Essai Clinique

Généré le 03 mai 2024 à partir de

Titre	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 JAK Inhibitor Therapy and Who Require Red Blood Cell Transfusions
Protocole ID	INDEPENDENCE (ACE-536-MF-002)
ClinicalTrials.gov ID	NCT04717414
Type(s) de cancer	NMP : Vaquez , Thrombocythémie essentielle, Métaplasie myéloide
Phase	Phase III
Type étude	Clinique
Médicament	Luspatercept versus placebo
Institution	CIUSSS DE L'ESTRIE – CENTRE HOSP. UNIV. DE SHERBROOKE H HOPITAL FLEURIMONT 3001 12e Avenue Nord, Sherbrooke, QC, J1H 5N4
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But étude	The purpose of this Phase 3 study is to evaluate the efficacy and safety of Luspatercept compared with placebo in subjects with myeloproliferative neoplasm (MPN)-associated Myelofibrosis (MF) and anemia on concomitant Janus kinase 2 (JAK2) inhibitor therapy and who require red blood cell count (RBC) transfusions.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 Posttreatment Follow-up Period.
Critères d'éligibilité	Subjects must satisfy the following criteria to be randomized in the study: • Subject is ≥18 years of age at the time of signing the ICF. • Subject has a diagnosis of PMF according to the 2016 World Health Organization (WHO) criteria or diagnosis of post-ET or post-PV MF according to the IWG-MRT 2007 criteria , confirmed by the most recent local pathology report. • 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. • 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 MPN-associated 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. • Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2. • 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. 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. • 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. *True abstinence is acceptable when it is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.] ** Agreement to use highly effective methods of contraception that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly throughout the course of the study. Such methods include: Combined (estrogen and progestogen containing) hormonal contraception: Oral, Intravaginal, Transdermal; Progestogen-only hormonal contraception associated with inhibition of ovulation: Oral, Injectable hormonal contraception, Implantable hormonal contraception; Placement of an intrauterine device (IUD); Placement of an intrauterine hormone-releasing system (IUS); Bilateral tubal occlusion; Vasectomized partner; Sexual Abstinence. • Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted. • 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.

Critères d'exclusion	The presence of any of the following will exclude a subject from randomization:
	• Subject with anemia from cause other than MPN-associated MForJAK2 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).
	• 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.
	  • 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.
	  • Iron chelation therapy (ICT) is permitted providing the subject is receiving a stable dose for the 8 weeks immediately up to randomization.
	• Subject with any of the following laboratory abnormalities at screening:
	  • Neutrophils: < 1 x 109/L
	  • White blood count (WBC): > 100 x 109/L
	  • Platelets: the lowest allowable level as approved for the concomitant JAK2 inhibitor but not < 25 x 109/L or > 1000 x 109/L
	  • Peripheral blood myeloblasts:> 5%
	  • Estimated glomerular filtration rate:< 40 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)
	  • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT):> 3.0 x upper limit of normal (ULN)
	  • 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)
	• 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.
	• 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:
	  • 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)
	• Subject with prior hematopoietic cell transplant or subject anticipated to receive a hematopoietic cell transplant during the 24 weeks from the date of randomization.
	• Subject with stroke, myocardial infarction, deep venous thrombosis, pulmonary or arterial embolism within 6 months immediately up to the date of randomization.
	• 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.
	• 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.
	• Subject with inadequately controlled heart disease and/or have a known left ventricular ejection

fraction < 35%.

- 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).
- 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.
- Subject with prior therapy of luspatercept or sotatercept.
- Subject with history of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product.
- Pregnant or breastfeeding females.
- Subject participation in any other clinical protocol or investigational trial that involves use of experimental therapy (including investigational agents) and/or therapeutic devices within 30 days or for investigational agents within five half-lives, whichever comes later, immediately up to the date of randomization.
- Subject with any significant medical condition, laboratory abnormality, psychiatric illness, or is considered vulnerable by local regulations (eg, imprisoned or institutionalized) that would prevent the subject from participating in the study or places the subject at unacceptable risk if he/she were to participate in the study.
- Subject with any condition or concomitant medication that confounds the ability to interpret data from the study.