemic fungal, bacterial, or viral infection
- Prior history of malignancies (except basal/squamous cell skin carcinoma, cervix carcinoma, breast carcinoma, or prostate cancer)
- Planned or prior hematopoietic cell transplant
- Stroke, myocardial infarction, deep venous thrombosis, or pulmonary or arterial embolism in the 6 months prior to randomization
- Prior use of sotatercept or luspatercept

Figure 2. INDEPENDENCE trial design



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[a]Patients on study can be unblinded after analysis of the primary endpoint and with data monitoring committee consultation. Patients receiving placebo have the opportunity to receive luspatercept treatment and be treated for ≥ 24 weeks in the open-label extension treatment period as long as they continue to demonstrate benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation. [b]BSC includes RBCTs, iron chelation therapy, and/or antibiotic, antiviral, or antifungal therapy.

AE, adverse event; IP, investigational product.

Results

Study endpoints

- The primary endpoint is the proportion of patients who achieve RBC-TI for any consecutive ≥ 12-week period starting from randomization up to and including week 24 of study
- The key secondary endpoint is the proportion of patients who become RBCT free over any consecutive ≥ 16-week period starting from randomization up to and including week 24 of study
- Other secondary endpoints include: maximum duration of RBC-TI response, cumulative duration of all separate ≥ 12-week episodes of RBC-TI for patients experiencing multiple episodes of RBC-TI response, proportion of patients achieving a ≥ 50% reduction in RBCT burden with a reduction of ≥ 4 RBC units transfused from baseline over any consecutive 12-week interval, mean hemoglobin increase ≥ 1 g/dL from baseline over any consecutive 12-week period in the absence of RBCTs, and change in serum ferritin levels from baseline

Safety

- Key safety assessments include: AE reporting (frequency, severity, and seriousness of AEs), prior/concomitant medicines/procedures, serum chemistry, hematology assessments, urinalysis/urine chemistry, electrocardiogram, vital signs and body weight, and monitoring for transformation to blast phase and other malignancies/premalignancies

Study status

- The study opened to enrollment in February 2021
  - The protocol was amended on December 9, 2022, to allow patients without clinical benefit at day 169 assessment to unblind and those on placebo to crossover to the treatment arm
- Target enrollment is 309 patients (206 receiving luspatercept and 103 receiving placebo)
  - As of May 2023, 53% (164/309) of the planned patients have been enrolled globally across 21 countries and 150 activated sites in Europe, North America, Asia, and Australia
  - Enrollment is currently ongoing
  - Of the 150 activated study sites, 11 have been closed/deactivated
- The trial is registered at ClinicalTrials.gov (NCT04717414)
- If you have a patient who could benefit from participation in this trial, please contact Clinical.Trials@bms.com (+1-855-907-3286)

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