The COMMANDS trial: a phase 3 study of the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anemia due to Revised International Prognostic Scoring System Very Low-, Low-, or Intermediate-risk myelodysplastic syndromes in erythropoiesis stimulating agent-naive patients who require red blood cell transfusions

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Introduction

• Studies of epoetin alfa and darbepoetin alfa have demonstrated efficacy among patients with LR-MDS, but the patient population in which a clinically significant effect is observed may be limited\(^1,2\).

• Luspatercept, a first-in-class erythroid maturation agent with a mechanism of action distinct from ESAs,\(^3\) is approved by the US FDA for the treatment of anemia failing an ESA and requiring 2 or more RBC units over 8 weeks in adult patients with Very Low- to Intermediate-risk MDS with RS or with MDS/MPN-RS-T.

• Luspatercept may also be beneficial in treating anemia in patients with ESA-naive LR-MDS who require RBC transfusions.

Study objectives

• COMMANDS is a randomized, open-label, phase 3 trial to evaluate the efficacy and safety of luspatercept versus epoetin alfa in anemic patients with IPSS-R-defined LR-MDS, either with or without \(\geq 15\%\) RS, who are ESA naive, and who require regular RBC transfusions.
The COMMANDS trial study design

Screening
Eligibility check

Randomization 1:1
(N = 350)

Luspatercept
(ACE-536)
1.0 mg/kg s.c. Q3W;
titration up to
1.75 mg/kg max.

Epoetin alfa
450 IU/kg s.c. QW
(max. total dose 40,000 IU);
titration up to 1,050 IU/kg
(max. total dose 80,000 IU)

MDS disease status assessment
24-week MDS disease assessment visit (Day 169 [i.e. 168 days after first dose of IP])

Continuation of treatment
MDS disease status assessment every 24 weeks

End of treatment (EOT)
Continue treatment unless discontinued early for evidence of progression,
death, unacceptable toxicity, patient/physician decision, or withdrawal of consent

Post-treatment follow-up
42-day follow-up: AE reporting until 42 days after last dose of IP
Collection of transfusion data: ≥ 8 weeks after last dose of IP or until EOT (whichever is later)
Long-term follow-up: monitoring for other malignancies/pre-malignancies, progression to AML, subsequent MDS therapies, and survival for 5 years from the date of the last dose of IP, or 3 years from the last dose (whichever occurs later), unless the patient withdraws consent from the study, dies, or is lost to follow-up

Study discontinuation

**Notes:**
- Crossover between the treatment arms is not permitted during the study treatment period.
- Individual epoetin alfa doses according to body weight will be rounded up to the next 2,000 IU dose level for starting dose level and dose level −1, and up to the next 4,000 IU for dose level +1 and dose level +2 for doses exceeding a calculated dosing of 56,000 IU according to body weight.
- AE, adverse event; AML, acute myeloid leukemia; EOT, end of treatment; IP, investigational product; IU, international units; MDS, myelodysplastic syndromes; QW, once every week; Q3W, once every 3 weeks; s.c., subcutaneous.
Methods - patient main eligibility criteria

• Inclusion criteria
  – Age ≥ 18 years at time of consent
  – Documented diagnosis of IPSS-R-defined LR-MDS with < 5% blasts in the bone marrow
  – Serum EPO levels < 500 U/L
  – An average RBC transfusion requirement of 2-6 units RBCs/8 weeks for ≥ 8 weeks immediately prior to randomization

• Exclusion criteria
  – Prior use of ESAs (≤ 2 doses of prior epoetin alfa permitted if ≥ 8 weeks from randomization date and serum EPO confirmed as ≤ 500 U/L)
  – Prior use of G-CSF or GM-CSF, unless given for the treatment of febrile neutropenia
  – Prior use of disease-modifying agents (e.g. lenalidomide) or hypomethylating agents
  – Presence of del(5q) cytogenetic abnormality

EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; U, units.
Methods - randomization and treatment

• Approximately 350 eligible patients will be randomized in a 1:1 ratio to receive either luspatercept (starting dose 1.0 mg/kg with titration up to 1.75 mg/kg) subcutaneously once every 3 weeks or epoetin alfa (starting dose 450 IU/kg with titration up to 1,050 IU/kg) subcutaneously once every week, for a minimum of 24 weeks

• Best supportive care, including RBC transfusions, may be used in combination with study treatment in both arms

• Randomization stratification factors
  – Baseline RBC transfusion burden (< 4 vs ≥ 4 units RBCs per 8 weeks)
  – RS status (with RS+ defined as RS ≥ 15%, or ≥ 5% if SF3B1 mutation is present)
  – Baseline serum EPO level (≤ 200 U/L vs > 200 U/L)
  – In addition, ≥ 40% and ≤ 60% of randomized patients will be RS+, and ≥ 25% will have serum EPO > 200 U/L

SF3B1, splicing factor 3B subunit 1.
## Methods - study endpoints

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<tr>
<th>Endpoints</th>
<th>Description</th>
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<tr>
<td><strong>Primary</strong></td>
<td>Proportion of patients who achieve RBC-TI for ≥ 12 weeks within the first 24 weeks on study, with a concurrent mean Hb increase of ≥ 1.5 g/dL compared with baseline</td>
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| **Secondary** | RBC-TI for 24 weeks  
Mean Hb change over 24 weeks  
Achievement of HI-E response per IWG 2006 criteria  
Time to achieve HI-E  
Safety (type, frequency, severity of AEs)  
Progression to AML |

Hb, hemoglobin; HI-E, hematologic improvement–erythroid; IWG, International Working Group; RBC-TI, red blood cell transfusion independence.
Clinical trial information

• This trial is currently recruiting patients. If you have a patient who could benefit from participation in this trial, please contact:
  – Dr Rodrigo Ito, MD, 86 Morris Avenue, Building A 146, Summit, NJ 08543, USA
  – Office phone: +1 (908) 673-2936
  – E-mail: Rodrigo.Ito@bms.com

• The COMMANDS trial is registered at ClinicalTrials.gov (NCT03682536) and EudraCT (number 2017-003190-34)
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