22 February 2024
EMA/112157/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Reblozyl

International non-proprietary name: Luspatercept

Procedure No. EMEA/H/C/004444/II/0021

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

1L	first line
ADA	antidrug antibodies
AE	adverse event
AML	acute myeloid leukemia or acute myelogenous leukemia
BSC	best supportive care
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
ECOG	Eastern Cooperative Oncology Group
EMH	extramedullary hematopoiesis
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
EP	erythroid precursors
E-R	exposure-response
ESA	erythropoiesis stimulating agent
ESMO	European Society for Medical Oncology
FACT-An	Functional Assessment of Cancer Therapy - Anemia
FACT-G	Functional Assessment of Cancer Therapy - General
Hb	hemoglobin
HI-E	hematologic improvement – erythroid response
HI-N	hematologic improvement – neutrophil response
HI-P	hematologic improvement – platelet response
HR	hazard ratio
HRQoL	health-related quality of life
HTB	high transfusion burden
IA	interim analysis
IP	investigational product
IPSS-R	International Prognostic Scoring System-Revised
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent to treat
IU	international unit

IWG	International Working Group
LEN	lenalidomide
LTB	low transfusion burden
LTE	long term efficacy
LTFU	long-term follow-up
MDS	myelodysplastic syndromes
MDS-MLD	MDS with multilineage dysplasia
MDS-RS	MDS with ring sideroblasts
MDS-SLD	MDS with single lineage dysplasia
MDS/MPL	myelodysplastic/myeloproliferative neoplasms
MID	minimally important difference
NCCN	National Comprehensive Cancer Network
NA	not applicable
NE	not evaluable
OS	overall survival
PK	pharmacokinetics
pRBC	packed red blood cell
PRO	patient reported outcome
PY	person years
QW	once weekly
Q3W	every 3 weeks
QoL	quality of life
QUALMS-P	Quality of Life in Myelodysplasia Scale - Physical Burden
RBC	red blood cell
RBC-TI	red blood cell transfusion independence
RD	risk difference
RS	ring sideroblast
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation
SE	standard error
sEPO	serum erythropoietin

Smad2/3	suppressor of mothers against decapentaplegic
TD	transfusion dependent
TEAE	treatment emergent adverse event
TGFβ	tumor growth factor beta
UK	United Kingdom
US	United States
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 7 March 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), based on results from study ACE-536-MDS-002 (COMMANDS), an active-controlled, open-label, randomized Phase 3 study comparing the efficacy and safety of luspatercept vs epoetin alfa in adult subjects with anemia due to IPSS-R very low, low or intermediate risk MDS, who are ESA naïve and require RBC transfusions, and studies ACE-536-MDS-001(MEDALIST), ACE-536-MDS-004 , A536-03, A536-05 and ACE-536-LTFU-001; As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Reblozyl was designated as an orphan medicinal product EU/3/14/1300 on 29.07.2014 in the following condition: treatment of beta (β)-thalassaemia intermedia and major.

Reblozyl was designated as an orphan medicinal product EU/3/14/1331 on 22.08.2014 in the following condition: treatment of myelodysplastic syndromes (MDS).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0254/2018 and P/0155/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001521-PIP01-13-M06 was not yet completed as some measures were deferred.

Similarity

Information relating to orphan market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition

related to the proposed indication.

Protocol assistance

The MAH received Protocol assistance from the CHMP on 22 March 2018 (EMA/CHMP/SAWP/152357/2018) and 14 December 2017 (EMA/CHMP/SAWP/791152/2017). The Protocol assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Ewa Balkowiec Iskra

Timetable	Actual dates
Submission date	7 March 2023
Start of procedure:	25 March 2023
CHMP Rapporteur Preliminary Assessment Report	19 May 2023
PRAC Rapporteur Preliminary Assessment Report	26 May 2023
PRAC Outcome	8 June 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 June 2023
Request for supplementary information and extension of timetable adopted by the CHMP on	22 June 2023
MAH's responses submitted to the CHMP on	10 August 2023
CHMP Rapporteur Preliminary Assessment Report	12 September 2023
PRAC Rapporteur Preliminary Assessment Report	15 September 2023
PRAC members comments	20 September 2023
PRAC Outcome	28 September 2023
CHMP members comments	02 October 2023
Updated CHMP Rapporteur Assessment Report	6 October 2023
2nd Request for supplementary information and extension of timetable adopted by the CHMP on	12 October 2023
MAH's responses submitted to the CHMP on	20 December 2023
CHMP Rapporteur Preliminary Assessment Report	23 January 2024
PRAC Rapporteur Preliminary Assessment Report	26 January 2024
PRAC members comments	31 January 2024
PRAC Outcome	08 February 2024
CHMP members comments	12 February 2024
Updated CHMP Rapporteur Assessment Report	20 February 2024
CHMP Opinion	22 February 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Myelodysplastic syndromes (MDS)

MDS are a group of clonal bone marrow (BM) neoplasms, which represent the most common class of acquired BM failure syndromes in adults (Ades, 2014; Bejar, 2014). Myelodysplastic syndromes are characterised by ineffective haematopoiesis, in which haematopoietic progenitor cells have reduced ability to differentiate and increased likelihood of apoptosis (Ades, 2014; Foran, 2012). This manifests in abnormal 'dysplastic' cell morphology in one or more haematopoietic cell lines and development of peripheral cytopenias (Ades, 2014; Bejar, 2014; Foran, 2012). Approximately two-thirds of patients with MDS are anemic at diagnosis and nearly all experience severe anemia during the disease (Steensma, 2006). Chronic anemia (ie, average Hgb levels < 10 g/dL) progressively leads to the requirement of regular RBC transfusions that carry both short-term and long-term risks (Buckstein, 2022). Short-term complications include allergic reactions, anaphylaxis, infections, volume overload, and long-term complications that include organ toxicity due to iron overload and worsened overall survival (Buckstein, 2022; Braga, 2021). The main therapeutic objectives for lower-risk MDS are to correct chronic anemia, achieve TI, optimise QoL, and treat cytopenias. In very low-, low-, or intermediate-risk MDS defined by the IPSS-R, patients' unmet medical need is primarily underlying cytopenia, most often anemia, rather than disease progression and decreased survival (Greenber, 2012).

In approximately 30% of patients with MDS, abnormal cell morphology/biology results in the potential for clonal evolution and development of acute myeloid leukemia (AML) (Bejar, 2014; da Silva-Coelho, 2017).

In the MDS Multicentre Registry study, the median time of survival from diagnosis was 75 months (range, 1.7 to 350 months). The 2- and 5-year survival probabilities were 86% and 61%, respectively. Transfusion-dependent (TD) patients had a median survival of 44 months compared to 97 months for transfusion-independent patients (Germing, 2012).

State the claimed the therapeutic indication

The MAH applied for the following indication: "Reblozyl is indicated for the treatment of adult patients with anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), who may require red blood cell (RBC) transfusions (see section 5.1)".

The CHMP agreed with the following indication: "Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS)."

Epidemiology

An analysis of 64 cancer registries from European countries indicates that the incidence of MDS was 1.5 per 100,000 individuals per year in 1995–2002 (Visser, 2012). Data from the Dusseldorf registry in Germany suggest that the crude incidence of MDS in 2002–2005 was approximately 4 per 100,000 person-years (3.40 for MDS as defined by World Health Organization [WHO] subtypes versus 4.15 using French-American-British [FAB] classification) (Neukirchen, 2011). The annual incidence of MDS reported by the Haematological Malignancy Research Network (HMRN) in the UK between 2010 and 2016 is 3.5 per 100,000 (HMRN, 2019). Incidence of MDS extracted from population-based registries such as SEER in the US and similar databases worldwide may not accurately capture the true number of MDS cases due to underdiagnoses and underreporting (Cogle, 2011). Data consistently demonstrate that MDS is most commonly diagnosed in patients with a median age at diagnosis in the seventh decade (Ma, 2012; Neukirchen, 2011) and is reported more frequently in men versus women (Ma, 2007; Neukirchen, 2011; Visser, 2012).

Biologic features, aetiology and pathogenesis

The cause of MDS is known only in 15% of cases (Ades, 2014; Fenaux, 2014). In approximately 30% of pediatric patients with MDS, the disease is due to an inherited predisposition, such as Down's syndrome, Fanconi anaemia, and neurofibromatosis (Ades, 2014; Fenaux, 2014). In adult patients without inherited predisposition, MDS may be attributed to a number of factors, including older age, prior treatment with chemotherapy agents or radiotherapy, and exposure to environmental irritants (Ades, 2014; Fenaux, 2014; Foran, 2012). Advanced age is the single greatest risk factor (Sekeres, 2010).
An abnormal karyotype is observed in approximately 40% to 60% of *de novo* MDS cases and 50% to 80% of cases in which prior therapy resulted in MDS (Ades, 2014; Bejar, 2014; Haase, 2007; Visconte, 2014a). Unlike AML, MDS is characterised by partial or complete loss or gain of chromosomes, the most frequent being: deleted 5q; −7 or deleted 7q; +8; deleted 20q; and deleted 17p (Ades, 2014). The chromosomal abnormality del(5q) leads to haplo-insufficiency of a variable number of genes according to the extent of the deleted region (Ades, 2014) and is one of the best understood pathogenic mechanisms in MDS.
Almost 80% of patients with MDS carry at least one mutation in one gene (Papaemmanuil, 2013). While founder mutations drive asymptomatic local expression, further mutations acquired within a clone will subsequently impair normal haematopoiesis, alter blood counts, and ultimately result in overt MDS (Kennedy, 2017; Papaemmanuil, 2013). Indeed, genomic instability (genetic defects, mutations) increases the propensity to develop AML (Papaemmanuil, 2013; Visconte, 2014a).

Clinical presentation, diagnosis and stage/prognosis

Many patients with MDS are asymptomatic; the lack of specific symptoms among patients with lower-risk MDS is a major diagnostic challenge (Foran, 2012). Diagnosis is often made during assessment of comorbidities, when peripheral blood or bone marrow (BM) features associated with MDS are revealed. Differential diagnosis is informed by the patient's medication history; exclusion of diseases, such as autoimmune disorders, renal failure, malignancies, chronic infections or inflammations, aplastic anaemia, and paroxysmal nocturnal haemoglobinuria, is also important (Fenaux, 2014).
The clinical presentation of MDS is heterogeneous and varies depending on the subtype and severity of the cytopenia (Foran, 2012). Anaemia is the most common peripheral erythroid maturation defect, occurring in 80% to 85% of cases (Steensma, 2006). Many patients with MDS who develop anaemia, particularly those with Revised International Prognostic Scoring System (IPSS-R) lower-risk MDS (approximately 40%), become transfusion dependent (Zeidan, 2013; Ades, 2014). Thrombocytopenia is observed in 30% to 45% of patients with MDS and neutropenia in 40% of patients (Steensma, 2006).

Symptoms are usually nonspecific but may be suggestive of the cytopenia involved. Fatigue and a decline in activities of daily living or quality of life (QoL) are indicative of anaemia. Recurrent infections may be related to neutropenia, and frequent and unexplained bruising or bleeding is suggestive of thrombocytopenia (Ades, 2014; Foran, 2012; Toma, 2012).
Patients with higher-risk MDS present with more severe symptoms (Foran, 2012). Analysis of the BM and blood samples is central to the diagnosis (Ades, 2014; Fenaux, 2014) and facilitates the exclusion of non-MDS causes of cytopenias (Ades, 2014; Bejar, 2014; Zini, 2017). Analysis of somatic mutations and flow cytometry analysis of BM cells can be useful when a diagnosis of MDS is uncertain (Fenaux, 2014).

Management

The main clinical guidance for the management of MDS in Europe is the European Society for Medical Oncology (ESMO) (Fenaux, 2014). Management of patients with MDS differs depending on the ultimate goal of treatment for each individual (Zeidan, 2013; Zeidan, 2017). Treatment of MDS is complicated by the advanced age of the affected population and, thus, high incidence of comorbid conditions and relative inability of patients to tolerate intensive treatment approaches (Greenberg, 2017). In addition, there is a growing role for consideration of genetic and epigenetic lesions in therapeutic decision-making.

• Patients with lower-risk MDS have a lower likelihood of AML progression and a longer survival expectancy (Fenaux, 2014); management of this population is focused on treating cytopenias (predominantly anaemia) and optimising QoL (Fenaux, 2014).

• Patients with higher-risk MDS are at greater risk of progression to AML and have shorter survival expectancy (Fenaux, 2014). Consequently, the aim of treatment in this population is to modify the natural disease course (Fenaux, 2014).

All patients with MDS receive supportive care (NCCN, 2021), which may include blood transfusions, clinical monitoring, management of iron overload, QoL assessment, granulocyte-colony stimulating factor (G-CSF) and psychosocial support (Fenaux, 2014; NCCN, 2021).

Treatment of IPSS-R Lower-risk Patients with MDS

The main focus of management in patients with IPSS-R lower-risk MDS is the treatment of cytopenia(s) and the improvement of QoL (Fenaux, 2014). The specific treatment approach will differ according to the type of cytopenia(s) observed, and there are benefits and challenges associated with currently available first-line treatment options. The majority (80% to 85%) of patients with MDS develop anaemia (Steensma, 2006). Erythropoiesis-stimulating agents (ESAs) are the first-line treatment option for anaemia in lower-risk MDS patients without del(5q) (Fenaux, 2014; NCCN, 2021). Despite an initial response to ESA treatment, approximately 70% of patients will become unresponsive to ESAs (Park, 2017). Careful monitoring for disease progression and consideration of the patient's preferences remain important factors in the tailoring of treatment in this population (NCCN, 2021).

Erythropoiesis-stimulating Agents

As anaemia is the most common cytopenia among patients with lower-risk MDS (Steensma, 2006), it tends to be the focus of treatment in this population (Fenaux, 2013; Fenaux, 2014). Erythropoiesis-stimulating agents, with or without granulocyte-colony stimulating factor (G-CSF), are used in patients with lower-risk MDS without del(5q) (Fenaux, 2014; NCCN, 2021). The major favourable prognostic factors for response to ESAs are low (< 2 units/month) or no RBC transfusion requirement and baseline serum EPO level < 500 U/L (Fenaux, 2013). The European ESA Scoring System uses a serum EPO level of ≤ 200 U/L as a prognostic factor for ESA responsiveness (Santini, 2013). Despite an initial response to ESA treatment, approximately 70% of patients become unresponsive to ESAs (Park, 2017).

Erythroblast differentiation and maturation during late-stage erythropoiesis is independent of the effect of erythropoietin (Eshghi, 2007; Hattangadi, 2011). Mutations in SF3B1 can cause impaired late-stage RBC differentiation (Obeng, 2016).

There are limited treatment options for lower-risk MDS patients who fail treatment with ESAs or have poor prognostic factors of response to ESAs (Santini, 2016). The second-line treatment options are restricted to anti-lymphocyte globulin and anti-thymocyte globulin (immunosuppressive therapies) in the < 60 to 65-year age category, and azacitidine and lenalidomide, both of which are myelosuppressants. Outcomes remain suboptimal despite the use of these second-line treatment options, and many patients will ultimately require long-term RBC transfusions (Fenaux, 2014; NCCN, 2021).

Lenalidomide

Lenalidomide (Revlimid) is recommended treatment of lower-risk patients with MDS with del(5q) (Fenaux, 2014; NCCN, 2021). In Europe, lenalidomide is indicated for use in adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate (Revlimid SmPC, 2019). Lenalidomide in MDS patients with del(5q) yields RBC-transfusion independence (RBC-TI) in two-thirds of this population for a median duration of 2 to 3 years, and cytogenetic responses in 50% to 70% of patients (Ades, 2014). The most common Grade 3 or 4 adverse events included myelosuppression (neutropenia, 55%; thrombocytopenia, 44%) that often requires treatment interruption or dose reduction (NCCN, 2021).

Red Blood Cell Transfusions

RBC transfusion forms the mainstay of treatment in patients with lower-risk MDS and anaemia. Many patients become transfusion dependent, which is associated with increased morbidity, a reduced QoL, and high social burden (Fenaux, 2013; Hellström-Lindberg, 2013; Platzbecker, 2012).

There is no internationally recognised haemoglobin level threshold below which transfusion should be given, and the use of transfusion should be tailored to the individual patient based on comorbidities (e.g., lung and cardiac function, the individual's level of physical activity) (Hellstrom-Lindberg, 2013). Guidelines based on expert opinion, such as those provided by ESMO, recommend administering transfusions at haemoglobin levels starting in the 8 to 10 g/dL range, since patients with comorbidities, poor functional tolerance, or poor QoL may experience significant clinical benefit from transfusions (Fenaux, 2014).

Red blood cell transfusions are time consuming, can have a deleterious effect on a patient's social functioning, increase the patient's dependence on the medical system, affecting the use of hospital resources and the supply of RBC concentrates (Fenaux, 2013; Hellström-Lindberg, 2013; Platzbecker, 2012). Chronic transfusions lead to secondary iron overload. The relatively long survival of low- and intermediate-risk MDS groups (Greenberg, 2006; Valent, 2007) places them at an increased risk of damage by iron overload from prolonged red blood cell transfusions compared to high-risk patients with a markedly reduced survival (Steensma, 2006). The MDS population consists mainly of elderly patients with comorbid conditions and a propensity to develop cardiac failure, infection, haemorrhage, and hepatic cirrhosis; iron overload may exacerbate these pre-existing conditions (Malcovati, 2005).

Iron Chelation Therapy

Iron chelation may be required in patients receiving frequent transfusions in order to avoid iron-related cardiac, hepatic, and endocrine toxicities (Fenaux, 2014; Platzbecker, 2012; Steensma, 2013). As such, monitoring of the number of RBC transfusions, cardiac function with magnetic resonance imaging, and serum ferritin levels is recommended (NCCN, 2018).

There is a lack of consensus on the use of iron chelation in patients with lower-risk MDS. Initiation of iron

chelation is generally recommended in management guidelines although specific treatment thresholds and prescribing practice vary (Fenaux, 2014; NCCN, 2018). Guidelines generally advocate starting iron chelation in patients with a relatively favourable prognosis (e.g., IPSS low- or intermediate-1-risk MDS), who have received 20 to 60 RBC concentrates, or if serum ferritin rises above 1000 U/L (Bennett, 2008; Fenaux, 2014; Malcovati, 2013).

Luspatercept

In Europe luspatercept is licensed since 2020 as a second line treatment option for adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy. In the US luspatercept is also indicated as second line therapy for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

Unmet Medical Need

The majority (80% to 85%) of patients with MDS develop anaemia (Steensma, 2006). Erythropoiesis-stimulating agents are the first-line treatment option for anaemia in lower-risk patients with MDS without del(5q); lenalidomide is the recommended treatment for patients with del(5q) (Fenaux, 2014; NCCN, 2018), luspatercept only as second line therapy after unsuccessful therapy with erythropoiesis stimulating agent (SmPC REBLOZYL; NCCN, 2021). Despite an initial response to ESA treatment, approximately 70% of patients will become unresponsive to ESAs (Park, 2017). In addition, ESAs are less effective in patients with either endogenous EPO level ≥ 200 U/L or those requiring RBC transfusion of ≥ 2 units/month.

Treatment options remain suboptimal in the lower-risk MDS patients who are not eligible or no longer respond to ESAs, and many patients will ultimately require long-term RBC transfusions (Fenaux, 2014; NCCN, 2021). Red blood cell-transfusion dependence and lower haemoglobin levels have been associated with a deleterious impact on outcomes and increased mortality in patients with MDS (Platzbecker, 2012; Fenaux, 2013; Hellström-Lindberg, 2013).

2.1.2. About the product

Luspatercept (REBLOZYL; BMS-986346; ACE-536; ATC code: B03XA06) is a recombinant fusion protein comprised of the modified extracellular domain of human ActRIIB linked to the Fc domain of human IgG1. Luspatercept binds selectively to transforming growth factor-beta (TGF-β) superfamily ligands. By binding to specific endogenous ligands (e.g., GDF-11, activin B), luspatercept inhibits Smad2/3 signalling, resulting in erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts) in the bone marrow. Smad2/3 signalling is abnormally high in disease models characterised by ineffective erythropoiesis, i.e., myelodysplastic syndromes (MDS) and β-thalassemia, and in the bone marrow of MDS patients.

Reblozyl is an orphan medication indicated as an erythroid maturation agent for the treatment of:

- Adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin -based therapy.
- Anaemia in adults associated with transfusion dependent and non transfusion dependent beta thalassaemia.

Reblozyl is under additional monitoring and is monitored intensively.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH sought initial Protocol Assistance (PA) from the SAWP/CHMP in October 2017 to obtain guidance on the proposed Phase 3 study design in adult subjects with very low, low or intermediate risk MDS as defined by the IPSS-R, who are naïve to ESA and are RBC-TD (EMEA/H/SA/3671/2/2017/PA/II). Follow-up PA was obtained in March 2018, specifically on the revised study design in terms of patient population, dose regimen of the comparator, and study endpoints (EMEA/H/SA/3671/2/FU/1/2018/PA/II).

Study population

As recommended by SAWP/CHMP, MDS/MPN patients were excluded. However, based on new analyses from ACE-536-MDS-001 showing benefit, a broader population was allowed to enroll (PA3). Further, as recommended, the original protocol included an enrollment cap of 40-60% of RS+ subjects. However, this cap was removed to not further impact recruitment (PA3).

The exclusion of prior treatment with G-CSF or GM-CSF were restricted to the period of 8 weeks prior to randomization, as recommended, and prior treatment of up to 2 prior doses of epoetin alfa (not darbepoetin) was allowed, with the last dose of epoetin alfa ≥ 8 weeks from the date of randomization.

However, the recommendation to limit the time separating inclusion from diagnosis (e.g. 2 years) to protect the trial from imbalances due to exceptional cases of long intervals was not followed.

Efficacy endpoints

The originally proposed primary endpoint (RBC-TI for 24 weeks from Week 1 – 24) was discouraged due to luspatercept's mechanism of action, suggesting an effect on hemoglobin levels to be faster compared to ESA. The advice to move the primary endpoint assessment to a later time-point was not followed. Instead, the primary endpoint was modified to "RBC-TI for 12 weeks (84 days) associated with a concurrent mean Hb increase ≥ 1.5 g/dL compared to baseline from randomization through Week 24". Two additional secondary endpoints were included: 1) proportion of subjects who are RBC-TI during Week 1-24 and 2) proportion of subjects who are RBC transfusion free for a consecutive 24 weeks period in the first 48 weeks of study treatment. It was emphasized that the latter is considered particularly adequate to capture clinical benefit in transfusion-dependent patients with lower risk MDS, being a direct measure of the actual proportion of patients that will overcome anaemia-and transfusion-related complications. Additional QoL measures (FACT-An as secondary endpoint and QUALMS-P as exploratory endpoint) were included, as requested.

It is however critically noted that the originally proposed and endorsed hierarchically tested secondary endpoint "Proportion of subjects achieving ≥ 1.5 g/dL mean increase in hemoglobin over the first 24 weeks from randomization compared to baseline in the absence of RBC transfusions" and "Proportion of subjects who are RBC Transfusion independence (RBC-TI) during Weeks 4-24" were finally not included in the study protocol.

2.1.4. General comments on compliance with GCP

In accordance with Article 8 (ib) of Directive 2001/83/EC, the Marketing Authorisation Holder, Bristol-Myers Squibb Pharma EEIG, confirms that clinical studies conducted outside of the European Union (EU) meet the ethical requirements of Directive 2001/20/EC.

A Potential Serious Breach of GCP was reported for study ACE-536-MDS-002. Several sites inadvertently collected additional samples (beyond the pre-specified time points in the protocol). The MAH provided information about the how and when the Serious Breach was identified. Further the results of a root cause analysis were presented together with corresponding corrective and preventive actions (CAPA).

According to the MAH the excess sampling was mainly caused by providing only one sort of sampling kit referring to a sampling schedule of "every 3 weeks" and including material for all sampling procedures that would be required for this sampling schedule. The Sponsor did not identify the excess sampling, which was not specified in the protocol, during the study. Still, the presented explanation can be followed and the proposed corrective measures to prevent such protocol violations in future studies seem reasonable.

Only PK and ADA samples have been analysed. In order to clarify whether the excess sampling data influence the overall results, plots depicting the PK profile data for all samples, samples without the excess samples and for the excess samples have been provided. Although data without the excess samples seem rather similar to the dataset containing all samples, it is noted that the excess samples seem to correspond to lower dose normalized luspatercept serum concentrations compared to the consented samples. The reasoning presented by the MAH for the claim that the inclusion or exclusion of the excess samples is unlikely to impact the final PopPK conclusions, can overall be followed (less than 10% of samples in the first year, similarity between all samples data and data without excess samples). Updated analyses are expected to be submitted by Q2 and Q3 2024 as recommendation. Depending on the results, an update of SmPC section 5.2 may be necessary.

The MAH committed to providing updated analyses for study ACE-536-MDS-002 excluding the excess samples with the Addendum to the primary CSR by the end of Q2 and updated modelling (popPK and E-R) by Q3 2024. The MAH is asked to provide not only the new analyses but also a comparison with the currently submitted results (all samples vs without excess samples). Any differences and a potential update of SmPC section 5.2 would have to be discussed.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

The luspatercept clinical development program for anemia in lower-risk MDS is extensive and continues to be active across multiple subpopulations. Study ACE-536-MDS-002 included a patient population with less favourable prognostic factors for ESA response that included patients with high transfusion burden, sEPO levels > 200 U/L, lower Hgb levels, and a higher number of somatic mutations. Key design features of the pivotal Study ACE-536-MDS-002 (also referred to as COMMANDS), and studies supporting the evidence of efficacy and safety data for the proposed indication are described in Table 1.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. However, a Potential Serious Breach has been reported. Although the integrity of the study seems to be not affected (Please see above), excess PK and ADA samples were included in the provided data. The MAH is expected to provide additional data as recommendations.

- Tabular overview of clinical studies

Table 1: Luspatercept Clinical Studies Relevant to 1L Transfusion-Dependent-MDS (Clinical Overview Table 1.4-1)

Identifier / Status	Design	Treatment Dose/Route	Treatment/Follow-up	Endpoints	No. Treated Subjects	Population/ Region
Pivotal Study						
ACE-536-MDS-002 (COMMANDS) / Ongoing	Phase 3, open-label randomized study to compare the efficacy and safety of luspatercept vs epoetin alfa for the treatment of anemia due to IPSS- R very low, low, or intermediate risk MDS	Luspatercept: Starting dose of 1.0 mg/kg SC Q3W; dose titrations to 1.33 or 1.75 mg/kg SC Q3W Epoetin alfa (EPREX® / ERYPO® [ex-US] or PROCRIT® [US]: Starting dose of 450 IU/kg SC QW; dose increases were allowed in a stepwise manner up to a max of 1,050 IU/kg	24 weeks for all subjects. Treatment continues beyond Week 24 if there is clinical benefit and absence of disease progression per IWG-MDS criteria. Post-treatment follow-up of 42 days for collection of AEs, concomitant drugs and RBC-transfusion data and 3 years from last dose or 5 years from the first dose for OS, progression to AML, other malignancies/pre-malignancies and subsequent MDS therapies	Primary: Proportion of subjects who were RBC transfusion-free for ≥ 12-weeks with a concurrent mean Hgb increase ≥ 1.5 g/dL compared to baseline. Key Secondary: Proportion of subjects who achieved HI-E over any consecutive 56-day period. During Week 1 to 24. Proportion of subjects who were RBC transfusion-free from Week 1 to 24 or over a consecutive 84-day period during Week 1 to 24.	Luspatercept: 182 Epoetin alfa: 179	ESA naive subjects with very low, low, or intermediate risk MDS who require RBC transfusions Global
Supportive Studies						
ACE-536-MDS-001 (MEDALIST)/ Completed	Phase 3, double-blind, randomized, placebo-controlled, multicenter study to compare the efficacy and safety of luspatercept vs placebo for the treatment of anemia due to IPSS- R very low, low, or intermediate risk MDS	Luspatercept: Starting dose level of 1.0 mg/kg SC Q3W; dose titrations to 1.33 or 1.75 mg/kg SC Q3W or dose reductions to 0.8, 0.6, or 0.45 mg/kg SC Q3W were permitted per protocol	24 weeks for all subjects and 48 weeks for subjects eligible to continue treatment after Week 25 visit Treatment continued beyond Week 48 if clinical benefit and absence of disease progression per IWG-MDS criteria were observed. Post-treatment follow-up of 42 days for all AEs and 3 years from last dose for OS, progression to AML, other malignancies/pre-malignancies and subsequent MDS therapies	Primary: Proportion of subjects who are RBC transfusion free over any consecutive 56-day (ie, 8-week) period during Week 1 to Week 24 Key Secondary: Proportion of subjects who are RBC transfusion free over any consecutive 84-day (ie, 12-week) period during Week 1 to Week 24 and during Week 1 to Week 48	Luspatercept: 153 Placebo: 76	ESA-refractory/ineligible subjects with very low, low, or intermediate risk MDS and RS+ who require regular RBC transfusions Global

Table 1: Luspatercept Clinical Studies Relevant to 1L Transfusion-Dependent-MDS (Clinical Overview Table 1.4-1)

Identifier / Status	Design	Treatment Dose/Route	Treatment/Follow-up	Endpoints	No. Treated Subjects	Population/ Region
ACE-536-MDS-004/Ongoing (Supporting safety analyses)	Phase 2, open-label single arm study to evaluate efficacy, pharmacokinetics and safety of luspatercept for the treatment of anemia due to IPSS- R very low, low, or intermediate risk MDS	Luspatercept: starting dose of 1.0 mg/kg through at least the first 24 calendar weeks of the study unless the subject experiences unacceptable toxicities, disease progression withdraws consent, or meets any other discontinuation criteria.	Post-treatment follow-up of 42 days for collection of AEs. Transfusion data collection will continue up until 16 weeks from the last dose of luspatercept or 16 weeks after end of treatment. Long-term follow-up starts 12 weeks after the last dose of luspatercept, and lasts until at least 3 years from the last dose.	RBC-TI ≥ 8 weeks	26	ESA-refractory Chinese and Japanese subjects with very low, low, or intermediate risk MDS and RS who require regular RBC transfusions Japan/China
Study A536-03/ Completed	Phase 2, open-label, multiple ascending dose, study of luspatercept in patients with low or intermediate-1 risk MDS	Ascending-dose cohorts: 0.125 mg/kg SC Q3W to 1.75 mg/kg SC Q3W planned; dose reductions were permitted per protocol within each cohort. Expansion cohorts: Starting dose level of 1.0 mg/kg SC Q3W; dose reductions and titrations were permitted per protocol; maximum dose of 1.75 mg/kg.	5 cycles; post-treatment follow-up 3 months from last dose for subjects not entering A536-05	Primary: Proportion of subjects with modified erythroid response, defined as: -Hgb increase of ≥ 1.5 g/dL from baseline for ≥ 14 days (in the absence of RBC transfusions) in LTB subjects -Reduction of either ≥ 4 units or ≥ 50% of units of transfused RBCs compared with pretreatment during any 8-week window in HTB subjects	Total: 116 TD: 80	Subjects with low or intermediate-1 risk MDS (Only TD subjects will be included the ISS) EU
Study A536-05/ Completed	Open-label extension study of long-term effects of Luspatercept in patients with low or intermediate -1 risk MDS previously enrolled in study A536-03	Starting dose level based on last dose level in Study A536-03 for subjects without treatment interruption. Starting dose level of 1.0 mg/kg for subjects with treatment interruption. Dose reductions and titrations were permitted	Up to 5 years; Post-treatment follow-up 3 months from last dose	Long-term safety and tolerability of luspatercept	Total: 75 TD: 43	Subjects with low or intermediate-1 risk MDS previously enrolled in study A536-03 (Only TD subjects will be included in the ISS) EU

Table 1: Luspatercept Clinical Studies Relevant to 1L Transfusion-Dependent-MDS (Clinical Overview Table 1.4-1)

Identifier / Status	Design	Treatment Dose/Route	Treatment/Follow-up	Endpoints	No. Treated Subjects	Population/ Region
		per protocol; maximum dose of 1.75 mg/kg.				
ACE-536-LTFU-001/Ongoing	Phase 3b, open-label, single-arm, rollover study	Same dose level and schedule of the last visit of the A536-05 study	Post-treatment follow-up of 42 days for all AEs and every 6 months for at least 5 years form first dose in the parental protocol for OS.	Long-term safety of luspatercept	78 (Safety: A536-05 or ACE-536-MDS-001). 2 (Efficacy: MDS subjects from A536-05)	Subjects who participated in other interventional luspatercept clinical trials defined as parent protocols

Abbreviations: AE, adverse event; AML, acute myeloid leukemia; ESA, erythropoiesis stimulating agent; HTB, high transfusion burden; IPSS- R, International Prognostic Scoring System - Revised; ISS, integrated summary of safety; IWG, International Working Group; LTB, low transfusion burden; MDS, myelodysplastic syndromes; OS, overall survival; Q3W, every 3 weeks; RBC, red blood cell; RS, ring sideroblast; SC, subcutaneous; TD, transfusion dependent

Source: ACE-536-MDS-002 Primary CSR[5], ACE-536-MDS-001 CSR[11], ACE-536-MDS-004 Protocol[12], A536-03 CSR[13], and A536-05 CSR[14].

2.3.2. Pharmacokinetics

The Pharmacokinetics of luspatercept was previously characterised and assessed during the initial MAA.

For the current extension of indication, the MAH submitted an updated population PK model based on the previously established model for patients with MDS from Studies A536-03 and ACE-536-MDS-001. This was updated by including ESA naive TD patients from study ACE-536-MDS-002. Subjects from Study ACE-536-MDS-003, which enrolled only Japanese patients, were included to evaluate the effect of race/ethnicity on luspatercept PK.

In addition, the MAH presented Exposure-Response models mainly based on study ACE-536-MDS-002. Please refer to the Pharmacodynamics section below.

Population PK model

Dataset

The PPK analysis of luspatercept was performed using data from all clinical studies conducted in subjects with MDS, except for one study (Study A536-05). The integrated PPK analysis included one Phase 2 dose finding/expansion study (A536-03), one Phase 2 study with Japanese subjects (ACE-536-MDS-003) and two Phase 3 pivotal studies (ACE-536-MDS-001 and ACE-536-MDS-002).

Study A536-05 was a long-term safety extension study for subjects previously enrolled in Study A536-03 and therefore was not included in the analysis.

The table below provides summary descriptions of these studies and indicates which studies were included in each of the planned analyses. Initially only an interim analysis was submitted (Data cutoff: 31. Aug 2022). With the first round of responses a brief overview of updated popPK and E-R models was provided. The updated report (data included up to 31. Mar 2023) was provided upon request. During the assessment a GCP violation was detected regarding the collection of unconsented samples. This includes mainly PK and ADA samples (please refer to the respective sections for more details). The provided updated modelling report includes these excess PK samples (~10% of included PK samples).

Table 2: Summary Description of Studies (31. Mar 2023)

Protocol #: Title (Data Cutoff Date)	Treatment	Total Subjects with Efficacy/Safety/PK Information[a]	Assessments: PK Sampling Schedule	Study Population	Analyses
A536-03: A phase 2, open-label, ascending dose study of ACE-536 for the treatment of anemia in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS) (22 Oct 2018)	Dose escalation cohorts: 0.125, 0.25, 0.5, 0.75, 1, 1.33, and 1.75 mg/kg, SC, Q3W. Dose expansion cohorts 1 & 2: 1 mg/kg, SC, Q3W, with intra-subject dose escalation to 1.33 and 1.75 mg/kg allowed.	PPK: 116	C1D1, C1D8, C1D11, C1D15, C2D1, C2D8, C4D1, C5D1, C5D8, C5D15, EOT, Follow-up, and EOS	TD and NTD	PPK
ACE-536-MDS-001: A phase 3, double-blind, randomized study to compare the efficacy and safety of luspatercept (ACE-536) versus placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk myelodysplastic syndromes in subjects with ring sideroblasts who require red blood cell transfusions (08 May 2018)	Starting dose = 1 mg/kg, SC, Q3W, with intra-subject dose escalation to 1.33 and 1.75 mg/kg allowed.	PPK: 153	Primary treatment phase: C1D1, C1D8, C1D15, C2D1, C4D1, C5D8, C6D1, C8D1, and Week 25 Extension treatment phase: Once every 4 cycles Posttreatment follow-up if treatment < 1 year: EOT and then once every 12 weeks Maximum 1 year of sampling	ESA refractory, intolerant, or ineligible, TD	PPK

Protocol #: Title (Data Cutoff Date)	Treatment	Total Subjects with Efficacy/Safety/PK Information[a]	Assessments: PK Sampling Schedule	MDS Study Population	Analyses
ACE-536-MDS-002: A phase 3, open-label, randomized study to compare the efficacy and safety of luspatercept (ACE-536) versus epoetin alfa for the treatment of anemia due to IPSS-R very low, low or intermediate risk myelodysplastic syndromes (MDS) in ESA-naïve subjects who require red blood cell transfusions (31-Mar-2023)	Starting dose = 1 mg/kg, SC, Q3W, with intra-subject dose modification to 1.33 and 1.75 mg/kg allowed.	PPK: 182 E-R Efficacy: 181 in the luspatercept arm E-R Safety: 181 in the luspatercept arm	W1D1, W2D1, W3D1, W4D1, W10D1, W16D1, W22D1, Week 24 and then every 12 weeks Maximum 1 year of sampling	ESA-naïve TD[a]	PPK E-R (efficacy) E-R (safety)
ACE-536-MDS-003: A phase 2, multicenter, single-arm study to evaluate the efficacy, pharmacokinetics, and safety of luspatercept (ACE-536) for the treatment of anemia due to IPSS-R very low, low or intermediate risk myelodysplastic syndromes (MDS) in Japanese subjects who are not requiring red blood cell transfusion (01-Jul-2022)	Starting dose = 1 mg/kg, SC, Q3W, with intra-subject dose modification to 1.33 and 1.75 mg/kg allowed.	PPK: 21	Dense (first N = 10): W1D1, W1D3, W2D1, W2D3, W3D1, W4D1, W10D1, W13D1, W16D1, W17D1, W18D1, W19D1, W22D1, Week 24 and then every 12 weeks Sparse (other N = 10): W1D1, W2D1, W3D1, W4D1, W10D1, W16D1, W22D1, Week 24 and then every 12 weeks Maximum 1 year of sampling.	NTD	PPK

[a] ESA-naïve TD is defined as subjects with IPSS-R very low, low, or intermediate risk MDS who are ESA-naïve with a baseline EPO level of < 500 U/L and baseline RBC transfusion burden of 2 to 6 units/8 weeks.

The initially submitted analysis (data cut off 31. Aug 2022) included subjects with MDS who received at least one dose of luspatercept and had measurable luspatercept serum concentrations in Studies A536-03 (N = 116), ACE-536-MDS-001 (N = 153), ACE-536-MDS-002 (N = 164), and ACE-536-MDS-003 (N = 21). The updated analysis (data cutoff 31. Mar 2023) included data from 17 additional patients from study ACE-536-MDS-002 (N = 182).

Initially a total of 4559 PK samples were collected from 468 subjects. In the updated report, a total of 4904 samples from 472 subjects were reported. Of the samples collected, the analysis included 4,356031 (98.1%) samples collected from 471 subjects. Of the samples excluded from the PPK analysis, the majority (465) samples were Day 1 pre-dose luspatercept concentrations and 59 BLQ samples observed

after the first dose. The remaining 24 excluded samples had missing dosing or sampling information, incorrect dosing or sampling information, or were excluded for other reasons.

Study ACE-536-MDS-003 excluded 2 subjects, however, these 2 individuals were still included in the current population pharmacometrics analysis. One subject did not have sufficient PK samples and another experienced a protocol deviation. Since these subjects still had observable post dose PK samples, they were retained in the current analysis.

No PK samples that were collected after the first dose and had a value above the limit of quantification were excluded from PPK analysis.

Table 3: Samples included in the Pharmacokinetic Analysis Dataset (31. Mar 2023)

Study	PK Database	Day 1 Pre-Dose Samples	Missing or erroneous dose or sample information	LLOQ	Samples included in analysis (%)[a]
A536-03	1192	116	6	14	1056 (98.1)
ACE-536-MDS-001	1604	151	13	26	1414 (97.3)
ACE-536-MDS-002	1864	177	5	18	1664 (98.6)
ACE-536-MDS-003	244	21	0	1	222 (99.6)
Total	4904	465	24	59	4356 (98.1)

[a] Day 1 pre-dose excluded from denominator

Table 4: Summary of subject covariates by study – categorical covariates (31 March 2023)

Parameter, n (%)	A536-03 (N = 116)	ACE-536-MDS-001 (N = 153)	ACE-536-MDS-002 (N = 181)	ACE-536-MDS-003 (N = 21)	Total (N = 471)
Sex					
Female	44 (37.9)	59 (38.6)	72 (39.8)	8 (38.1)	183 (38.9)
Male	72 (62.1)	94 (61.4)	109 (60.2)	13 (61.9)	288 (61.1)
Race					
White	116 (100)	107 (69.9)	145 (80.1)	0 (0)	368 (78.1)
Black/African American	0 (0)	1 (0.7)	2 (1.1)	0 (0)	3 (0.6)
Asian	0 (0)	0 (0)	19 (10.5)	21 (100)	40 (8.5)
Others	0 (0)	45 (29.4)	15 (8.3)	0 (0)	60 (12.7)

Table 4: Summary of subject covariates by study – categorical covariates (31 March 2023)

Parameter, n (%)	A536-03 (N = 116)	ACE-536-MDS-001 (N = 153)	ACE-536-MDS-002 (N = 181)	ACE-536-MDS-003 (N = 21)	Total (N = 471)
Transfusion dependence					
transfusion dependent	79 (68.1)	153 (100)	174 (96.1)	0 (0)	406 (86.2)
transfusion independent	37 (31.9)	0 (0)	7 (3.9)	21 (100)	65 (13.8)
Baseline IPSS-R					
Very Low	3 (2.6)	18 (11.8)	16 (8.8)	0 (0)	37 (7.9)
Low	60 (51.7)	109 (71.2)	129 (71.3)	15 (71.4)	313 (66.5)
Intermediate	41 (35.3)	25 (16.3)	34 (18.8)	5 (23.8)	105 (22.3)
High	11 (9.5)	1 (0.7)	1 (0.6)	0 (0)	13 (2.8)
Very High	1 (0.9)	0 (0)	0 (0)	0 (0)	1 (0.2)
Missing	0 (0)	0 (0)	1 (0.6)	1 (4.8)	2 (0.4)
Baseline ring sideroblast status					
No	40 (34.5)	0 (0)	49 (27.1)	8 (38.1)	97 (20.6)
Yes	65 (56.0)	153 (100)	132 (72.9)	13 (61.9)	363 (77.1)
Unknown	11 (9.5)	0 (0)	0 (0)	0 (0)	11 (2.3)
Baseline EPO category					
<=200	64 (55.2)	103 (67.3)	145 (80.1)	14 (66.7)	326 (69.2)
>200	51 (44.0)	50 (32.7)	36 (19.9)	7 (33.3)	144 (30.6)
Missing	1 (0.9)	0 (0)	0 (0)	0 (0)	1 (0.2)
Baseline hepatic function category					
Group A: Normal	67 (57.8)	96 (62.7)	132 (72.9)	16 (76.2)	311 (66.0)
Group B: Mild	38 (32.8)	44 (28.8)	42 (23.2)	3 (14.3)	127 (27.0)
Group C: Moderate	11 (9.5)	12 (7.8)	7 (3.9)	2 (9.5)	32 (6.8)
Group D: Severe	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.2)
Classification of renal function					
Normal renal function	22 (19.0)	50 (32.7)	55 (30.4)	10 (47.6)	137 (29.1)
Mild renal impairment	66 (56.9)	72 (47.1)	83 (45.9)	7 (33.3)	228 (48.4)

Table 4: Summary of subject covariates by study – categorical covariates (31 March 2023)

Parameter, n (%)	A536-03 (N = 116)	ACE-536-MDS-001 (N = 153)	ACE-536-MDS-002 (N = 181)	ACE-536-MDS-003 (N = 21)	Total (N = 471)
Moderate renal impairment	28 (24.1)	31 (20.3)	43 (23.8)	4 (19.0)	106 (22.5)
Prior ESA therapy					
No	65 (56.0)	5 (3.3)	181 (100)	20 (95.2)	271 (57.5)
Yes	51 (44.0)	148 (96.7)	0 (0)	1 (4.8)	200 (42.5)
Antidrug antibody (subject level)					
Negative	94 (81.0)	135 (88.2)	165 (91.2)	21 (100)	415 (88.1)
Preexisting	8 (6.9)	7 (4.6)	4 (2.2)	0 (0)	19 (4.0)
Treatment-Emergent	14 (12.1)	11 (7.2)	11 (6.1)	0 (0)	36 (7.6)
Missing	0 (0)	0 (0)	1 (0.6)	0 (0)	1 (0.2)
Class of individual renal function					
Normal renal function	36 (31.0)	63 (41.2)	63 (34.8)	7 (33.3)	169 (35.9)
Mild renal impairment	54 (46.6)	61 (39.9)	79 (43.6)	10 (47.6)	204 (43.3)
Moderate renal impairment	25 (21.6)	28 (18.3)	32 (17.7)	4 (19.0)	89 (18.9)
Severe renal impairment	0 (0)	0 (0)	1 (0.6)	0 (0)	1 (0.2)
Missing	1 (0.9)	1 (0.7)	6 (3.3)	0 (0)	8 (1.7)

Table 5: Summary of Subject Covariates by Study - Continuous Covariates (31. Mar 2023)

	A536-03 (N = 116)	ACE-536-MDS-001 (N = 153)	ACE-536-MDS-002 (N = 181)	ACE-536-MDS-003 (N = 21)	Total (N = 471)
Age (years)					
Mean (SD)	70.4 (10.7)	70.5 (8.68)	73.5 (8.95)	74.5 (8.47)	71.8 (9.40)
Median [Min, Max]	72.0 [27.0, 90.0]	71.0 [40.0, 95.0]	74.0 [46.0, 93.0]	75.0 [57.0, 91.0]	72.0 [27.0, 95.0]
Baseline body Weight (kg)					
Mean (SD)	77.2 (14.8)	76.2 (15.1)	73.2 (16.2)	61.9 (7.84)	74.6 (15.5)

Table 5: Summary of Subject Covariates by Study - Continuous Covariates (31. Mar 2023)

	A536-03 (N = 116)	ACE-536-MDS-001 (N = 153)	ACE-536-MDS-002 (N = 181)	ACE-536-MDS-003 (N = 21)	Total (N = 471)
Median [Min, Max]	77.0 [48.0, 118]	76.0 [46.0, 124]	73.0 [33.0, 123]	61.7 [48.8, 87.9]	74.0 [33.0, 124]
Baseline hemoglobin (g/dL)					
Mean (SD)	8.44 (0.899)	8.30 (0.951)	7.62 (0.874)	8.56 (0.987)	8.08 (0.982)
Median [Min, Max]	8.47 [5.49, 10.4]	8.30 [5.90, 11.0]	7.80 [4.70, 9.18]	8.80 [6.40, 9.90]	8.10 [4.70, 11.0]
Baseline AST (U/L)					
Mean (SD)	27.9 (16.5)	23.9 (13.6)	20.2 (8.08)	24.0 (13.6)	23.5 (13.0)
Median [Min, Max]	22.1 [8.00, 96.0]	19.0 [7.00, 77.0]	18.0 [6.00, 51.0]	18.0 [9.00, 54.0]	19.0 [6.00, 96.0]
Baseline total bilirubin (mg/dL)					
Mean (SD)	0.855 (0.520)	1.03 (0.589)	0.911 (0.521)	0.743 (0.489)	0.930 (0.547)
Median [Min, Max]	0.705 [0.200, 3.05]	0.877 [0.234, 3.98]	0.819 [0.175, 3.63]	0.600 [0.300, 2.20]	0.819 [0.175, 3.98]
Baseline albumin (g/L)					
Mean (SD)	43.4 (4.32)	44.2 (3.35)	44.6 (3.47)	44.3 (3.20)	44.2 (3.67)
Median [Min, Max]	44.1 [31.0, 52.6]	44.0 [35.0, 51.0]	45.0 [34.0, 54.0]	43.0 [40.0, 52.0]	44.0 [31.0, 54.0]
Baseline individualized eGFR (mL/min)					
Mean (SD)	79.4 (22.9)	84.0 (24.2)	80.8 (24.4)	78.9 (20.6)	81.4 (23.8)
Median [Min, Max]	77.0 [32.6, 133]	83.4 [33.5, 150]	78.9 [29.1, 162]	78.0 [48.4, 115]	80.1 [29.1, 162]
Missing	1 (0.9%)	1 (0.7%)	6 (3.3%)	0 (0%)	8 (1.7%)
Baseline EPO (U/L)					
Mean (SD)	332 (431)	219 (326)	125 (114)	385 (685)	218 (335)
Median [Min, Max]	154 [9.80, 2030]	117 [10.4, 2450]	76.3 [7.80, 496]	86.5 [28.9, 2920]	104 [7.80, 2920]

Table 5: Summary of Subject Covariates by Study - Continuous Covariates (31. Mar 2023)

	A536-03 (N = 116)	ACE-536-MDS-001 (N = 153)	ACE-536-MDS-002 (N = 181)	ACE-536-MDS-003 (N = 21)	Total (N = 471)
Missing	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
Base RBC TB 12 weeks (Unit/12 weeks)					
Mean (SD)	5.64 (5.05)	8.73 (4.15)	5.58 (2.73)	0 (0)	6.37 (4.32)
Median [Min, Max]	5.79 [0, 26.0]	8.00 [3.00, 22.0]	5.00 [2.00, 21.0]	0 [0, 0]	6.00 [0, 26.0]

Table 5: Summary of Subject Covariates by Study - Continuous Covariates (31. Mar 2023)

	A536-03 (N = 116)	ACE-536-MDS-001 (N = 153)	ACE-536-MDS-002 (N = 181)	ACE-536-MDS-003 (N = 21)	Total (N = 471)
Base RBC TB 15 weeks (Unit/15 weeks)					
Mean (SD)	7.02 (6.11)	11.0 (5.08)	7.21 (3.49)	0 (0)	8.06 (5.32)
Median [Min, Max]	6.47 [0, 28.0]	10.0 [3.00, 28.0]	6.43 [2.00, 26.3]	0 [0, 0]	7.37 [0, 28.0]
Base RBC TB 24 weeks (Unit/24 weeks)					
Mean (SD)	11.4 (9.54)	18.3 (8.18)	11.8 (5.61)	0 (0)	13.3 (8.58)
Median [Min, Max]	11.1 [0, 40.2]	16.6 [5.46, 43.4]	10.4 [2.00, 42.0]	0 [0, 0]	12.0 [0, 43.4]
Baseline ALT (U/L)					
Mean (SD)	33.0 (27.6)	32.1 (24.3)	19.9 (12.2)	18.8 (15.8)	27.1 (22.0)
Median [Min, Max]	22.2 [5.00, 190]	23.0 [6.00, 133]	17.0 [0.100, 67.0]	13.0 [4.00, 54.0]	19.0 [0.100, 190]
Baseline LDH (U/L)					
Mean (SD)	215 (65.9)	182 (63.9)	217 (138)	218 (63.5)	205 (100)
Median [Min, Max]	203 [107, 620]	168 [96.0, 434]	193 [94.0, 1170]	193 [135, 363]	189 [94.0, 1170]
Missing	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (0.4%)
Baseline ALP (U/L)					
Mean (SD)	80.2 (43.7)	73.6 (24.2)	74.0 (22.6)	71.2 (17.1)	75.2 (29.6)
Median [Min, Max]	72.5 [36.0, 301]	69.0 [26.0, 156]	71.0 [34.0, 178]	68.0 [40.0, 108]	70.0 [26.0, 301]

Model development and covariate

A previous luspatercept PPK model established for subjects with MDS (Report ACE-536-MPK-002) was used as the starting base model. It was a one-compartment model with first-order absorption and elimination. The model was parameterised in term of the absorption rate constant (Ka), apparent clearance (CL/F) from the central compartment, and apparent volume of distribution of the central compartment (V/F). In this model, body weight, age, and baseline albumin were included as the covariates of CL/F, while body weight and baseline albumin were included as the covariate of V/F.

The following intrinsic factors (Table 6) were evaluated as potential covariates on PPK model parameters by a full model approach (Report ACE-536-MPK-008 + Addendum). Given that a full covariate analysis was completed in the previous analysis, the current analysis focused on selected characteristics of interest that might be enriched or expanded numerically impacted by the addition of new subjects.

Table 6: Covariate-Parameter Relationship to be evaluated in Population Pharmacokinetic Analyses

Potential Covariate	CL/F	V1/F
Race/ethnicity (Asian and non-Asian)	x	x
Age (continuous)	✓	x
Weight (continuous)	✓	✓
Baseline IPSS-R risk (very low, low, intermediate, and high)	x	x
Baseline ring sideroblast status (negative and positive)	x	x
Baseline serum EPO (continuous or categorical as ≤ 200 and > 200 U/L)	x	x
Baseline RBC transfusion burden (continuous)	x	x
Baseline hemoglobin (continuous)	x	x
Baseline aspartate aminotransferase (continuous)	x	x
Baseline total bilirubin (continuous)	x	x
Baseline albumin (continuous)	✓	✓
Baseline hepatic function category	x	x
Baseline individual eGFR (continuous)	x	x
Prior ESA therapy (yes and no)	x	x
Antidrug antibody (occasion level)	x	-

X, to be tested; ✓, included as part of the previous final model[16] (current base model)

Final model

The final model is a one-compartment model with first order elimination and absorption with a log-additive residual error model, including covariate effects of baseline weight, baseline albumin, baseline age, baseline eGFR and previous ESA therapy on CL/F and baseline weight and baseline albumin on V1/F.

The final covariate models on CL/F and V/F are as follows:

$$CL_{TV,i} = CL_{TV,REF} \times CL_{cov}$$

$$CL_{cov} = \left(\frac{BW_i}{BW_{REF}}\right)^{CL_{BW}} \times \left(\frac{AGE_i}{AGE_{REF}}\right)^{CL_{AGE}} \times \left(\frac{IEGFR_i}{IEGFR_{REF}}\right)^{CL_{IEGFR}} \times \left(\frac{ALB_i}{ALB_{REF}}\right)^{CL_{ALB}} \times (CL_{ESA}[if\ ESA = Yes])$$

$$V_{TV,i} = V_{TV,REF} \times V_{cov}$$

$$V_{cov} = \left(\frac{BW_i}{BW_{REF}}\right)^{V_{BW}} \times \left(\frac{ALB_i}{ALB_{REF}}\right)^{V_{ALB}}$$

where $CL_{TV,REF}$ and $V_{TV,REF}$ were the typical values of CL/F and V/F at the reference values of WT (70 kg), IEGFR (73 mL/min), AGE (72 years), ALB (44 g/L); and no previous ESA therapy; CL_{BW}, CL_{AGE}, CL_{IEGFR}, CL_{ALB}, CL_{ESA}, V_{BW}, and V_{ALB} were estimated model parameters contributing to the multiplicative covariate effects CL_{cov} and V_{cov} for $CL_{TV,i}$ and $V_{TV,i}$, respectively.

The parameter estimates from the final model and bootstrap are provided below.

Table 7: Parameter Estimates for Final PPK Model (31. Mar 2023)

Name[a,b] [Units]	Symbol	Estimate (Interim Analysis: 31-Aug- 2022)[c]	New Estimate (Primary Analysis: 31-Mar-2023)[c]
Fixed Effects			
1 TVCL (L/day)	θ_1	0.420	0.422
2 TVV1 (L)	θ_2	9.29	9.27
3 TVKA (/day)	θ_3	0.402	0.396
5 CLAGE1	θ_5	-0.551	-0.541
6 CLALBB1	θ_6	-1.30	-1.24
7 CLESA1	θ_7	0.151	0.148
8 CLIEGFRMBI1	θ_8	0.187	0.179
9 CLWTB1	θ_9	0.820	0.816
10 V1ALBB1	θ_{10}	-0.623	-0.620
11 V1WTB1	θ_{11}	0.888	0.892
Random Effects			
BSVCL	$\omega_{1,1}$	0.113 (0.336)	0.110 (0.332)
BSVV1	$\omega_{2,2}$	0.0522 (0.228)	0.0504 (0.224)
BSVCL:BSVV1	$\omega_{1,2}$	0.0347 (0.453)	0.0335 (0.449)
Residual Error			
4 AddErr	θ_4	0.239	0.235
FIXED[f]	$\sigma_{1,1}$	1.00 (1.00)	1.00 (1.00)

[a] Parameters with fixed values (not estimated) are denoted with a superscript '*f*' after the names, with the fixed value given in the Estimate column

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($w_{i,i}$ or $s_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($w_{i,j}$ or $s_{i,j}$)

Source: /global/pkms/data/CA/luspatercept/1L-mds/prd/ema-ar-0523/final/R2/scripts/3-response-q3-ppk.Rmd

Table 7: Parameter estimates for model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
1 TVCL (L/day)	θ_1	0.422	0.00851 (2.02)	0.405 - 0.439
2 TVV1 (L)	θ_2	9.27	0.132 (1.42)	9.01 - 9.53
3 TVKA (/day)	θ_3	0.396	0.0232 (5.84)	0.351 - 0.442
5 CLAGE1	θ_5	-0.541	0.108 (19.9)	-0.753 - -0.330
6 CLALBB1	θ_6	-1.24	0.196 (15.7)	-1.63 - -0.860
7 CLESA1	θ_7	0.148	0.0349 (23.5)	0.0801 - 0.217
8 CLIEGFRMBI1	θ_8	0.179	0.0554 (30.9)	0.0709 - 0.288
9 CLWTB1	θ_9	0.816	0.0770 (9.43)	0.665 - 0.967
10 V1ALBB1	θ_{10}	-0.620	0.172 (27.7)	-0.957 - -0.283
11 V1WTB1	θ_{11}	0.892	0.0627 (7.03)	0.770 - 1.02
Random Effects				
BSVCL	$\omega_{1,1}$	0.110 (0.332)	0.0105 (9.52)	0.0898 - 0.131
BSVV1	$\omega_{2,2}$	0.0504 (0.224)	0.0101 (20.0)	0.0306 - 0.0701
BSVCL:BSVV1	$\omega_{1,2}$	0.0335 (0.449)	0.00655 (19.6)	0.0206 - 0.0463
Residual Error				
4 AddErr	θ_4	0.235	0.0220 (9.34)	0.192 - 0.278
FIXED*f*	$\sigma_{1,1}$	1.00 (1.00)		

[a] Parameters with fixed values (not estimated) are denoted with a superscript '*f*' after the names, with the fixed value given in the Estimate column

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[c] Random Effects and Residual Error parameter estimates are shown as Variance (Standard Deviation) for diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$) and Covariance (Correlation) for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

Table 8: Summary of Bayesian estimation of pharmacokinetic and exposure parameters – all subjects

	Total (N = 471)
CL/F (L/day)	
Geo. mean (CV%)	0.472 (42.4%)
V/F (L)	
Geo. mean (CV%)	9.57 (26.5%)
Half-life (day)	
Geo. mean (CV%)	14.0 (31.6%)
Cmax (ug/mL)	
Geo. mean (CV%)	5.64 (19.7%)
Cmax,ss (ug/mL)	
Geo. mean (CV%)	9.45 (29.7%)
Cavg,ss (ug/mL)	
Geo. mean (CV%)	7.36 (36.9%)
AUCss (day*ug/mL)	
Geo. mean (CV%)	155 (36.9%)
Tmax (day)	
Median [Min, Max]	6.04 [3.29, 7.38]

Exposure Metrics were calculated with a nominal dose of 1 mg/kg

Model evaluation

Diagnostic evaluation demonstrated the adequacy of the established population PK model in describing the PK data in patients with MDS. Both population and individual predicted concentrations were consistent with the observed data.

Figure 1: Diagnostic Plots from the Final Model Study (31. Mar 2023)

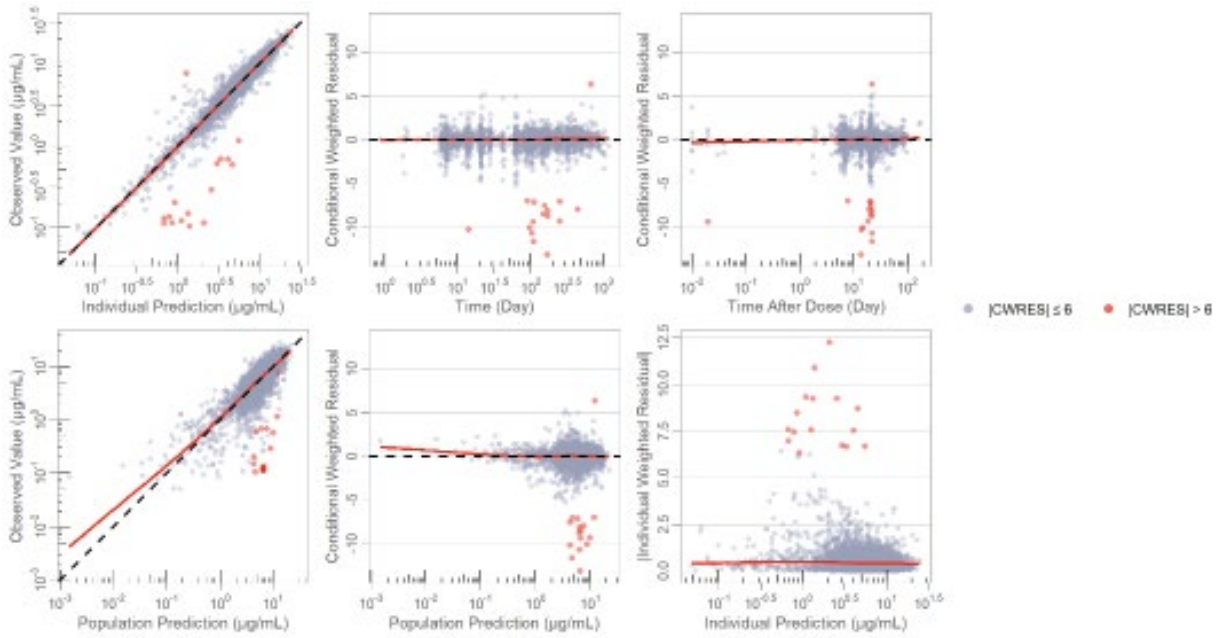


Figure 2 – Prediction-Corrected Visual Predictive Checks by Study – Final Model (Linear Scale, Time After Previous Dose) Study (31. Mar 2023)

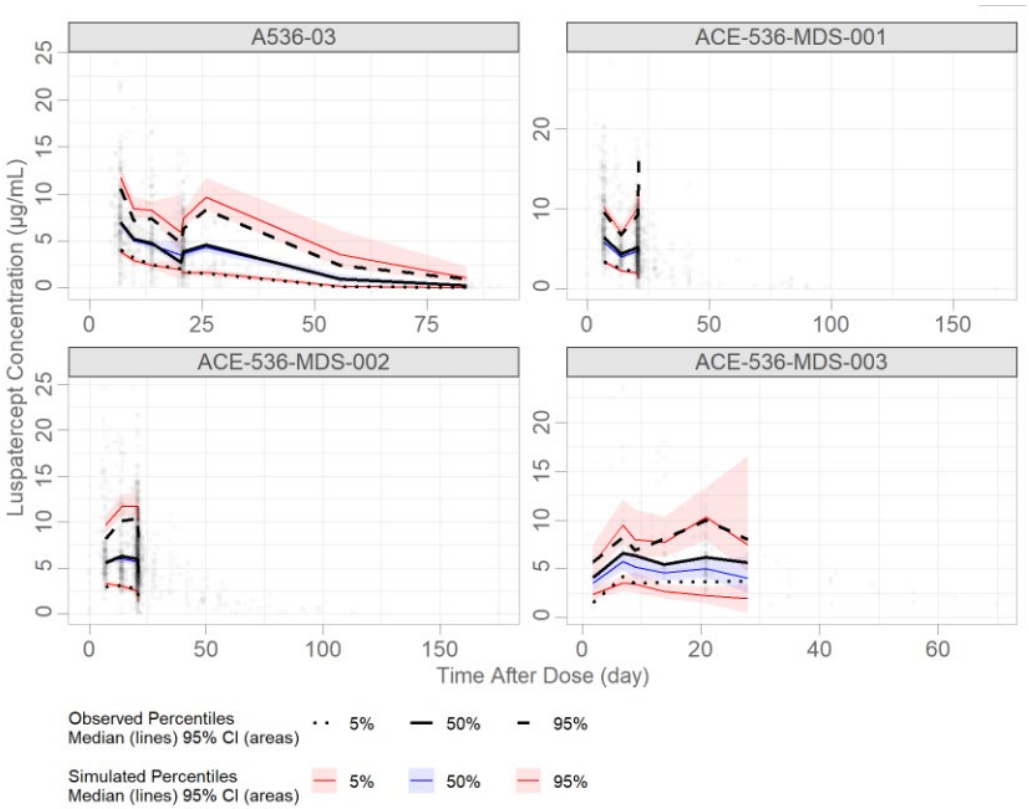


Figure 3 – Prediction-Corrected Visual Predictive Checks by Study – Final Model (Linear Scale, Time After First Dose) Study (31. Mar 2023)

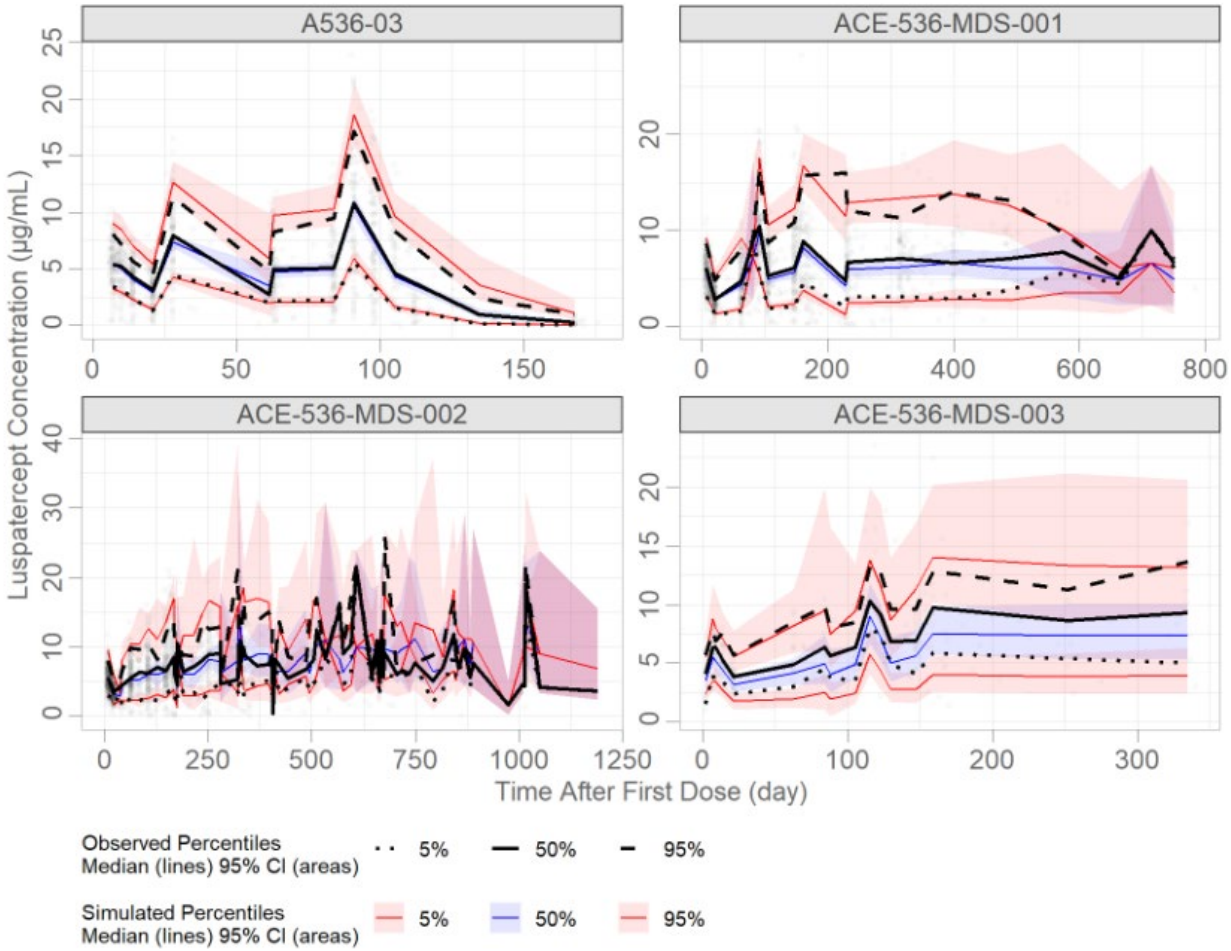
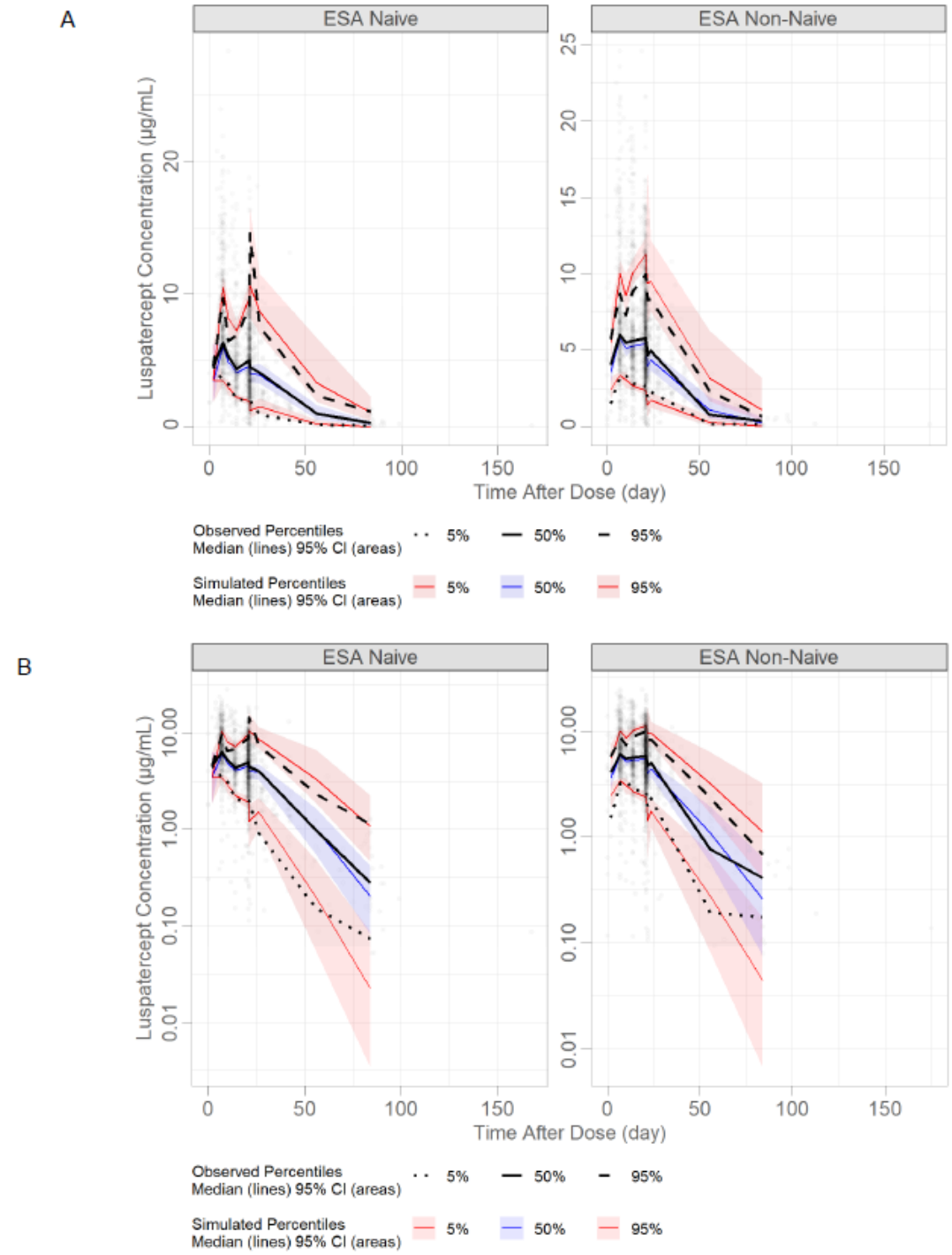
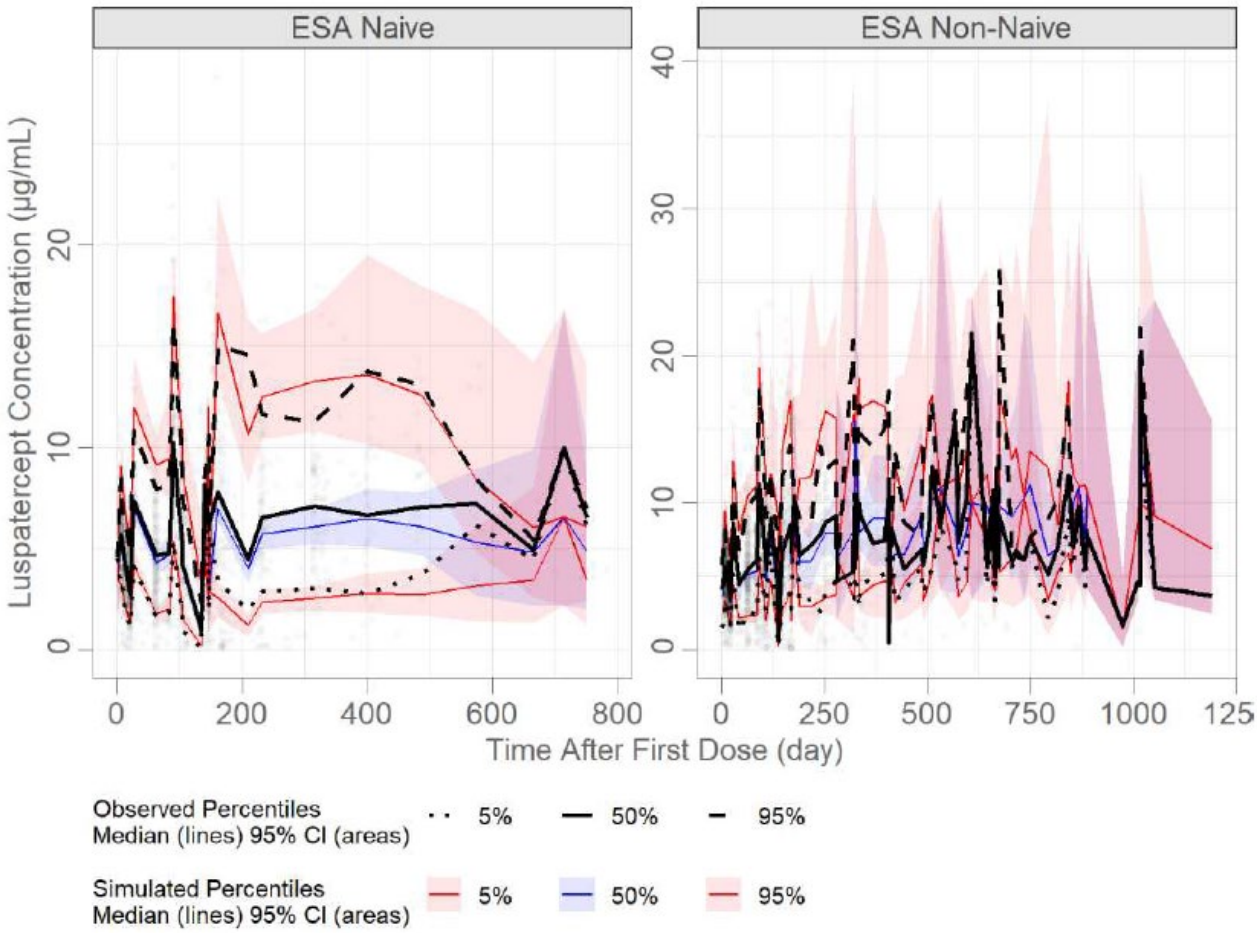


Figure 4: Prediction-corrected Visual Predictive Check for the Concentration-Time Profiles of Luspatercept by Previous ESA Therapy



Panel A: Linear-scale; Panel B: Log-scale

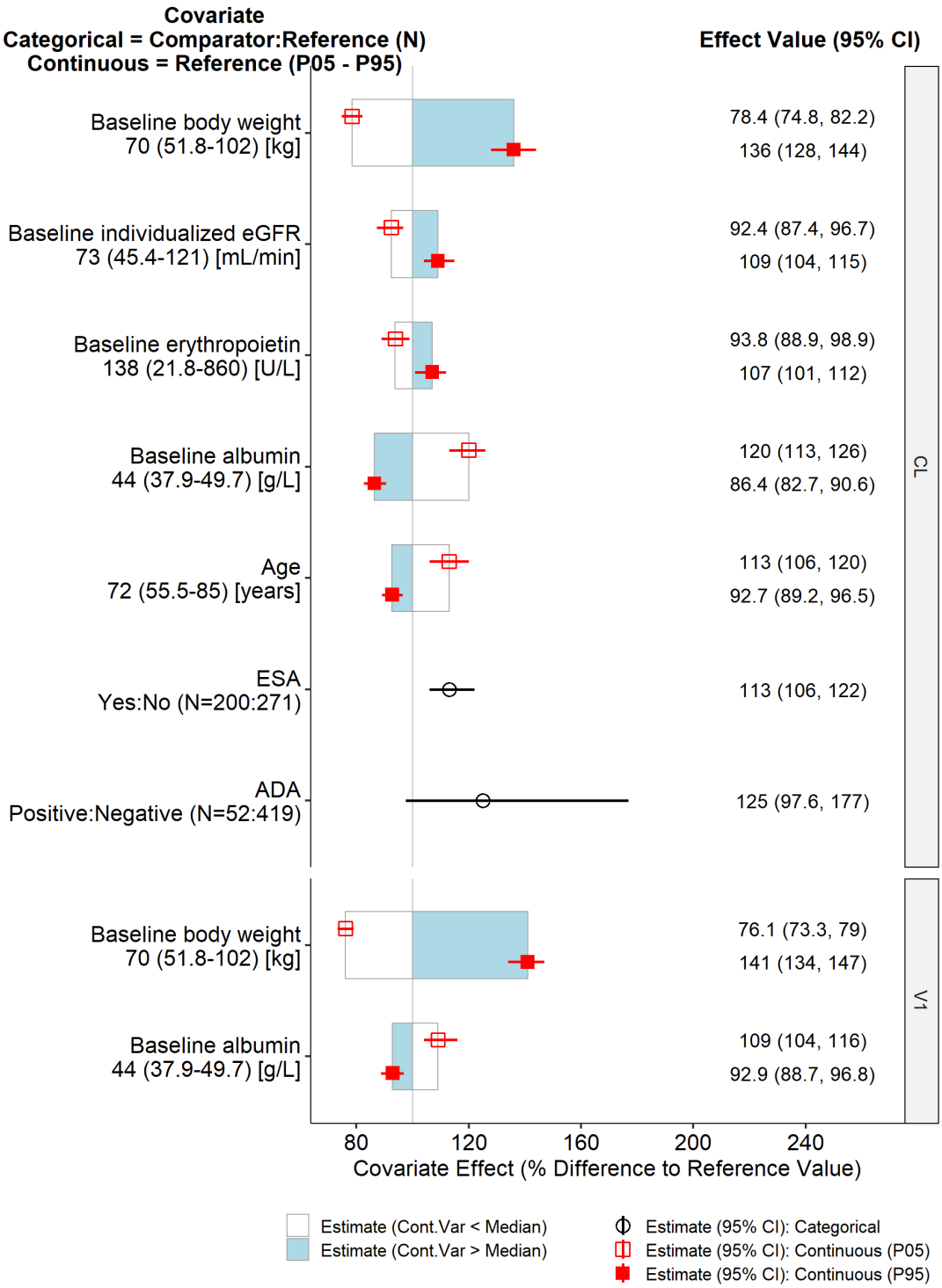
Figure 5 – Prediction-Corrected Visual Predictive Checks by ESA – Final Model (Liner Scale, Time After First Dose) Study (31. Mar 2023)



Covariate effect

The magnitude of the covariate effect on luspatercept PK parameters was assessed during model development and is presented for the full model in Figure 6. As shown, body weight is the most influential full model covariates on clearance and volume of distribution, consistent with allometric relationship.

Figure 6: Covariate-Parameter Relationships: Full Model Study (31. Mar 2023)



Note: a reference individual is ESA-naive without the presence of ADA, with a baseline age of 72 years, baseline body weight of 70 kg, individual eGFR of 73 mL/min, baseline serum erythropoietin level of 138 U/L, and baseline albumin of 44 g/L.

Results from the PPK analysis suggest:

The estimates of the updated PPK analysis are very similar to the initially submitted model. Hence, the following analyses are still considered to also appropriately reflect the updated dataset.

☐ Luspatercept exhibits linear and time-invariant PK with moderate variability. The empirical Bayesian estimate of CL/F and V1/F for the starting dose of 1 mg/kg in patients with MDS was 0.473 L/day and 9.60 L, respectively. The elimination half-life of luspatercept was 14.1 days. These estimates are similar to those from the previous PK analysis.

☐ Body weight is the primary factor responsible for luspatercept PK variability, supporting body weight-based dosing. No other intrinsic factors including demographics (age, sex, race/ethnicity), mild to moderate hepatic or renal impairment, as well as baseline disease characteristics (RBC transfusion burden, RS status, serum EPO level) have a clinically significant effect on luspatercept PK.

☐ PK was similar between ESA-naive TD MDS and other MDS subjects.

Comparison of Pharmacokinetics across Studies

The PK (absorption, distribution, and elimination) of luspatercept in patients with MDS refractory to ESA treatment has been well characterised and extensively described in original market application for MDS indication. In general, the pharmacokinetics of luspatercept is best described by first order SC absorption and linear elimination. Following SC administration, the concentration-time profile of luspatercept was characterised by an SC absorption phase followed by the single exponential elimination phase. The most notable factor explaining the variability in luspatercept disposition is body weight.

Comparison of Pharmacokinetics Between ESA-Naive and Other MDS Subjects

ESA therapy status was identified as a covariate for CL/F in the PPK analysis. The table below compares the post hoc PK estimates between ESA-naive and other MDS subjects. There is no clinically meaningful difference noted in both luspatercept PK parameters (CL/F and V/F) and exposure, supporting the similarity in luspatercept PK across the overall MDS population, irrespective of the prior ESA therapy status.

Table 9: Summary of Bayesian estimation of Pharmacokinetic and Exposure Parameters by ESA Status

	ESA Naïve (N = 271)	ESA Non-naïve (N = 200)	Total (N = 471)
CL/F (L/day)			
Geo. mean (CV%)	0.436 (41.1%)	0.526 (41.4%)	0.472 (42.4%)
V/F (L)			
Geo. mean (CV%)	9.48 (26.9%)	9.70 (26.0%)	9.57 (26.5%)
Half-life (day)			
Geo. mean (CV%)	15.1 (29.6%)	12.8 (31.6%)	14.0 (31.6%)
Cmax (ug/mL)			
Geo. mean (CV%)	5.71 (19.3%)	5.56 (20.3%)	5.64 (19.7%)
Cmax,ss (ug/mL)			
Geo. mean (CV%)	9.93 (28.6%)	8.83 (29.8%)	9.45 (29.7%)
Cavg,ss (ug/mL)			
Geo. mean (CV%)	7.87 (34.8%)	6.73 (37.6%)	7.36 (36.9%)
AUCss (day*ug/mL)			
Geo. mean (CV%)	165 (34.8%)	141 (37.6%)	155 (36.9%)
Tmax (day)			
Median [Min, Max]	6.21 [3.79, 7.33]	5.88 [3.29, 7.38]	6.04 [3.29, 7.38]

Exposure Metrics were calculated with a nominal dose of 1 mg/kg

Potential sources of variability (including special populations)

Age

Age is a covariate of CL/F with lower CL/F expected in older patients. Over the range of age (27 to 95 years, median of 72 years) evaluated in the population PK analysis, the difference in CL/F is within 20% variation from the typical value over the 5 to 95% percentile. Consistently, there was no clinically meaningful difference in luspatercept *post hoc* PK parameters and exposure across the age groups. Safety subgroup analysis indicated no major difference in the overall safety profile in subjects aged ≤64 years, 65-74 years, and >75 years. No starting dose adjustment for age is recommended in patients with MDS.

Table 10: Summary of PK Parameters in Subjects with MDS by Age (31. Mar 2023)

	≤ 64 Years (N = 87)	65 to 74 Years (N = 191)	≥ 75 Years (N = 193)	Total (N = 471)
CL/F (L/day)				
Geo. mean (Geo. CV%)	0.527 (34.2%)	0.512 (45.0%)	0.415 (39.4%)	0.472 (42.4%)
V1/F (L)				
Geo. mean (Geo. CV%)	9.48 (22.7%)	9.73 (26.4%)	9.46 (28.2%)	9.57 (26.5%)
Half-life (day)				

Table 10: Summary of PK Parameters in Subjects with MDS by Age (31. Mar 2023)

	≤ 64 Years (N = 87)	65 to 74 Years (N = 191)	≥ 75 Years (N = 193)	Total (N = 471)
Geo. mean (Geo. CV%)	12.5 (26.2%)	13.2 (32.6%)	15.8 (28.7%)	14.0 (31.6%)
Tmax (day)				
Median [Min, Max]	5.75 [4.17, 6.88]	5.92 [3.29, 7.08]	6.29 [3.79, 7.38]	6.04 [3.29, 7.38]
Cmax (µg/mL)				
Geo. mean (Geo. CV%)	5.72 (17.8%)	5.59 (21.1%)	5.67 (19.3%)	5.65 (19.8%)
Cmax,ss (µg/mL)				
Geo. mean (Geo. CV%)	8.93 (26.4%)	9.03 (32.0%)	10.1 (27.6%)	9.45 (29.8%)
Cavg,ss (µg/mL)				
Geo. mean (Geo. CV%)	6.78 (32.3%)	6.93 (40.0%)	8.12 (33.5%)	7.37 (37.0%)
AUCss (day*µg/mL)				
Geo. mean (Geo. CV%)	142 (32.3%)	146 (40.0%)	171 (33.5%)	155 (37.0%)

Race/ethnicity

The initial descriptive analysis did not show notable exposure difference across the racial groups. Therefore, race (White N=353, Asian N=38, Black/African American N=3, and others N=60) and ethnicity (Japanese N=21) were not evaluated as covariates for luspatercept PK. The PPK analysis assessed the effect of Asian vs Non-Asian groups and did not identify a statistically significant impact. As shown in the table below, despite that there were small numeric differences in luspatercept PK exposure (CL/F and AUCss) across the groups, these were not considered clinically significant. No starting dose adjustment for race/ethnicity is recommended in patients with MDS.

Table 11: Summary of PK Parameters by Ethnicity (White, Asian, Japanese) (31. Mar 2023)

	White (N = 368)	Asian (N = 40)	Japanese (N = 21)
CL/F (L/day)			
Geo. mean (Geo. CV%)	0.481 (41.4%)	0.352 (35.7%)	0.325 (23.1%)
V1/F (L)			
Geo. mean (Geo. CV%)	9.69 (25.5%)	7.86 (24.5%)	7.87 (21.2%)
Half-life (day)			
Geo. mean (Geo. CV%)	14.0 (32.1%)	15.5 (27.7%)	16.8 (15.7%)
Tmax (day)			
Median [Min, Max]	6.04 [3.29, 7.38]	6.33 [4.17, 7.33]	6.42 [5.79, 7.17]
Cmax (µg/mL)			
Geo. mean (Geo. CV%)	5.66 (19.8%)	5.75 (18.1%)	6.00 (20.3%)
Cmax,ss (µg/mL)			
Geo. mean (Geo. CV%)	9.45 (29.9%)	10.1 (25.3%)	11.1 (21.8%)
Cavg,ss (µg/mL)			
Geo. mean (Geo. CV%)	7.36 (37.3%)	8.09 (31.1%)	9.03 (23.3%)
AUCss (day*µg/mL)			
Geo. mean (Geo. CV%)	154 (37.3%)	170 (31.1%)	190 (23.3%)

Sex

There is no apparent difference in the observed luspatercept concentrations between female and male subjects in the MDS studies. Population PK analysis of data from 177 female and 277 male subjects did not identify sex as significant covariate of luspatercept PK. No starting dose adjustment for sex is recommended in patients with MDS.

Table 12: Summary of PK Parameters by Sex (31. Mar 2023)

	Male (N = 288)	Female (N = 183)	Total (N = 471)
CL/F (L/day)			
Geo. mean (Geo. CV%)	0.496 (39.6%)	0.437 (45.3%)	0.472 (42.4%)
V1/F (L)			
Geo. mean (Geo. CV%)	10.1 (23.4%)	8.73 (28.4%)	9.57 (26.5%)
Half-life (day)			
Geo. mean (Geo. CV%)	14.2 (31.7%)	13.9 (31.5%)	14.0 (31.6%)
Tmax (day)			
Median [Min, Max]	6.08 [3.29, 7.38]	6.04 [3.96, 7.33]	6.04 [3.29, 7.38]
Cmax (µg/mL)			
Geo. mean (Geo. CV%)	5.78 (18.9%)	5.44 (20.5%)	5.65 (19.8%)
Cmax,ss (µg/mL)			
Geo. mean (Geo. CV%)	9.73 (29.0%)	9.03 (30.5%)	9.45 (29.8%)
Cavg,ss (µg/mL)			
Geo. mean (Geo. CV%)	7.60 (36.5%)	7.02 (37.3%)	7.37 (37.0%)
AUCss (day*µg/mL)			
Geo. mean (Geo. CV%)	160 (36.5%)	147 (37.3%)	155 (37.0%)

Albumin

Albumin (31.0 to 53.0 g/L, median of 44.0) is a covariate for luspatercept CL/F with lower CL/F value expected in subjects of higher albumin level. Over 5 to 95% percentile range of albumin distribution in the analysis population, the difference in CL/F is less than 20% boundaries from the typical value. No starting dose adjustment for baseline albumin level is recommended in patients with MDS.

Hepatic impairment

Luspatercept, as a therapeutic protein, is not cleared through the liver, but instead eliminated primarily by proteolytic catabolism by the reticulo-endothelial system distributed throughout the body. As such, no formal study was conducted to assess the effect of hepatic impairment on luspatercept PK.

In the population PK analysis, hepatic function of patients was classified according to the NCI-ODWG criteria (normal N=299, mild N=124, moderate N=30, severe N=1). Hepatic impairment (mild to moderate) has no significant effect on luspatercept PK. Similarly, no appreciable difference in *post hoc* estimates of luspatercept exposure and PK parameters was found in subjects across the categories of hepatic impairment. No starting dose adjustment for mild to moderate hepatic impairment is recommended in patients with MDS. There was only one subject with severe hepatic impairment, precluding definitive assessment for this hepatic function category in patients with MDS.

Table 13: Summary of EBE of Pharmacokinetic and Exposure Parameters in Subjects with MDS by Hepatic Function Category

	Normal (N = 311)	Mild (N = 127)	Moderate (N = 32)	Severe (N = 1)	Total (N = 471)
CL/F (L/day)					
Geo. mean (CV%)	0.459 (42.4%)	0.494 (42.4%)	0.522 (41.1%)	0.485 (NA)	0.472 (42.4%)
V/F (L)					
Geo. mean (CV%)	9.54 (26.6%)	9.62 (27.2%)	9.71 (23.7%)	8.97 (NA)	9.57 (26.5%)
Half-life (day)					
Geo. mean (CV%)	14.4 (30.9%)	13.5 (32.7%)	12.9 (32.2%)	12.8 (NA)	14.0 (31.6%)
Cmax (ug/mL)					
Geo. mean (CV%)	5.65 (19.3%)	5.61 (21.0%)	5.72 (20.0%)	6.44 (NA)	5.64 (19.7%)
Cmax,ss (ug/mL)					
Geo. mean (CV%)	9.59 (29.2%)	9.19 (31.3%)	9.12 (28.5%)	10.1 (NA)	9.45 (29.7%)
Cavg,ss (ug/mL)					
Geo. mean (CV%)	7.52 (36.2%)	7.10 (38.3%)	6.97 (38.2%)	7.77 (NA)	7.36 (36.9%)
AUCss (day*ug/mL)					
Geo. mean (CV%)	158 (36.2%)	149 (38.3%)	146 (38.2%)	163 (NA)	155 (36.9%)
Tmax (day)					
Median [Min, Max]	6.08 [3.29, 7.38]	6.00 [3.96, 7.33]	6.02 [3.46, 6.71]	5.83 [5.83, 5.83]	6.04 [3.29, 7.38]

Exposure Metrics were calculated with a nominal dose of 1 mg/kg

Renal impairment

Luspatercept is unlikely to be renally excreted due to its high molecular weight (~76 kDa) which is above the cut off of 69 kDa typically considered for significant renal excretion. Therefore, renal impairment is not expected to have a significant effect on luspatercept elimination. No formal study was conducted to assess the effect of renal impairment on luspatercept PK.

In the population PK analysis, individual eGFR (MDRD method, mL/min) was identified as a covariate for CL/F with lower value of CL/F in patient of lower eGFR. Nevertheless, effect of the eGFR on luspatercept CL/F appeared to be marginal within the physiological range (90% percentile range [45 to 121 mL/min] within the 20% boundaries of the typical value).

As shown below, geometric mean of luspatercept AUCss was similar between subjects of normal renal function and mild renal impairment. Higher AUCss (~27%) was noted in subjects of moderate renal impairment compared to those with normal renal function. These numerical differences have been observed in previous analyses and were likely attributed to by the imbalance of other PK covariates (e.g. body weight, age, etc) in addition to the expected minor effect of renal function. This modest exposure increase is not considered clinically meaningful, given the lack of exposure-safety relationship (Section 3.2.2). Consistently, subgroup analysis of safety did not indicate major difference in the safety profile in subjects with eGFR <60, eGFR ≥60 to <90, or eGFR>90 mL/min. No starting dose adjustment for mild to modest renal impairment is recommended in patients with MDS. There was only one subject with severe renal impairment, precluding the definitive evaluation for this renal impairment category from the PPK analysis in patients with MDS.

Table 14: Summary of EBE of Pharmacokinetic and Exposure Parameters in Subjects with MDS by Renal Function Category

	Normal (N = 169)	Mild (N = 204)	Moderate (N = 89)	Severe (N = 1)	Missing (N = 8)	Total (N = 471)
CL/F (L/day)						
Geo. mean (CV%)	0.544 (41.2%)	0.462 (39.6%)	0.389 (41.2%)	0.257 (NA)	0.398 (29.7%)	0.472 (42.4%)
V/F (L)						
Geo. mean (CV%)	9.98 (26.0%)	9.48 (26.4%)	9.11 (26.4%)	4.65 (NA)	9.49 (21.6%)	9.57 (26.5%)
Half-life (day)						
Geo. mean (CV%)	12.7 (30.3%)	14.2 (30.6%)	16.2 (29.4%)	12.5 (NA)	16.5 (30.9%)	14.0 (31.6%)
Cmax (ug/mL)						
Geo. mean (CV%)	5.55 (20.1%)	5.66 (20.1%)	5.76 (19.0%)	5.15 (NA)	6.01 (11.1%)	5.64 (19.7%)
Cmax,ss (ug/mL)						
Geo. mean (CV%)	8.79 (29.0%)	9.53 (28.8%)	10.5 (29.7%)	7.97 (NA)	11.1 (28.3%)	9.45 (29.7%)
Cavg,ss (ug/mL)						
Geo. mean (CV%)	6.70 (36.4%)	7.46 (35.6%)	8.45 (35.7%)	6.11 (NA)	8.93 (34.3%)	7.36 (36.9%)
AUCss (day*ug/mL)						
Geo. mean (CV%)	141 (36.4%)	157 (35.6%)	177 (35.7%)	128 (NA)	188 (34.3%)	155 (36.9%)
Tmax (day)						
Median [Min, Max]	5.88 [3.46, 7.00]	6.08 [3.29, 7.17]	6.38 [4.17, 7.38]	5.79 [5.79, 5.79]	6.31 [5.71, 7.17]	6.04 [3.29, 7.38]

Exposure Metrics were calculated with a nominal dose of 1 mg/kg

Disease characteristics and biomarkers

Based on the PPK analysis, none of the baseline disease characteristics (IPSS-R risk, ring sideroblast status [positive vs. negative], serum EPO [range: 7.80 to 2920 U/L], RBC transfusion burden [range: 0 to 43.4 unit/24 weeks], and hemoglobin [range: 4.70 to 11.0 g/dL]) has significant effect on luspatercept PK, suggesting that disease severity/risk is unlikely to influence luspatercept PK in patients with MDS.

ADA

In the PPK analysis, the effect of ADA on CL/F was tested by including ADA status (positive or negative) as a time-varying covariate on CL/F (Figure 2.3.2-1). Among the small number of ADA positive subjects (7.5% treatment emergent ADA among PPK analysis population), there was a numeric trend of higher CL/F (~25%) in those subjects compared to subjects ADA negative. Nevertheless, the effect of ADA did not reach statistical significance in the full covariate model analysis (95% CI included null value).

Pharmacokinetic interaction studies

Luspatercept undergoes proteolytic degradation and is not a cytokine modulator. Therefore, the clinically significant drug interaction via drug metabolising enzymes and transporters is not expected. In the original market application, the concomitant use of iron chelation therapy during luspatercept treatment (yes vs. no) had no effect on luspatercept CL/F.

Conclusion on Pharmacokinetics

Luspatercept serum concentration-time profiles in MDS were adequately described with a one compartment PK model with first-order absorption and linear elimination, which is consistent with the previous PPK analysis. Luspatercept exhibited linear and time-invariant PK with moderate variability in serum exposure (38% overall). The typical value of CL/F and V1/F of luspatercept in patients with MDS was 0.42 L/day and 9.29 L, respectively. The typical elimination half-life of luspatercept was 15.3 days. These updated PK parameter estimates are consistent with previous values. Luspatercept PK is consistent across the overall MDS population, irrespective of the prior history of ESA therapy.

Body weight is the primary factor responsible for luspatercept PK variability. Other baseline intrinsic factors including age, gender, albumin, race/ethnicity, lab parameters (AST, ALT, total bilirubin), disease characteristics, and hepatic and renal impairment (mild to moderate) do not have a clinically meaningful effect on luspatercept pharmacokinetics. The occurrence of ADA might influence CL/F but the data are too limited for robust conclusions and the observed difference was not statistically significant.

Exposure-Response relationship

The E-R analyses of luspatercept were conducted using data from the Phase 3 pivotal study of luspatercept versus epoetin alfa in subjects with LR MDS, ACE-536-MDS-002 only. A pooled E-R analysis for efficacy was not conducted due to the small number of ESA-naïve MDS subjects requiring RBC transfusions, shorter (15 weeks) treatment period, and limited number of subjects treated at < 1 mg/kg in Study A536-03. Extensive E-R analyses for safety were previously conducted using all luspatercept-treated subjects from Studies A536-03/05 and ACE-536-MDS-001, and there was no notable E-R relationship identified for safety.

<u>Dose/Exposure-Response Analysis for Efficacy</u>

The analysis included subjects (Study ACE-536-MDS-002 only) who received at least one dose of luspatercept and had both EBEs of individual luspatercept PK parameters (derived by the PPK analysis) and information on the specified efficacy endpoints:

☐ Proportion of subjects who are RBC transfusion free (RBC-TI) for any 12-week period associated with a concurrent mean Hgb increase ≥ 1.5 g/dL compared to baseline (Week 1 to 24).

☐ Proportion of subjects who are RBC transfusion free from Week 1 through 24.

☐ Time from first dose to first RBC transfusion on treatment (Week 1 to data cutoff).

A total of 181 luspatercept-treated patients were included in this analysis. The evaluation consisted of initial exploratory graphic univariate analysis and multivariate model base E-R modelling (logistic regression and cox proportional hazard regression). Relevant intrinsic factors, including demographics, baseline disease characteristics and lab parameters, were assessed for their potential effect on the efficacy response.

In addition, dose response relationship was also assessed for selected efficacy measure(s) (responders only, Week 1 to data cutoff date).

Exposure-Response Analysis for Safety

The exposure-safety analysis included subjects (Study ACE-536-MDS-002 only) who received at least one dose of luspatercept and had both empirical Bayesian estimates of individual luspatercept PK parameters (AUC at the time of the event [AUCAE]) derived from the PPK analysis) and the specified safety data. A total of 181 luspatercept-treated patients were included in this analysis.

The exposure-safety relationship during Weeks 1 to 6 (the period of no dose escalation) and Weeks 1 to 48 were evaluated for the following safety endpoints:

☐ ≥ Grade 3 TEAEs

☐ TEAEs leading to dose modifications (dose reduction, dose delay, or discontinuation)

☐ Fatigue-like events (fatigue, asthenia) (all grade)

☐ Bone pain-like events (bone pain, arthralgia) (all grade)

☐ Hypertension (all grade)

☐ Dizziness (all grade)

The evaluation consisted of initial exploratory graphic univariate analysis and subsequently multivariate logistic regression analyses to evaluate the relationship between luspatercept serum exposure (defined as AUC at the time of the event [AUCAE]) and the probability of the specified TEAEs. Relevant intrinsic factors, including demographics, baseline disease characteristics and lab parameters, were assessed for their potential effect on the safety.

Exposure-response for Efficacy

The exposure-efficacy analysis included subjects from Study ACE-536-MDS-002 only (i.e., ESA-naive TD), who received at least one dose of luspatercept and had both EBEs of individual luspatercept PK parameters (derived by the PPK analysis) and the specified efficacy data. Subjects treated with epoetin alfa were included in the graphical data comparison, but they were excluded from exposure-efficacy modelling analysis. Subjects who were ESA-naive TD were defined as subjects with IPSS-R very low, low, or intermediate risk MDS who were ESA-naive with a baseline serum EPO level of < 500 U/L and baseline RBC transfusion burden of 2 to 6 units/8 weeks.

For selected efficacy endpoints, two sets of exposure-efficacy analysis were conducted: one included all luspatercept-treated subjects and the other included only the subjects without dose escalation.

The analysis with all subjects was conducted to provide an exposure-response relationship under the titration dosing regimen that is representative of clinical practice and more suitable for identifying risk factors for response. A second sensitivity analysis with subjects who did not have any dose escalation was performed to assess an exposure-dependent relationship without the confounding effect of dose titration. As such, the combination of both approaches allowed for an adequate assessment of exposure-efficacy.

Achievement of RBC-TI for ≥12 Weeks with Concurrent Mean Hgb Increase >= 1.5 g/dL in Weeks 1 to 24 (ACE-536-MDS-002 Primary Endpoint)

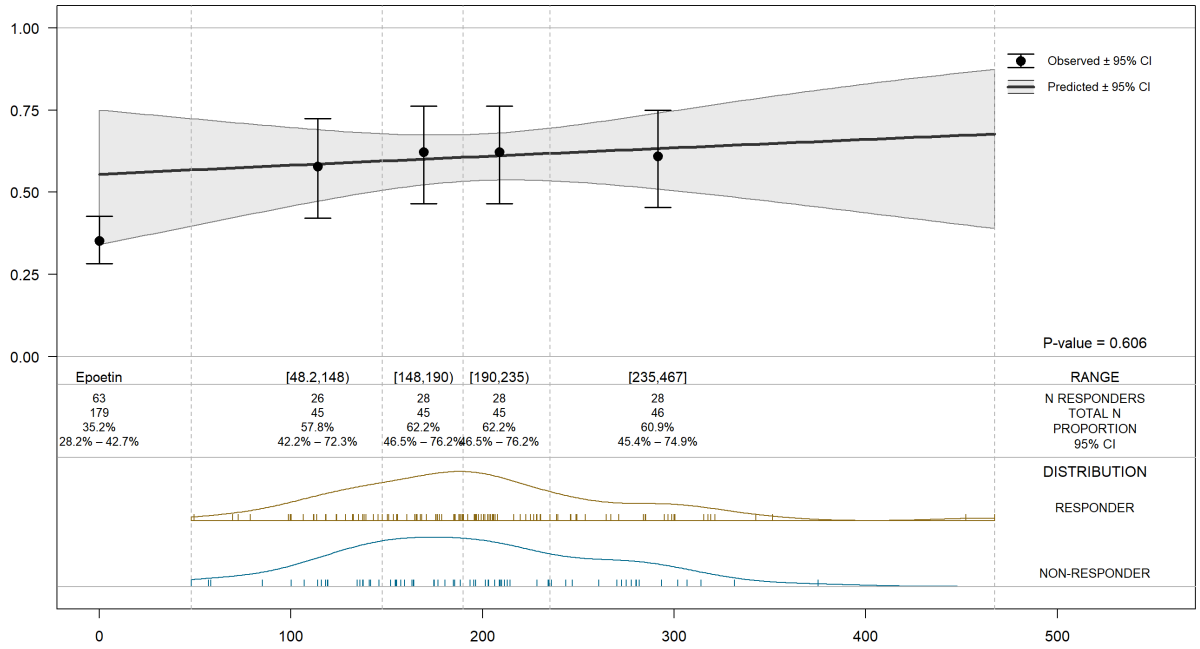
The E-R relationship for the primary efficacy endpoint was analyzed by logistical regression, where time-averaged AUC during an evaluation period (e.g., AUCavg24) was used as the exposure measure. A total 181 ESA-naive TD MDS subjects who received at least one dose of luspatercept were included in the

analysis. The potential E-R relationship was also explored in the subset of patients with no dose escalation.

All Subjects

Exploratory plotting showed an exposure-dependent trend for RBC-TI for ≥ 12 consecutive weeks with concurrent increase in mean Hgb ≥ 1.5 g/dL in Weeks 1 to 24 in luspatercept-treated subjects.

Figure 7: Relationship between Luspatercept Serum Exposure and Probability of Achieving RBC-TI >= 12 Consecutive Weeks with Concurrent Mean Hgb Increase >= 1.5 g/dL in Weeks 1 to 24 (univariate analysis) (Figure based on data cutoff 31. Mar 2023)



In the multivariate analysis, baseline transfusion burden, baseline serum erythropoietin, and ring sideroblast status were statistically significant predictors of the probability of response. The results indicated that the probability of achieving RBC-TI for ≥ 12 consecutive weeks with a concurrent mean Hgb ≥ 1.5 g/dL in Weeks 1 to 24 was higher in subjects with ring sideroblast (RS+), with an odds ratio of 2.43 corresponding to over a two-fold increase in the probability of achieving the efficacy endpoint. The probability of response is also predicted to increase with lower baseline transfusion burden or lower baseline serum erythropoietin. After accounting for these baseline disease characteristics, the effect of AUCavg24 was not significant.

Overall, the nearly flat E-R relationship for the primary efficacy endpoint suggested that the maximum effective exposure of luspatercept was reached or approached under the current titration dosing regimen.

Table 15: Parameter Estimates of Final Model for RBC-TI for ≥ 12 Consecutive Weeks with Concurrent Mean Hb Increase ≥ 1.5 g/dL from Weeks 1 to 24 – All Subjects

	Estimate	SE	OR	95% CI of OR	P-value
Luspatercept AUCavg24 (day*ug/mL)	0.00207	0.00246	1.00	(0.997, 1.01)	0.400
Baseline Erythropoietin (U/L)	-0.00668	0.00159	0.993	(0.990, 0.996)	<0.001
Baseline Transfusion Burden (units/8 weeks)	-0.422	0.131	0.655	(0.507, 0.848)	0.001
Baseline Ring Sideroblasts	0.886	0.384	2.43	(1.14, 5.14)	0.021

Subjects with No Dose Escalation

Subsequently, sensitivity analysis was conducted for subjects receiving 1 mg/kg dose with no dose up titration to assess the exposure-response relationship without the modifying effect of dose escalation. This exposure-efficacy analysis included ESA-naive TD MDS subjects (N=55) from Study ACE-536-MDS-002 who received at least one dose of luspatercept and did not undergo dose escalations from weeks 1 to 24.

In this patient subset, an exposure-dependent increase in response was observed in the univariate analysis which appeared to plateau at the 4th AUCaavg24 quartile. AUCavg24 remained a statistically significant predictor of response (Table below). No additional covariate was identified in this subset of patients.

Figure 8: Relationship between Luspatercept Serum Exposure and Probability of Achieving RBCTI >= 12 Consecutive Weeks with Concurrent Mean Hgb Increase >= 1.5 g/dL in Weeks 1 to 24 No Dose Escalation (univariate analysis) (31. Mar 2023)

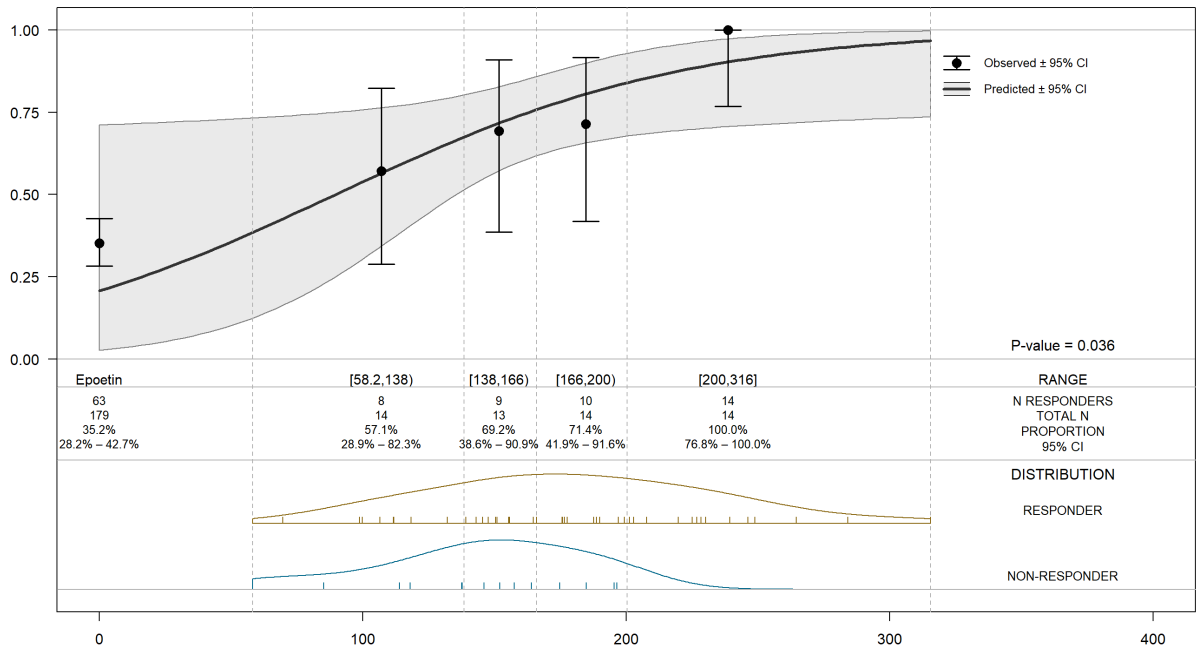


Table 16: Parameter Estimates of Final Model for RBC-TI for >= 12 Consecutive Weeks with Concurrent Mean Hgb Increase >= 1.5 g/dL from Weeks 1 to 24 No Dose Escalation

	Estimate	SE	OR	95% CI of OR	P-value
Luspatercept AUCavg24 (day*ug/mL)	0.0150	0.00714	1.02	(1.00, 1.03)	0.036

Collectively, the present results suggested a positive E-R relationship in patient receiving 1 mg/kg with no dose escalation. The E-R trend was more evident over the lower exposure range and approached response plateau at the upper exposure quartiles in those patients. Under the individual response-based titration regimen of 1 to 1.75 mg/kg, the absence of appreciable E-R in the overall study population suggested that the maximum effective exposure of luspatercept was attained in individual patients to optimize the probability of the clinical response.

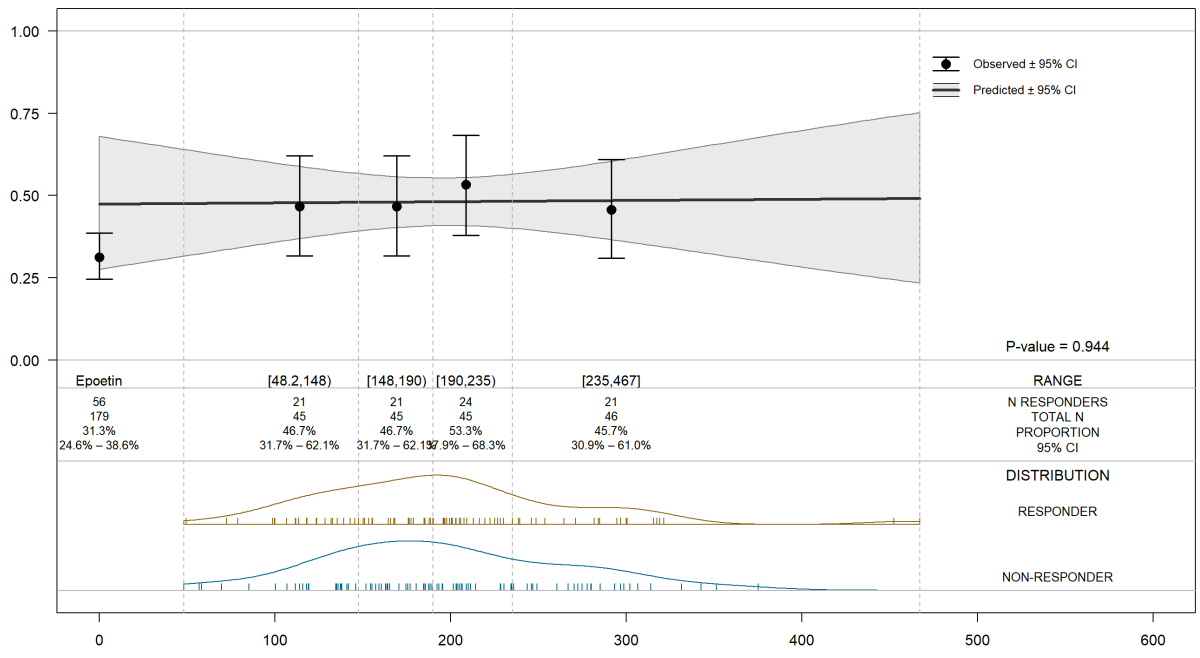
Achievement of RBC-TI for 24 weeks from Week 1 to 24

The E-R relationship for the key secondary efficacy endpoint was analyzed by logistical regression, where time-averaged AUC during an evaluation period (e.g., AUCavg24) was used as the exposure measure. Two sets of analyses were conducted either in all luspatercept-treated patients (N=181) or in patients with no dose escalation (N=55).

All Subjects

In the univariate exploratory analysis, the proportion of subjects achieving RBC-TI from Weeks 1 to 24 in each luspatercept exposure group was statistically greater than that in epoetin alfa-treated subjects. A shallow exposure-dependent trend was observed for the endpoint. However, the trend was not statistically significant.

Figure 9: Relationship between Luspatercept Serum Exposure and Probability of Achieving RBC-TI from Weeks 1 to 24 (univariate analysis) (31. Mar 2023)



In the multivariate analysis, baseline transfusion burden, baseline serum erythropoietin, and the baseline weight were statistically significant predictors for the probability of response. Higher probability of response was predicted in subjects of lower baseline transfusion burden, lower serum erythropoietin, or heavier subject. When accounting for these covariates, the effect of AUCavg24 was not statistically significant.

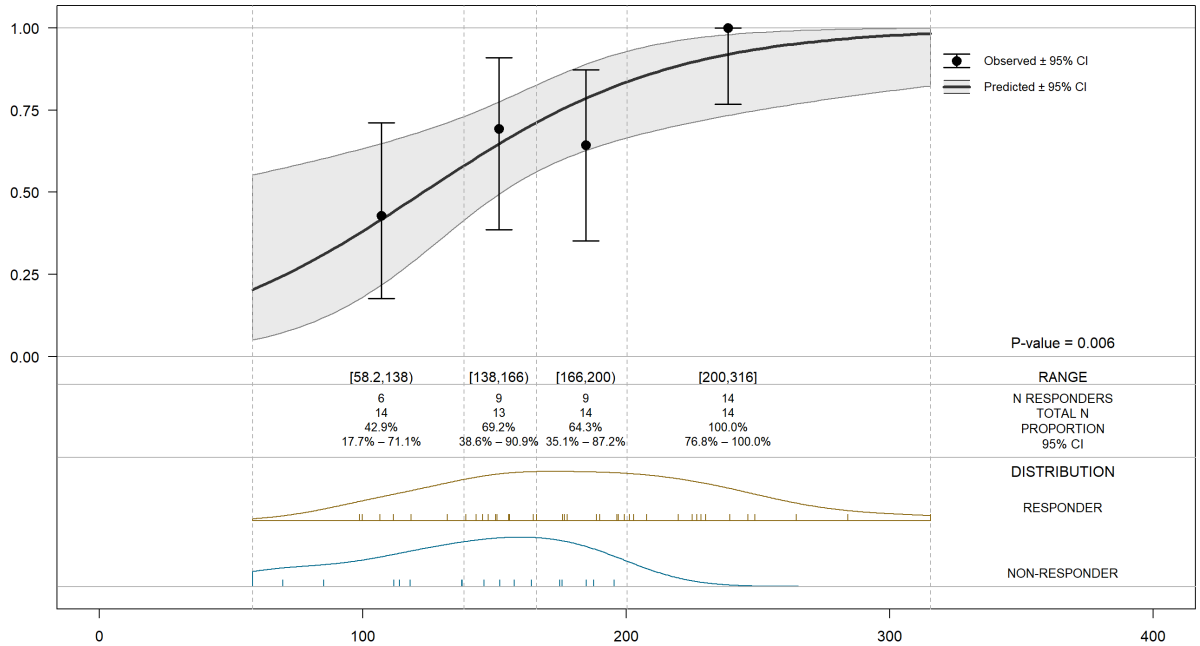
Table 17: Parameter Estimates of Final Model for RBC-TI from Weeks 1 to 24

	Estimate	SE	OR	95% CI of OR	P-value
Luspatercept AUCavg24 (day*ug/mL)	0.000991	0.00252	1.00	(0.996, 1.01)	0.695
Baseline Erythropoietin (U/L)	-0.00818	0.00190	0.992	(0.988, 0.996)	<0.001
Baseline Transfusion Burden (units/8weeks)	-0.571	0.147	0.565	(0.423, 0.754)	<0.001
Baseline Body Weight(kg)	0.0289	0.0112	1.03	(1.01, 1.05)	0.010

Subjects with No Dose Escalation

When only subjects with constant dose or no dose escalation were included (N = 55), an exposure-dependent increase was observed for the probability of achieving RBC-TI from Weeks 1 to 24. In this population subset, the exposure-dependent trend of the probability of achieving the endpoint was more visible as statistically significant and appeared to plateau at the 4th AUCavg24 quartile.

Figure 10: Relationship between Luspatercept Serum Exposure and Probability of Achieving RBC-TI from Weeks 1 to 24 – No Dose Escalation (31. Mar 2023)



In the multivariate analysis of subjects with no dose escalation, both AUCavg24 and positive baseline ring sideroblast status were statistically significant predictors of the probability of response. Baseline weight was a significant predictor of the probability of achieving RBC-TI from Weeks 1 to 24 in the final model. The results suggest the probability to achieve RBC-TI was slightly higher in heavier subjects, with an odds ratio with 1.07.

Table 18: Parameter Estimates of Final Model for RBC-TI from Weeks 1 to 24 – No Dose Escalation

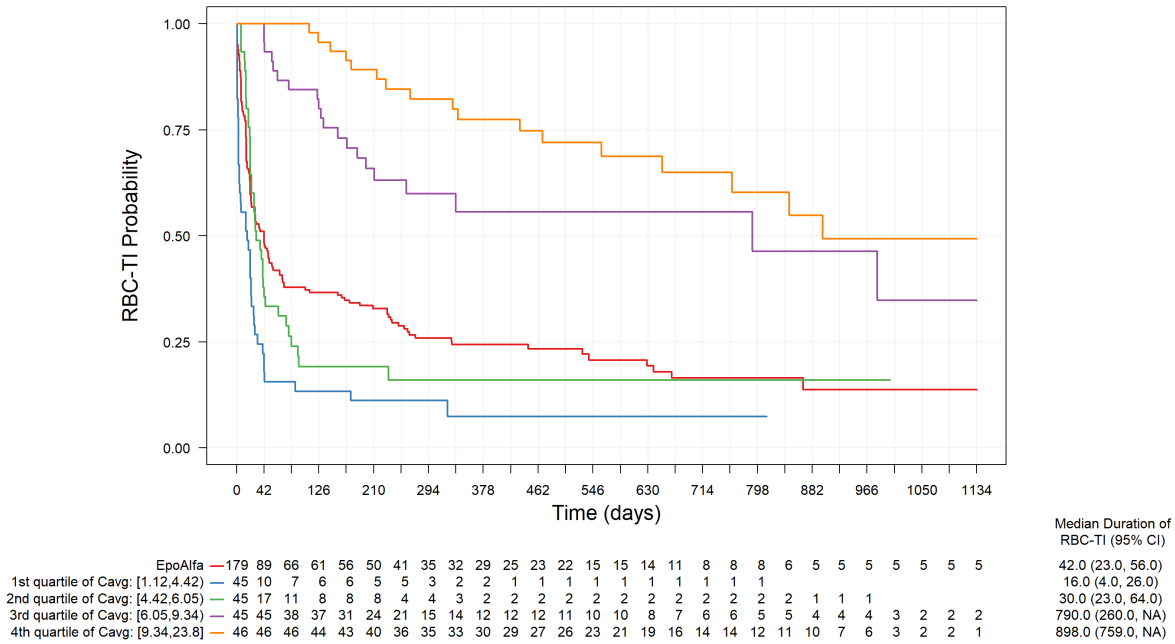
	Estimate	SE	OR	95% CI of OR	P-value
Luspatercept AUCavg24 (day*ug/mL)	0.0278	0.00964	1.03	(1.01, 1.05)	0.004
Baseline Body Weight (kg)	0.0542	0.0261	1.06	(1.00, 1.11)	0.038

Similar to the primary efficacy endpoint, the present analyses of RBC-TI 24-week response suggested a positive E-R relationship in patients receiving no dose escalation. The steep E-R trend over the lower exposure range became shallower at the upper exposure quartiles, suggesting saturation in response. In the overall study population receiving the individual response-based titration regimen of 1 to 1.75 mg/kg, the E-R was nearly flat, indicating that the maximum effective exposure of luspatercept was achieved in individual patients to achieve the response following dose up titration.

Time from First Dose to First RBC Transfusion (Week 1 to Data Cutoff Date)

The E-R relationship for the time from first dose to first RBC transfusion event was explored initially by Kaplan-Meier curves stratified by luspatercept serum exposure (i.e., daily Cavg on the day of event or censoring) quartiles in 146 luspatercept-treated subjects, where an E-R relationship was apparent based on the ascending order of exposure quartiles. There was notable separation in the third and fourth luspatercept quartiles groups from those of epoetin alfa (control group), the first quartile group, and the second quartile group. Median time to first RBC transfusion was significantly longer in the third (652 days) and fourth luspatercept quartiles (847 days), as compared to the epoetin alpha arm (42 days), the first quartile (21 days), and the second quartile (28.5 days). This difference reflected the rapid drops in the proportion of transfusion-free individuals in the first and second exposure quartiles before Day 42, during which dose modifications were not permitted. Likewise, there was a significant difference in time to first RBC transfusion between the luspatercept exposure groups. There are limitations in the univariate analysis, such as the exclusion of additional covariates and stratifying exposure by daily Cavg on the day of event or censoring. Thus, any differences in the Kaplan Meier curves may be confounded by varying patient baseline factors, as well as the use of non-time varying Cavg unrepresentative of the entire time course of luspatercept dosing.

Figure 11: Kaplan-Meier Curve for Time from First Dose to First RBC Transfusion Event (31. Mar 2023)



The multivariate Cox proportional hazards regression analysis was further performed to determine the effects of baseline disease characteristics and luspatercept exposure on the time to first RBC transfusion event. Baseline RBC transfusion burden and weight were covariates retained in the final model along with luspatercept exposure, suggesting that the duration of RBC-TI was shorter in subjects with higher RBC transfusion burden and lower baseline body weight (Table below).

The effect of time-varying Cavg was not significant.

Table 19: Parameter Estimates of Final Cox Model for Time to First RBC Transfusion

Parameter	Estimate	SE	HR	95% CI of HR	P-value
Cavg of Luspatercept (µg/mL)	-0.00461	0.0532	0.995	(0.897, 1.1)	0.931
Baseline RBCT Burden (units/8 weeks)[b]	0.323	0.0574	1.38	(1.23, 1.55)	1.85e-08
Baseline body Weight (kg)	-0.0123	0.00586	0.988	(0.976, 0.999)	0.0351

Abbreviations: RBC, red blood cell; RBCT, red blood cell transfusion

Dose Assessment in Relation to Efficacy

Dose assessments in relation to maintenance of RBC-TI were performed for the 138 subjects who were able to achieve RBC-TI for any 12 consecutive weeks from Week 1 to the end of treatment, and 117 subjects who achieved RBC-TI for any 24 consecutive weeks from Week 1 to end of treatment, irrespective of change in hemoglobin levels. In this analysis, subjects were stratified by dose level received by each responder over the duration of these 12 or 24 RBC-TI periods. As such, the prevalence of these mg/kg dose levels required for the maintenance of RBC-TI were examined.

The dose levels in the table below were used to describe the following doses received by subjects, from Day 1 to Weeks 12 or 24 of RBC-TI. Those in the "0.8 mg/kg", "1 mg/kg", "1.33 mg/kg" and "1.75 mg/kg" stayed at a single dose level (of the respective mg/kg dose) and those in the "multiple increased" and "multiple reduced" received one or more dose escalations or reductions (respectively) during the maintenance of RBC-TI.

Table 20: Dose Level Definitions

Dose Level	Potential Doses Received from Day 1 to Weeks 12 or 24 of RBC-TI
0.8 mg/kg	Subject received 0.8 mg/kg only over the duration of RBC-TI
1 mg/kg	Subject received 1 mg/kg only over the duration of RBC-TI
1.33 mg/kg	Subject received 1.33 mg/kg only over the duration of RBC-TI
1.75 mg/kg	Subject received 1.75 mg/kg only over the duration of RBC-TI.
Multiple reduced	Subject received 0.8 mg/kg and 1 mg/kg doses over the duration of RBC-TI
	Subject received <0.8 mg, 0.8 mg/kg, and 1 mg/kg doses over the duration of RBC-TI
Multiple increased	Subject received 0.8 mg/kg, 1 mg/kg, and 1.33 mg/kg doses over the duration of RBC-TI
	Subject received 1 mg/kg and 1.33 mg/kg doses over the duration of RBC-TI
	Subject received 1.33 mg/kg and 1.75 mg/kg doses over the duration of RBC-TI
	Subject received 1 mg/kg, 1.33 mg/kg, and 1.75 mg/kg doses over the duration of RBC-TI
	Subject received 0.8 mg/kg, 1 mg/kg, 1.33 mg/kg, and 1.75 mg/kg doses over the duration of RBC-TI

The Figure below shows the time to 12-week and 24-week RBC-TI, among subjects who achieved these responses. Subjects were stratified by the above-mentioned dose levels received over the duration of the 12- or 24-week RBC-TI periods.

During the maintenance of this 12-week period, 39.9% (55/138) of responders received multiple dose escalations. A total of 50% (69/138) of responders received doses higher than 1 mg/kg (the starting dose) over the duration of RBC-TI . Similarly, among 117 responders in the luspatercept arm who were able to maintain RBC-TI for any 24 weeks, 46.2% (54/117) of responders required multiple dose escalations. A total of 54.7% (64/117) of responders received doses higher than 1 mg/kg over the duration of RBC-TI.

Results indicate that a large portion of responders required doses higher than 1 mg/kg during the 12- or 24-week periods where RBC-TI was maintained.

Table 21: Number of Responders by Efficacy Endpoints and Dose Level

Endpoint	0.8 mg/kg	1 mg/kg	1.33 mg/kg	1.75 mg/kg	Multiple Increased	Multiple Reduced	Total
RBC-TI for 12 consecutive weeks	4	61	5	9	55	4	138
RBC TI for 12 consecutive weeks	2.90%	44.20%	3.60%	6.50%	39.90%	2.90%	100.00%
RBC TI for 24 consecutive weeks	5	40	2	8	54	8	117
RBC TI for 24 consecutive weeks	4.30%	34.20%	1.70%	6.80%	46.20%	6.80%	100.00%

Distribution of luspatercept exposure and baseline disease characteristics that might impact efficacy and dose escalation were inspected by the maximum dose administered in the primary treatment phase of Week 1 to 24. This analysis included AUCss, which was derived from individual subject parameters as estimated from the PPK model with an assumed constant dose of 1 mg/kg. AUC over 24 weeks (AUCavg) was also included to reflect actual luspatercept serum exposure with dose escalations, reductions, and dose delays. These two AUC measures provide comparison between exposures with (AUCavg) and without (AUCss) dose escalation.

Patients with dose escalation had lower median exposure at the same starting dose of 1 mg/kg compared to those with no dose titration.

With dose escalations, AUCavg increased with maximum dose level, corresponding to an exposure increase after dose up-titration. Baseline disease characteristics indicating more severe disease also appear more prevalently in subjects requiring higher maximum dose levels.

Based on the data cutoff 31. Mar 2023; baseline intermediate IPSS-R was observed in 17.2% subjects requiring a maximum dose of 1.75 mg/kg, as compared to 14.7% and 29.4% of subjects requiring maximal doses of 1 mg/kg and 1.33 mg/kg, respectively. RBC transfusion burden of ≥ 4 units/8 weeks was seen in 23.5% of subjects requiring a maximum dose of 1 mg/kg, 29.4% of subjects requiring maximal doses of 1.33 mg/kg, and 29.9% of subjects requiring a maximum dose of 1.75 mg/kg. Baseline median serum erythropoietin also seemed to increase with increasing maximum dose level. There was no apparent trend in the proportion of RS- patients across the different maximum dose levels.

Table 22: Summary of Luspatercept Exposure and Key Factors Related to Efficacy by Dose Escalation Status for 12 Weeks

	1 mg/kg (N = 34)	1.33 mg/kg (N = 17)	1.75 mg/kg (N = 87)	Total (N = 138)
AUCss (day*µg/mL)				
Median [95 PI]	196.95 [121.47, 280.49]	188.18 [116.64, 243.57]	170.05 [93.78, 241.63]	182.18 [99.00, 261.77]
[min, max]	[111.08, 325.78]	[109.08, 253.70]	[59.71, 334.20]	[59.71, 334.20]
AUCavg24 (day*µg/mL)				
Median [95 PI]	170.83 [104.35, 261.14]	185.56 [131.94, 288.13]	203.54 [99.14, 320.69]	191.30 [100.07, 315.84]

Table 22: Summary of Luspatercept Exposure and Key Factors Related to Efficacy by Dose Escalation Status for 12 Weeks

	1 mg/kg (N = 34)	1.33 mg/kg (N = 17)	1.75 mg/kg (N = 87)	Total (N = 138)
[min, max]	[49.49, 315.54]	[118.36, 300.43]	[58.23, 467.30]	[49.49, 467.30]
Baseline EPO (U/L)				
Median [95 PI]	31.45 [14.30, 158.07]	67.86 [18.33, 447.73]	75.82 [28.25, 314.54]	63.95 [16.89, 311.46]
[min, max]	[7.80, 266.46]	[7.99, 495.77]	[10.09, 442.33]	[7.80, 495.77]
Baseline IPSS-R				
Intermediate	5 (14.7%)	5 (29.4%)	15 (17.2%)	25 (18.1%)
Low	23 (67.6%)	11 (64.7%)	63 (72.4%)	97 (70.3%)
Very Low	5 (14.7%)	1 (5.9%)	9 (10.3%)	15 (10.9%)
Missing	1 (2.9%)	0 (0%)	0 (0%)	1 (0.7%)
Baseline ring sideroblast status				
No	10 (29.4%)	6 (35.3%)	13 (14.9%)	29 (21.0%)
Yes	24 (70.6%)	11 (64.7%)	74 (85.1%)	109 (79.0%)
Baseline EPO category (U/L)				
≤ 200	33 (97.1%)	14 (82.4%)	71 (81.6%)	118 (85.5%)
> 200	1 (2.9%)	3 (17.6%)	16 (18.4%)	20 (14.5%)
Base RBCT Burden category				
< 4 RBC units/8 weeks	26 (76.5%)	12 (70.6%)	61 (70.1%)	99 (71.7%)
≥ 4 RBC units/8 weeks	8 (23.5%)	5 (29.4%)	26 (29.9%)	39 (28.3%)

Abbreviations: AUCss, area under the concentration-time curve at steady state; AUCavg24, time-averaged AUC from Week 1 to 24; EPO, endogenous erythropoietin; IPSS-R, Revised International Prognostic Scoring System; RBC, red blood cells; RBCT, red blood cell transfusion.

Exposure-Response for Safety

The exposure-safety analysis included subjects from Study ACE-536-MDS-002 only who received at least one dose of luspatercept and had both empirical Bayesian estimates of individual luspatercept PK parameters (derived from the PPK analysis) and the specified safety data. Subjects treated with epoetin alfa were included in the graphical data comparisons, but they were excluded from exposure-safety modelling.

Treatment-emergent adverse events included adverse events that started on or after the first dose of luspatercept until 42 days after the last dose. Only the first event occurring during Week 1 to 48 was included. The E-R analysis for safety was conducted for the following two evaluation periods:

☐ Weeks 1 to 6, during which intra-subject dose escalation was not allowed. The purpose of this analysis is to explore the exposure-safety relationship in luspatercept-treated patients without the influence of dose titration.

☐ Weeks 1 to 48, during which intra-subject dose escalation was allowed.

TEAEs >= Grade 3

In the Week 1 to 6 evaluation period, luspatercept exposure was not associated with a higher incidence of ≥ Grade 3 TEAEs (Figure 3.2.2.1-1). In the Week 1 to 48 evaluation period, lower luspatercept exposure appeared to trend with a higher incidence of ≥ Grade 3 TEAEs, although not statistically significant. (Figure 3.2.2.1-2).

Figure 12: Relationship between Luspatercept AUCAE and Probability of >= Grade 3 TEAEs, Week 1 to 6 (univariate analysis) (Figure based on data cutoff 31. Aug 2022)

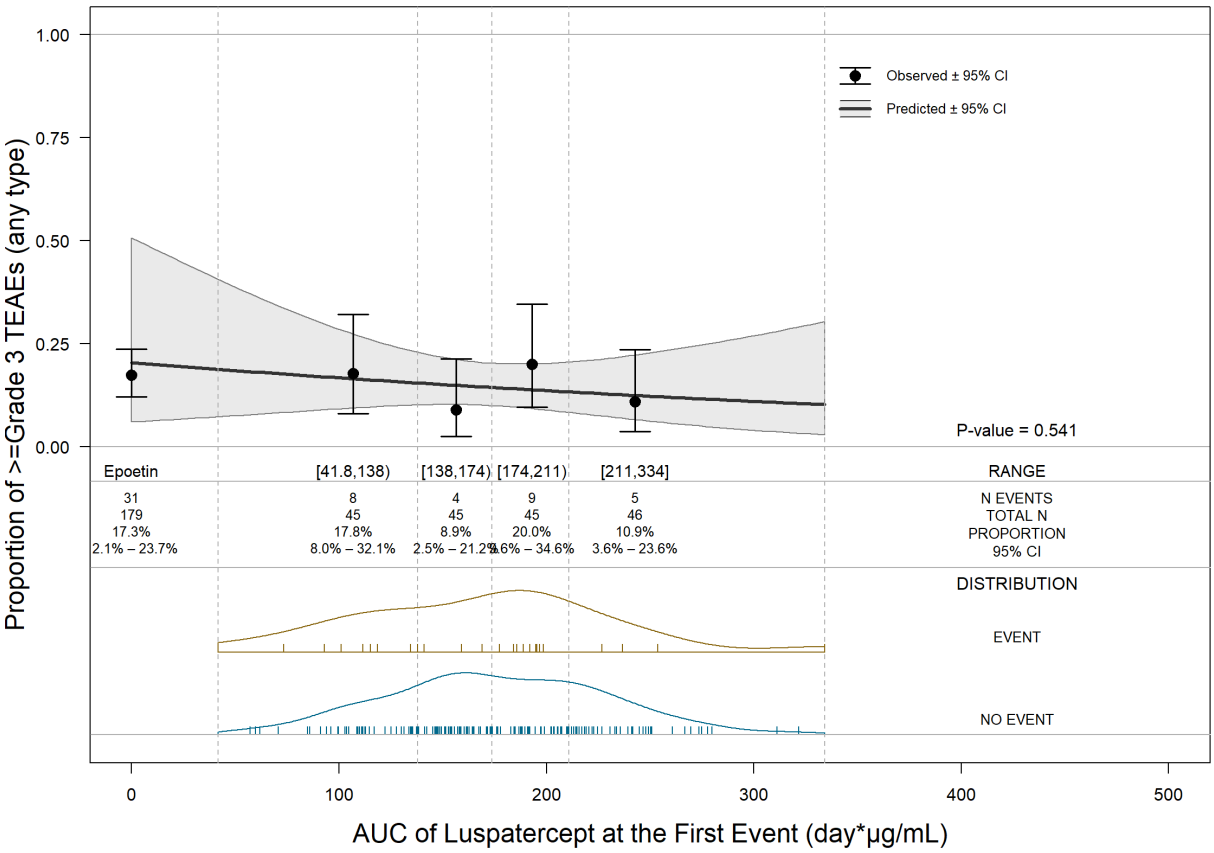
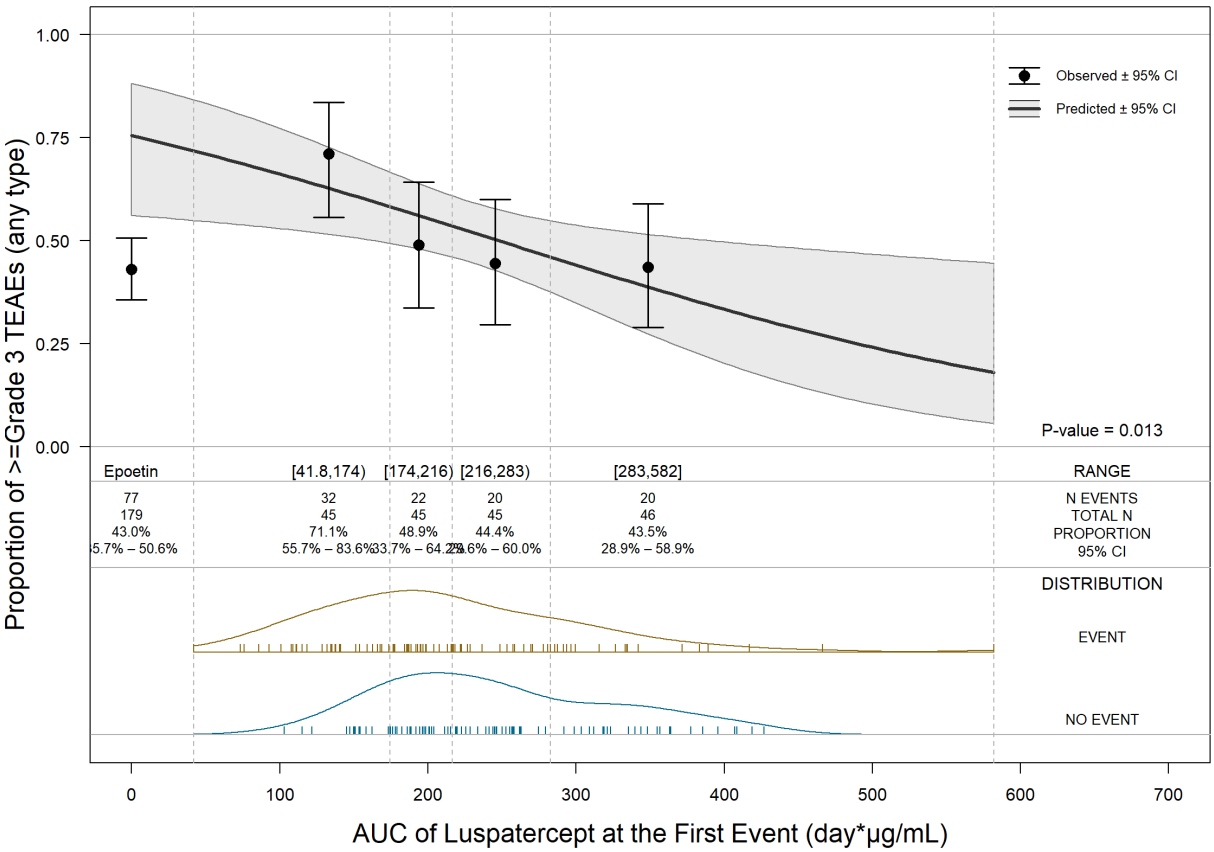


Table 23: ≥ Grade 3 TEAEs (any type) Parameter Estimates, Weeks 1-6

Parameter	Estimate	SE	OR	OR_CI	p-value
AUCavg (day*ug/mL)	-0.00244	0.00399	0.998	0.99-1.005	0.541

Figure 13: Relationship between Luspatercept AUCAE and Probability of >= Grade 3 TEAEs, Week 1 to 48 (31. Mar 2023)



The multivariate logistic analysis showed that the E-R relationship was not statically significant (p=0.056577, based on interim data (cutoff 31. Aug 2022, update requested), indicating an overall flat relationship between luspatercept AUCavg and incidence of ≥ Grade 3 TEAEs in Week 1 to 48. No covariate was identified as a significant risk factor according to the analysis.

Table 24: ≥ Grade 3 TEAEs (any type) Parameter Estimates, Weeks 1-48

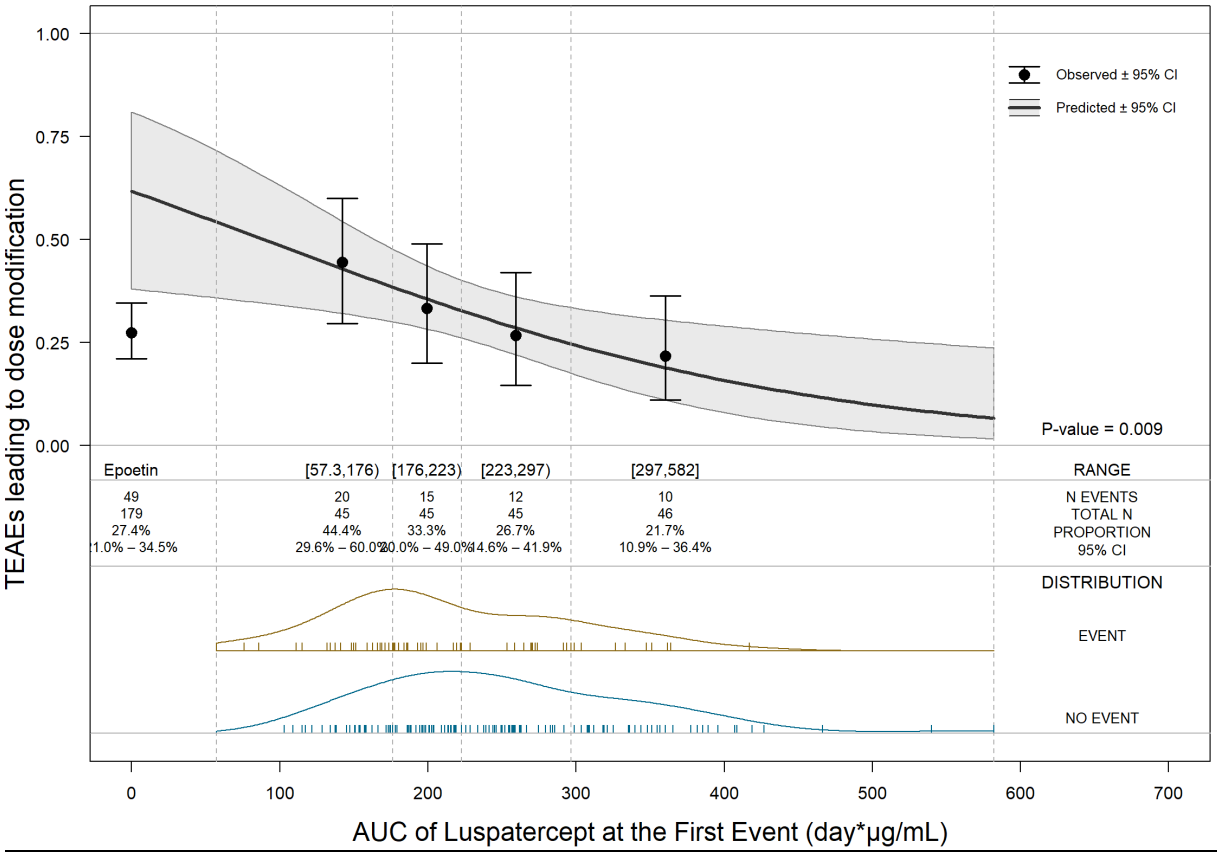
	Estimate	SE	OR	95% CI of OR	p-value
AUCavg (day*ug/mL)	-0.00455	0.00183	0.995	0.992-0.999	0.0132

TEAEs Leading to Dose Modification

In the Week 1 to 6 evaluation period, no significant relationship was observed between luspatercept exposure and the probability of TEAE leading to dose modification (i.e., dose reduction, dose delay, or treatment discontinuation).

In the Week 1 to 48 evaluation period, a statistically significant inverse relationship was observed between luspatercept exposure and the probability of TEAE leading to dose modification (Figure 3.2.2.2-1). The specific reason for the lower incidence of TEAE related dose modifications at higher exposure is not well understood and could be accounted for by unknown baseline disease characteristics or the titration regimen.

Figure 14: Relationship between Luspatercept AUCAE and Probability of TEAEs Leading to Dose Modification, Week 1 to 48 (univariate analysis) (31. Mar 2023)



Fatigue-Like Events (Fatigue, Asthenia, all grades)

In the Week 1 to 6 evaluation period, no correlation was observed between luspatercept exposure and fatigue or asthenia event of all grades.

Table 25: Parameter Estimates: Fatigue-like events (≥ Grade 1), Weeks 1 to 6

	Estimate	SE	OR	95% CI of OR	p-value
AUCavg (day*ug/mL)	-0.00045	0.0039	1	0.992-1.007	0.90784

Table 26: Parameter Estimates: Fatigue-like events (≥ Grade 1), Weeks 1 to 48

	Estimate	SE	OR	95% CI of OR	p-value
AUCavg (day*ug/mL)	-0.01028	0.00268	0.990	0.985-0.995	0.00012
Red Blood Cell Transfusion Burden (units/8 weeks)	0.25172	0.12717	1.286	1.002-1.65	0.04778

Hypertension (all grades)

In both the Week 1 to 6 and the Week 1 to 48 evaluation periods, luspatercept exposure was not statistically associated with increased probability of hypertension of all grades. The logistic regression plot for the Week 1 to 48 period is shown below.

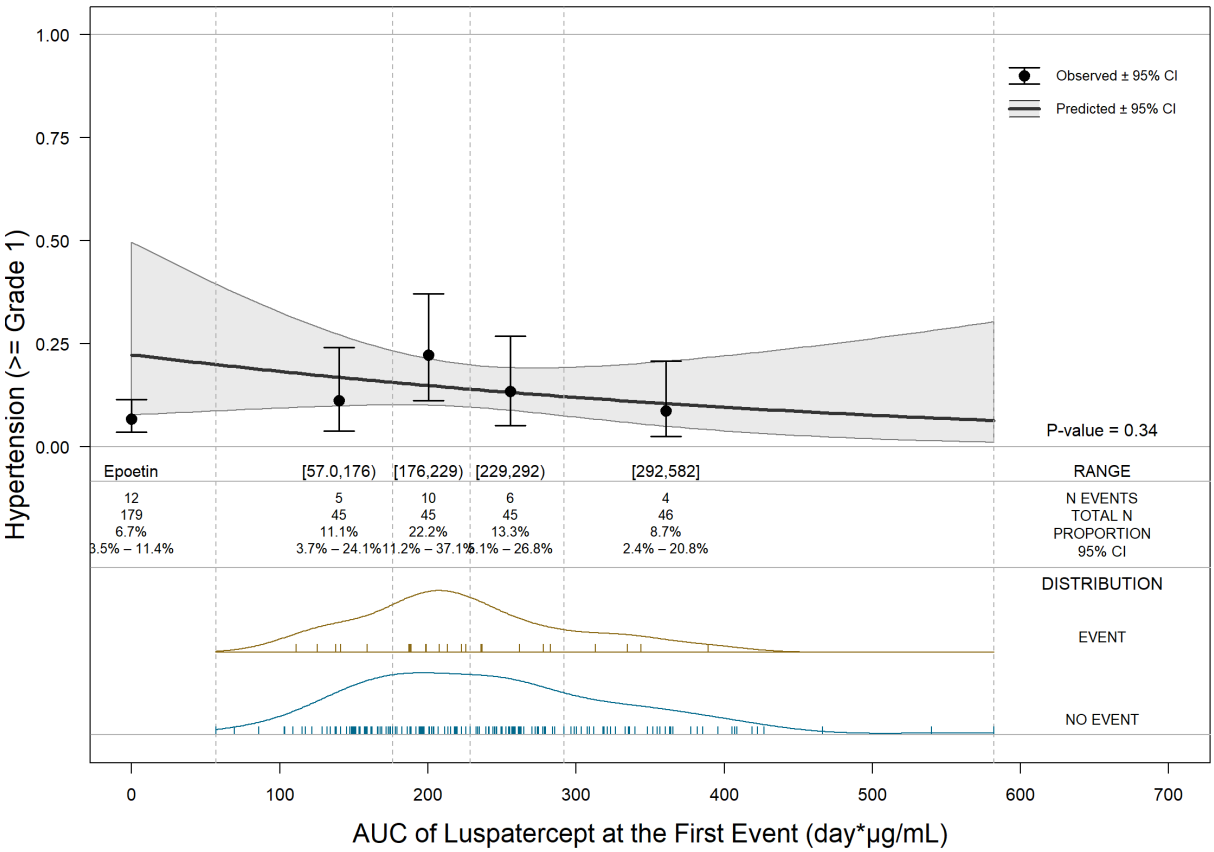
Table 27: Parameter Estimates, Hypertension (≥ Grade 1) Weeks 1-6

	Estimate	SE	OR	95% CI of OR	p-value
AUCavg (day*ug/mL)	0.00514	0.00533	1.005	0.995-1.016	0.33522

Table 28: Parameter Estimates, Hypertension (≥ Grade 1) Weeks 1-48

	Estimate	SE	OR	95% CI of OR	p-value
AUCavg (day*ug/mL)	-0.00249	0.00261	0.998	0.992-1.003	0.33971

Figure 15: Relationship between Luspatercept AUCAE and Probability of Experiencing Hypertension (all grades), Week 1 to 48 (univariate analysis) (31. Mar 2023)



Other Treatment-Emergent Adverse Events

No statistically significant E-R relationship was found for the following TEAEs over Week 1 to 6 or 1 to 48 periods:

☐ Bone Pain-Like Events (Bone pain, Arthralgia, all grades)

☐ Dizziness (all grades)

Exposure-Response Conclusion

Efficacy

- A positive E-R relationship was observed in patients receiving 1 mg/kg with no dose scalation for the probability of RBC-TI for 12 weeks with a concurrent mean Hgb increase ≥ 1.5 g/dL in Week 1 to 24. The noted E-R trend was evident at the lower exposure range and approached response plateau at the upper exposure quartiles. There was no appreciable E-R in the overall study population receiving the individual response-based titration regimen of 1 to 1.75 mg/kg, suggesting the attainment of the maximum effective exposure of luspatercept in individual patients to optimize the probability of clinical response.

- Higher probability of response is associated with lower baseline RBC transfusion burden, lower baseline serum erythropoietin or positive ring sideroblast status.
- Similarly, a positive E-R relationship was only identified in patient receiving 1 mg/kg with no dose scalation for the probability of RBC-TI for 24 weeks and the E-R trend approached plateau at the upper exposure quartiles. Under the individual response-based titration regimen of 1 to 1.75 mg/kg, E-R relationship was nearly flat in the overall study population, indicating that the maximum effective exposure of luspatercept was achieved in individual patients to achieve clinical response.
- Higher probability of response is associated with lower baseline RBC transfusion burden, lower baseline serum erythropoietin or higher body weight.
- RBC-TI was achieved under the dose titration regimen of 1 to 1.75 mg/kg. There was no association between luspatercept exposure and time to first RBC transfusion:
- Baseline transfusion burden and body weight were identified as baseline characteristics influencing clinical response.
- Dose titration regimen extends the duration of transfusion independence, among the 138 responders of RBC-TI of any 12 weeks, 39.9% (55/138) of responders received multiple dose escalations. A total of 50% (69/138) of responders received doses higher than 1 mg/kg (the starting dose) over the duration of RBC-TI. Similarly, among 117 responders who were able to maintain RBC-TI for any 24 weeks, 46.2% (54/117) of responders required multiple dose escalations. A total of 54.7% (64/117) of responders received doses higher than 1 mg/kg over the duration of RBC-TI. The results support dose escalation for adequate maintenance of durable response in a large proportion of patients.
- A trend of higher baseline serum erythropoietin and RBC transfusion burden was more frequently noted in patients with dose escalation to 1.75 mg/kg, supporting the clinical benefit of dose escalation in patients of higher disease severity. There was no notable difference in the proportion of RS- patients across the maximum dose levels.

Safety

- During the period of Weeks 1 to 6, no statistically significant E-R relationship was observed for probability of all grade events of fatigue or asthenia, bone pain or arthralgia, hypertension, and dizziness. There was also no E-R association for dose modifications due to TEAEs or the occurrences of Grade $\geq$ 3 TEAEs.
- During the period of Weeks 1 to 48, no statistically significant E-R relationships were observed for the events of bone pain or arthralgia, hypertension, and dizziness, as well as Grade $\geq$ 3 TEAEs.
- During the period of Weeks 1 to 48, an inverse E-R relationship was observed for fatigue or asthenia event and dose modifications due to TEAEs. However, this was not observed between Weeks 1 to 6 (no dose escalation). The inverse trend may be related to underlying disease progression or imbalance of the unknown disease characteristics.

Effect of Immunogenicity on Pharmacokinetics

ADA incidences are summarized for the two pivotal studies (ACE-536-MDS-002 and ACE-536-MDS-001) in patients with MDS receiving 1 mg/kg luspatercept as starting dose with intra-subject dose escalation to 1.33 and 1.75 mg/kg allowed. As shown from Table 4.1.3.2-1, the incidences of treatment emergent ADA and neutralizing ADA were generally comparable across the MDS population.

Table 29: Summary of Treatment-Emergent Anti-Drug Antibodies Incidence in Subjects with MDS

Treatment-emergent Anti-Drug Antibodies	ACE-536-MDS-001		ACE-536-MDS-002	Total
	Placebo (N=76), n (%)	Luspatercept (N=153), n (%)	Luspatercept (N=178), n (%)	Luspatercept (N=331), n (%)
ADA against luspatercept	3 (3.95)	11 (7.19)	10 (5.6)	21 (6.34)
Specificity for ACE-mECD	1 (1.32)	5 (3.27)	5 (2.8)	10 (3.02)
Specificity for ActRIIB ECD	1 (1.32)	3 (1.96)	2 (1.1)	5 (1.51)
Neutralizing luspatercept	2 (2.63)	5 (3.27)	9 (5.1)	14 (4.23)

ActRIIB = activin receptor type IIB; ACE-mECD: modified ECD of human ActRIIB on luspatercept; ActRIIB ECD = natural ECD of human ActRIIB; ADA = anti-drug antibodies; ECD = extracellular domain; N = total number of subjects providing evaluable ADA sample; n = number of subjects with treatment-emergent ADA.

The potential effect of ADA on luspatercept pharmacokinetics was evaluated in the PPK analysis.

In the analysis, ADA status was defined as a time-varying variable. Even though there was a small trend of higher clearance associated with positive ADA, the effect was not statistically significant, with 95% confidence interval including the null value. The result suggested a limited effect of ADA affecting luspatercept PK.

Conclusions on E-R analyses

- A positive E-R relationship was observed in patients receiving 1 mg/kg with no dose scalation for the probability of RBC-TI for 12 weeks with a concurrent mean Hgb increase ≥ 1.5 g/dL in Week 1 to 24. The noted E-R trend was evident at the lower exposure range and approached response plateau at the upper exposure quartiles. There was no appreciable E-R in the overall study population receiving the individual response-based titration regimen of 1 to 1.75 mg/kg, suggesting the attainment of the maximum effective exposure of luspatercept in individual patients to optimise the probability of clinical response.
- Higher probability of response is associated with lower baseline RBC transfusion burden, lower baseline serum erythropoietin or positive ring sideroblast status.
- Similarly, a positive E-R relationship was only identified in patient receiving 1 mg/kg with no dose scalation for the probability of RBC-TI for 24 weeks and the E-R trend approached plateau at the upper exposure quartiles. Under the individual response-based titration regimen of 1 to 1.75 mg/kg, E-R relationship was nearly flat in the overall study population, indicating that the maximum effective exposure of luspatercept was achieved in individual patients to achieve clinical response.
- Higher probability of response is associated with lower baseline RBC transfusion burden, lower baseline serum erythropoietin or higher body weight.

- RBC-TI was achieved under the dose titration regimen of 1 to 1.75 mg/kg. There was no association between luspatercept exposure and time to first RBC transfusion. Baseline transfusion burden and body weight were identified as baseline characteristics influencing clinical response.
- Assessment of dose-response for efficacy support the benefit of dose titration to 1.75 mg/kg for adequate maintenance of durable RBC-TI response in a large proportion of patients. The titration regimen extended the duration of transfusion independence and improved clinical response in all patients, including those of higher disease severity (baseline transfusion burden, serum erythropoietin).
- No positive association between luspatercept exposure and the incidences of Grade ≥ 3 TEAEs, dose modifications due to TEAEs, and AESIs including fatigue or asthenia or hypertension.
- The overall incidences of treatment-emergent ADA and neutralising ADA in patients with MDS were low following luspatercept treatment. ADA incidence was similar between ESA-naive TD MDS and other TD MDS subjects. ADA titres were mostly low.
- The development of ADA has no clinically significant effect on luspatercept PK, efficacy, and safety.

Dose Justification

Collectively, the clinical pharmacology data support the recommended luspatercept dose titration regimen of 1 to 1.75 mg/kg for the treatment of ESA-naive TD MDS.

The recommended starting dose of 1.0 mg/kg Q3W and titration to 1.33 mg/kg and then 1.75 mg/kg per patient's response is supported by efficacy, safety, PK, and E-R data in subjects with MDS.

- The recommended dosing regimen (1.0 to 1.75 mg/kg) that is currently approved for patients with lower-risk TD-MDS was confirmed to be effective and safe in Study ACE-536-MDS-002. The study met the primary efficacy endpoint (RBC-TI for 12 weeks with an associated concurrent mean Hgb increase ≥ 1.5 g/dL) and demonstrated durability of RBC-TI compared to epoetin alpha. Luspatercept dose titration up to 1.75 mg/kg was well tolerated, with the majority of AEs managed by dose modifications.
- Assessment of dose-response for efficacy support the benefit of the 1.0 mg/kg starting dose and suggested that dose escalations to 1.33 mg/kg and 1.75 mg/kg improved the clinical response and the duration of transfusion independence in all patients.
- The E-R analyses for efficacy and safety showed that the exposure level across the therapeutic dose range (1.0 to 1.75 mg/kg) led to reliable, robust, and durable response with manageable TEAEs. The overall nearly flat E-R relationships suggested that the maximum effective exposure of luspatercept was reached in most subjects under the recommended titration to response dosing regimen.
- No dose adjustment is recommended for any intrinsic factors, including demographics (age, sex, race/ethnicity), mild to moderate hepatic or renal impairment, as well as baseline disease characteristics (RBC transfusion burden, RS status, and sEPO level).

2.3.3. Discussion on clinical pharmacology

The Pharmacokinetics of luspatercept was previously characterised and assessed during the initial MAA.

With this application, the MAH submitted a population PK model based on the previously established model for patients with MDS, additionally including ESA naive TD MDS patients from study ACE-536-MDS-002 and Japanese patients from study ACE-536-MDS-003. In total, the population PK model is based on 4904 PK samples from 472 subjects in four studies in MDS patients: one Phase 2 dose finding/expansion study (A536-03, N=116), one Phase 2 study with Japanese subjects (ACE-536-MDS-003, N=21) and two Phase 3 pivotal studies (ACE-536-MDS-001, N=153 and ACE-536-MDS-002, N=182). The vast majority of samples was included in the model (4,356 (98.1%) samples from 471 subjects), which is appreciated. During the procedure the MAH submitted an updated model including additional data from study ACE-536-MDS-002 (addition of 17 subjects and 325 observable samples). Overall, the size of the dataset is considered suitable to allow a comprehensive description of the PK in the overall MDS population. Nevertheless, the baseline characteristics of the population included in the dataset indicate some limitations of the model. While the inclusion of Japanese subjects is appreciated, this is highly confounded with study and transfusion dependence since the patients from study ACE-536-003 represent 1/3 of the transfusion independent patients. Since no other race/ethnicity groups besides White and Asian/Japanese are included, no conclusions can be drawn in this regard. Further limitations have been identified regarding conclusions about severe renal or hepatic impairment where only 1 patient from each category was included. Data for moderate renal or hepatic impairment are also limited (hepatic: 30 patients (6.6%), renal: 87 (20%)). (Note: These data are still based on the interim data cutoff 31. Aug 2022. An update is requested.). However, updated data based on cut-off date of 31 March 2023 have been provided in the procedure.

In addition to the updated popPK model, the MAH presented Exposure-Response models mainly based on study ACE-536-MDS-002, which were also updated during the procedure. These models are discussed below.

During the assessment a GCP violation was detected regarding the collection of unconsented samples. This includes mainly PK and ADA samples. The provided updated modelling report includes these excess PK samples (~10% of included PK samples). An update of the models is currently not requested for this procedure but the MAH committed to submit the updated results by Q3 2024 (REC).

The MAH clarified that the latest provided report includes the final data set including the excess samples. The MAH claims that currently analyses are ongoing without the excess samples included updates on the popPK and E-R models. The MAH estimated that the respective data will be submitted by the end of Q2 2024 and Q3 2024. The respective updates should also include a comparison between data derived with and without the excess samples. The MAH committed to the respective RECs.

The model development is based on the previous luspatercept popPK model established for subjects with MDS. Given that a full covariate analysis was completed in the previous analysis, the current analysis focused on selected characteristics of interest that might be enriched or expanded numerically impacted by the addition of new subjects. This is acceptable and the list of respective covariates seems adequate.

The final model is a one-compartment model with first order elimination and absorption with a log-additive residual error model, including covariate effects of baseline weight, baseline albumin, baseline age, baseline eGFR and previous ESA therapy on CL/F and baseline weight and baseline albumin on V1/F.

Body weight and baseline albumin are identified as most influential covariates. The MAH states that this would support weight-based dosing and provided additional data upon request. It can be agreed that no dose modification for overweight and underweight patients is required, also given the intended titration-to-response regimen and the respective rules for adverse events. This is important given that in the E-R

analysis (see discussion below) the MAH showed that efficacy seems to be related with exposure, consequently patients with lower body weight might require a higher dose to achieve an efficacious exposure. The following observation from the E-R analysis of safety parameters supports this assumption: A higher probability for fatigue or asthenia was observed for patients with lower exposure. This might also be indicative of a lower efficacy since these events are also related to anaemia.

Besides the significant covariates, ADAs status also seem to influence CL/F, however the influence was just not found as significant, this might however just be missed due to lower numbers. An influence can nevertheless not be excluded. Although only ~6% of patients developed ADA in study ACE-536-MDS-002, this is not neglectable since these were already during the first year and luspatercept is intended as long-term treatment. Upon request further discussions on the influence on PK, efficacy and safety were provided. Although subjects with treatment-emergent ADA exhibited a trend of numerically lower exposure compared to those of negative ADA status (GMRs of exposure parameters ~0.73 to 0.85), no effect on efficacy or safety could be observed and the CI for the PK analysis were largely overlapping. While this is reassuring, it must be noted that only a very limited number of patients developed treatment emergent ADAs during the study and no long-term data are available. However, no further concerns are raised since any effects on efficacy or safety should be covered by dose modifications/Stopping rules included in the SmPC.

Overall, the population PK model seems to describe the observed data well. Nevertheless, some discrepancies have been identified. The observed outliers seem to have a neglectable effect on the popPK model and no differences regarding efficacy or safety were identified in these patients. Furthermore, the VPC for time after previous dose indicate the occurrence of rather high luspatercept concentrations within the first 25 days after the previous dose, which were not observed in the presentations for time after first dose. The MAH provided an acceptable explanation for the different concentrations observed in different VPC plots. The accumulation apparent in the plots depicting time after first dose is only apparent as variability in the plots for time after last dose. The observed accumulation cannot be neglected. But the titration-to-effect dosing regimen and the implemented stopping rules should prevent patients from adverse events related to accumulated luspatercept.

In addition, it has been noted that data from study -002, the main source for ESA naïve patients is quite variable also in contrast to the provided distributions for all other studies. This is also reflected in the VPC plots depicted by ESA status that seem to indicate a higher variability in ESA naïve patients. The MAH provided an acceptable explanation for the observed variability in the VPC plots, which is mainly due to the chosen presentation in binned time points and is not apparent in other presentations. Furthermore, the MAH provided a discussion regarding other covariates/baseline characteristics that might be more likely to result in the observed differences than ESA naïve status. The discussion can be followed, and the conclusions are acceptable.

It was further noted that for studies -001 and -002 sampling was described with a maximum of 1 year after treatment initiation. However, the provided VPC plots depict data up to more than 750 days. The MAH clarified that several sites inadvertently collected additional PK and ADA samples (beyond the pre-specified time points in the protocol) from subjects in Study ACE-536-MDS-002, which was reported as a Potential Serious Breach of GCP. This is an acceptable explanation for the additional data points. Further implications for the PK analysis were discussed above.

The MAH states that PK of Luspatercept exhibits linear and time-invariant PK with moderate variability. The empirical Bayesian estimate of CL/F and V1/F for the starting dose of 1 mg/kg in patients with MDS was 0.472 L/day and 9.57 L, respectively. The elimination half-life of luspatercept was 14.0 days. These estimates are similar to those from the previous PK analysis. While this is overall agreed, some differences have been observed between ESA naïve and other MDS patients. A slightly higher AUSss has been observed for ESA naïve patients together with a longer half-life (15.1 days compared to 12.8 days).

The MAH acknowledged this finding but pointed out that the individual steady-state exposure largely overlapped between the 2 sub-populations. Further, no differences in efficacy or safety have been observed. This can be followed. The MAH is of the opinion that it is not necessary to report the data in the SmPC. Given the titration-to-effect dosing regimen and the implemented stopping criteria, this can be agreed on.

The MAH further explored potential sources of variability including demographics (age, sex, race/ethnicity), mild to moderate hepatic or renal impairment as well as baseline disease characteristics (RBC transfusion burden, RS status, serum EPO level).

1. In older subjects (≥75 years of age) a higher AUCss and longer half-life were observed. This might be related to a lower clearance potentially influenced by comorbidities. The MAH clarified that observed differences in PK parameters should not be expected to be clinically relevant. Based on the results of the point estimates for the GMR of the PK exposure parameters for AUCss, Cminss and Cmaxss it can be agreed that the values can be considered similar for the age groups. Moreover, in the E-R analysis no significant effect of age impacting the E-R relationship for the safety and efficacy in the ESA naïve population at the proposed dosing regimen was reported. Furthermore, in an age subgroup analysis the clinically meaningful responses to luspatercept treatment were observed across all age subgroups.

2. Similar observations have been made in Japanese/Asian patients. Given the titration-to-effect dosing regimen and the implemented stopping criteria, this can be agreed on. No information for other race/ethnicity groups are available.

3. Patients with hepatic impairment have not been studied separately but were included in the popPK analysis, which is acceptable. However, as discussed above no statements regarding patients with severe impairment can be made due to lack of data. The data for patients with mild and moderate hepatic impairment suggest however a slight increase in clearance and reduction in AUSss. The MAH concludes that for these patients no starting dose adjustment is necessary, which can be agree, a dose modification might be necessary, which would be in line with the proposed overall dose modifications.

4. In contrast, patients with renal impairment seem to exhibit increased AUSss with increasing impairment. But again, no statements regarding patients with severe renal impairment can be made. While it can be agreed that no starting dose adjustment might be required, potential dose modifications seem to be in line with the proposed modifications for the overall population.

5. No differences have been observed for gender, IPSS-R risk, ring sideroblast status [positive vs. negative], serum EPO [range: 7.80 to 2920 U/L], RBC transfusion burden [range: 0 to 43.4 unit/24 weeks], and baseline hemoglobin [range: 4.70 to 11.0 g/dL]

The MAH performed exposure-response analyses based on data derived from study -002 only. Several efficacy and safety aspects were evaluated.

The E-R analysis regarding the primary efficacy endpoint (RBC-TI for 12 weeks with a concurrent mean Hgb increase ≥ 1.5 g/dL in Week 1 to 24) and a related endpoint (Achievement of RBC-TI for 24 weeks from Week 1 to 24) showed an exposure-dependent trend that might reach an efficacy plateau, but this is difficult to conclude since only four exposure categories based on the exposure quartiles have been presented. Several parameters have been identified as statistically significant predictors of the probability of response for the primary endpoint: baseline transfusion burden, baseline serum erythropoietin and ring sideroblast status (please refer to the efficacy section for further discussion of subgroups). The MAH provided the same analysis for the total population and for subjects without dose modifications. The latter showed a steeper curve of the observed relationship. This might indicate that the applied dose modifications might be beneficial to reach the apparent efficacy plateau.

The MAH additionally presented an analysis of Time from First Dose to First RBC Transfusion (Week 1 to Data Cutoff Date). The presented data suggests that for the lower exposure quartiles the effect seems to be less than for the comparator epoetin alfa and that the probability to remain free of RBC transfusion is higher with higher exposure. However, also for the highest quartile a drop after approximately half a year of treatment was observed. It is however not clear whether this is really the case, which could indicate a reduced efficacy or whether this effect is due to the uncomplete dataset. The MAH acknowledged the apparent drop and is of the opinion that this is likely a consequence of the visualisation limitations of KM plot as well as the shorter follow-up of the interim data. The results did not change with the updated E-R models. This issue can currently not be further assessed due to the lack of longer-term data. This issue might require reassessment when the final study report will be submitted.

Safety aspects were evaluated for a period of weeks 1-6 and exploratory analyses for weeks 1-48.

During the period of Weeks 1 to 6, no statistically significant E-R relationship was observed for all tested safety parameter: probability of all grade events of fatigue or asthenia, bone pain or arthralgia, hypertension, dizziness, Grade $\geq$ 3 TEAEs. Further, during the period of Weeks 1 to 48, no statistically significant E-R relationships were observed for the events of bone pain or arthralgia, hypertension, and dizziness, as well as Grade $\geq$ 3 TEAEs. The MAH clarified that results indicating inverse relationship observed between luspatercept exposure and the probability of TEAE leading to dose modification should be treated with caution because may have been confounded by the trial design. Moreover, sensitivity analysis did not confirm these observations.

During the period of Weeks 1 to 48, an inverse E-R relationship was observed for fatigue or asthenia event and dose modifications due to TEAEs. However, this was not observed between Weeks 1 to 6 (no dose escalation). The MAH claims that this inverse trend may be related to underlying disease progression or imbalance of the unknown disease characteristics. While these aspects might have some influence, it is more likely that these events are indicative of lack of efficacy.

The MAH performed additional analyses to show that the proposed dose titration regimen extends the duration of transfusion independence. The presented data suggest that about 40% of responders received multiple dose escalations and about half of the responders received doses higher than 1 mg/kg (the starting dose) over the duration of RBC-TI. The analysis showed also similar results for patients that remained on the 1 mg/kg starting dose. The MAH claims that the presented analyses justify the dose modifications presented in the SmPC. While the arguments are acknowledged, it is not clear whether the proposed dosing is optimal (see also discussion above) but is overall acceptable from a pharmacological perspective as it allows for individual adjustments. A concern is raised in the efficacy section regarding more frequent dose delays due to increased Hb $\geq$12.0 g/dL. Please refer to the efficacy section for further details.

2.3.4. Conclusions on clinical pharmacology

Overall, the PK of Luspatercept in the current population is similar to the PK previously established for other MDS patients.

Since excess samples have been collected due to a GCP violation and used for the presented analyses, new analyses without these samples are currently ongoing.

The MAH committed to submit the respective results as recommendations (REC) in June 2024 and September 2024.

2.4. Clinical efficacy

Primary efficacy data (31-Mar-2023 data cut-off) are presented from all subjects in pivotal Study ACE-536-MDS-002 (COMMANDS). In addition, supporting efficacy data are provided from select MDS subjects in Phase 2 Study A536-03, including available follow-up data from its extension study A536-05 and patients who subsequently rolled over into the Phase 3b long term safety Study ACE-536-LTFU-001 (Table 30).

Table 30: Summary of clinical studies supporting the proposed indication

Study	Design/ Primary Objective	No. Planned/ Treated Subjects	No. COMMANDS -like Subjects Included in SCE[a]	Population	Dose and Schedule	Study Status
Pivotal Study						
ACE-536-MDS-002 (COMMANDS)	Randomized, open-label, active-controlled, multicenter study/ RBC-TI for 12 weeks with an associated concurrent mean Hgb increase ≥ 1.5 g/dL	**350/361**	Not applicable.	Adults with anemia due to IPSS-R very low- to intermediate-risk MDS who are ESA naïve and require red blood cell transfusions	Luspatercept: 1.0 mg/kg SC Q3W (titration to 1.33 or 1.75 mg/kg SC Q3W or reduction to 0.8, 0.6, or 0.45 mg/kg Q3W was permitted per protocol) Epoetin alfa: 450 IU/kg SC Q1W, titration to 787.5 or 1050 IU/kg or reduction to 337.5 IU/kg was permitted per protocol)	Ongoing
Supporting Studies						
A536-03	Open-label, multiple ascending dose, multicenter study/ Proportion of subjects who had erythroid response	74-153/116	4 (MDS subjects only)	All cohorts: Subjects with IPSS low or intermediate-1 risk MDS and anemia who were ESA naïve. Expansion cohort 1: HTB (≥ 4 units RBC/8 wks) and LTB (< 4 units RBC/ 8 wks) subjects. Expansion cohort 2A: RS+ LTB subjects with < 4 wks of exposure to ESAs and sEPO level ≤ 200 U/L. Expansion cohort 2B: RS- and ≤ 6 units RBC/8 wks; ESA exposure < 4 wks and ≥ 4 wks	Ascending-dose cohorts: 0.125 mg/kg SC Q3W to 1.75 mg/kg SC Q3W (dose reductions were permitted per protocol within each cohort) Expansion cohorts: 1.0 mg/kg SC Q3W (dose reductions and titrations were permitted per protocol; maximum dose of 1.75 mg/kg)	Completed
A536-05	Open-label, multicenter, extension study/ Long-term safety and tolerability of luspatercept for subjects from A536-03	128/75	16 (MDS subjects only)	Eligible subjects from Study A536-03	Starting dose level based on last dose level in study A536-03 for subjects without treatment interruption Starting dose level of 1.0 mg/kg for subjects with treatment interruption Dose reductions and titrations permitted per protocol; maximum dose of 1.75 mg/kg	Completed
ACE-536-LTFU-001	Open-label, single-arm, rollover study/ Long-term safety of luspatercept in subjects who have participated in other interventional luspatercept clinical trials defined as parent protocols	Not applicable	2 (MDS subjects only from A536-05)	Subjects who have participated in other interventional luspatercept clinical trials defined as parent protocols	Same dose level and schedule of the last visit of the A536-05 study	Ongoing

[a] Subjects who participated in both A536-03/05 studies and ACE-536-LTFU-001 study, if applicable, were treated as 1 subject.

Source: ACE-536-MDS-002 Primary CSR[2], A536-03 CSR[3], A536-05 CSR[4], and ACE-536-LTFU-001 Protocol[5].

2.4.1. Main study

ACE-536-MDS-002 (COMMANDS)

An active-controlled, open-label, randomized Phase 3 study to compare luspatercept vs. epoetin alfa in ESA naive subjects with anemia due to IPSS-R very low-, low-, or intermediate-risk MDS who require RBC transfusions.

Approximately 350 randomized subjects were planned. The pre-specified interim analysis of the primary endpoint was planned when approximately 300 subjects completed 24 weeks of treatment, or discontinued before reaching 24 weeks of treatment.

Subjects were randomized 1:1 using a central randomization procedure to treatment with either Luspatercept (starting dose of 1.0 mg/kg SC Q3W) or the active comparator Epoetin alfa (starting dose of 450 IU/kg SC QW). Dose levels could have been adjusted in a stepwise manner (for details see section "*Treatments*").

Subjects were treated through to a minimum of the 24-Week MDS Disease Assessment Visit scheduled at Day 169. To remain on treatment beyond Day 169, both of the following criteria had to be confirmed:

- **Evidence of clinical benefit** defined as a transfusion reduction of ≥ 2 pRBC units/8 weeks compared with baseline (for any consecutive 8-week period within the 12 weeks immediately preceding Day 169 and every 24 weeks thereafter [ie, Day 337, Day 505, etc.]).
- **Absence of disease progression** per IWG criteria for altering natural history of MDS based on central morphological assessment of bone marrow, peripheral blood and cytogenetics results.

Based on the outcome of these assessments, subjects were either discontinued from treatment and entered into the Post-treatment Follow-up Period or continued open-label treatment, as long as the above criteria continued to be met or until the subject experienced unacceptable toxicities, withdrew consent, or met any other discontinuation criteria.

Methods

Study participants

Main inclusion criteria:

- ≥ 18 years of age the time of signing the informed consent form (ICF)
- documented diagnosis of MDS according to WHO 2016 classification (Arber et al, 2016) that meets IPSS-R classification (Greenberg, 2012) of very low, low, or intermediate risk disease and < 5% blasts in bone marrow
- endogenous serum erythropoietin (sEPO) level < 500 U/L
- transfusion requirement of 2 to 6 pRBCs units/8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization
    - Hb levels at the time of or within 7 days prior to administration of a RBC transfusion must have been ≤ 9.0 g/dL (5.6 mmol/L) with symptoms of anemia or ≤ 7 g/dL (4.3 mmol/L) in the absence of symptoms in order for the transfusion to be counted towards meeting eligibility criteria. Red blood cell transfusions administered when Hb levels were > 9.0 g/dL (or > 7 g/dL in the absence of symptoms) and/or RBC transfusions

administered for elective surgery, infections or bleeding events will not qualify as a required transfusion for the purpose of meeting eligibility criteria or stratification.

- Hb level after the last RBC transfusion prior to randomization must be < 11.0 g/dL (6.8 mmol/L) (centrally or locally analyzed)

- Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2

Main exclusion criteria:

- Subject with the any of the following prior treatments:
  - Erythropoiesis-stimulating agents (ESAs)
    - no more than 2 doses of epoetin alfa (prior treatment with darbepoetin not acceptable) ≥ 8 weeks from the date of randomization. A blood sample to determine the endogenous sEPO level (central laboratory) for stratification must be taken within 5 days of randomization unless a prior screening sample analyzed by the central laboratory demonstrated an endogenous sEPO level ≤ 500 U/L.
  - Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colonystimulating factor (GM-CSF), within 8 weeks prior to randomization, unless given for treatment of febrile neutropenia
  - Disease modifying agents (eg, immune-modulatory drug [IMiDs such as lenalidomide]
    - Except if the subject received ≤ 1 week of treatment with a disease modifying agent ≥ 8 weeks from randomization, at the investigator' s discretion.
  - Hypomethylating agents
    - Subjects may be randomized at the investigator's discretion contingent that the subject received no more than 2 doses of HMA. The last dose must be ≥ 8 weeks from the date of randomization.
  - Luspatercept, sotatercept, immunosuppressive therapy for MDS or a prior hematopoietic cell transplant
- MDS associated with del(5q) cytogenetic abnormality or MDS unclassifiable (MDS-U) according to WHO 2016 classification
- Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) according to WHO 2016 classification (ie, Chronic myelomonocytic leukemia (CMML), Atypical chronic myeloid leukemia (aCML), BCR-ABL12, Juvenile myelomonocytic leukemia (JMML), MDS/MPN unclassifiable
- Secondary MDS, ie, MDS that is known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases
- Clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or hypothyroidism, or any type of known clinically significant bleeding or sequestration, or drug induced anemia (eg, mycophenolate)
  - Iron deficiency to be determined by serum ferritin < 100 µg/L and additional testing if clinically indicated (eg, calculated transferrin saturation [iron/total iron binding capacity ≤ 20%] or bone marrow aspirate stain for iron)
- Known history of diagnosis of AML

- Subject with uncontrolled hypertension, defined as repeated elevations of systolic blood pressure (SBP) of ≥ 150 mmHg and/or diastolic blood pressure (DBP) ≥ 100 mmHg despite adequate treatment.
- Subject with any of the following laboratory abnormalities:
    - Absolute neutrophil count (ANC) < 500/µL (0.5 x 10^9/L)
    - Platelet count < 50,000/µL (50 x 10^9/L)
    - Estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m2
    - Serum aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN)
    - Total bilirubin ≥ 2.0 x ULN.
        - Higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (ie, ineffective erythropoiesis) or in the presence of known history of Gilbert Syndrome.

Treatments

- **Luspatercept:** starting dose of 1.0 mg/kg SC injection Q3W. Dose levels could have been increased in a stepwise manner beyond the starting dose to 1.33 mg/kg, and up to a maximum of 1.75 mg/kg. Luspatercept was administered by the study staff at the clinical site.
- **Epoetin alfa:** starting dose of 450 IU/kg (maximum total starting dose: 40,000 IU) SC QW. Dose levels could have been increased in a stepwise manner beyond the starting dose to 787.5 IU/kg, and up to a maximum of 1,050 IU/kg (with a maximum total dose of 80,000 IU). Individual epoetin alfa doses (according to body weight) were 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. Epoetin alfa was administered by the clinical site staff at site visits every third visit and self-administration was permitted between dosing site visits at the discretion of the investigator.

The choice of the active comparator epoetin alfa ensured that all subjects on the control arm were treated according to standard of care as per international treatment guidelines. However, different ESAs are available in different regions, specifically PROCRIT is available in the US and EPREX/ERYPO is available outside of the US.

The protocol included dose adjustments of study drug to maintain Hb concentrations within the target range of 10 to 12 g/dL (6.2 to 7.5 mmol/L), independent of transfusions.

Luspatercept Dose Adjustment and Dose Modification

Starting as soon as with dosing visit W7D1 (ie, Dose 3) of luspatercept, and assessed by the investigator prior to every subsequent luspatercept dosing, subjects may have the dose level increased in a stepwise manner (Table below), if all of the following criteria are met:

- Subject Hb levels are below the target range of 10 g/dL to 12 g/dL (6.2 mmol/L to 7.5 mmol/L). If the Hb levels are within 10 g/dL to 12 g/dL (6.2 mmol/L to 7.5 mmol/L) due to the influence of transfusions, the dose may still be adjusted (please consider the other three criteria noted below).

- Subject Hb level increase compared to the Hb sample taken prior to the previous luspatercept dose is ≤ 1 g/dL (0.6 mmol/L). If the Hb level increase is > 1 g/dL due to the influence of transfusions, the dose may still be adjusted.
- The two most recent prior luspatercept administrations assessed must be at the same dose level.
- Subject must not have met protocol dose delay and/or reduction criteria in the two most recent luspatercept administrations (exception of dose delay required due to influence of RBC transfusions). Refer to Table 5.

Table 31: Luspatercept starting dose level with dose reductions and dose titration

3rd Dose Reduction	2nd Dose Reduction	1st Dose Reduction	Starting Dose Level	1st Dose Titration Increase	2nd Dose Titration Increase
0.45 mg/kg	0.6 mg/kg	0.8 mg/kg	1.0 mg/kg	1.33 mg/kg	1.75 mg/kg

Table 32: Luspatercept dose modifications: dose delay, dose reduction and discontinuation guidelines

Event at the Day of Dosing (Assessed prior to each IP administration at the respective visit[b])	Action
Any suspected related AE ≥ Grade 3[a,b]	Dose delay[c] until resolved to ≤ Grade 1 or baseline, and then reduce dose by one dose level according to Table 4
> 2 dose reductions due to suspected related AE[a]	Discontinue treatment
ΔHgb > 2.0 g/dL (1.2 mmol/L) (not influenced by RBC transfusions[d]) compared to pre-dose Hgb of the previous luspatercept administration	Reduce dose by one dose level according to Table 4
Predose Hgb ≥ 12.0 g/dL (7.5 mmol/L)	Dose delay until Hgb < 11.0 g/dL (6.8 mmol/L)[d]
≥ 50% increase in white blood cell count (WBC) compared to pre-dose WBC of previous treatment cycle and above upper limit of normal in the absence of an associated condition (eg, infection or concomitant corticosteroid use)	Dose delay; recheck complete blood count (CBC), including WBC, at least weekly during dose delay. Treatment may be resumed if: WBC values below upper limit of normal[e] within 2 weeks If WBC remains above upper limit of normal[e] for ≥ 2 consecutive weeks in absence of an associated condition (eg, infection or concomitant corticosteroid use); continue dose delay and collect bone marrow/peripheral blood samples to assess MDS disease status. Treatment may be resumed if: Absence of disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) **AND** WBC values return below upper limit of normal Discontinue treatment if: Disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) **OR** WBC remain above upper limit of normal[e]

Presence of ≥ 1% blasts in peripheral blood (based on either local or central laboratory hematology sample)	Dose interruption; immediately prepare peripheral blood smear[f,g] for cytomorphology assessment by central pathology laboratory. • If central pathology laboratory cytomorphology assessment confirms ≥ 1% blasts in the peripheral blood; discontinue treatment[h] • If central pathology laboratory cytomorphology assessment determines < 1% peripheral blasts are present, repeat hematology assessment. – If presence of < 1% blasts in peripheral blood, treatment can be resumed at next scheduled luspatercept administration. – If presence of ≥ 1% blasts in peripheral blood; discontinue treatment[h]
Leukopenia, Neutropenia and/or Thrombocytopenia A worsening by ≥ 2 grades[i] leukopenia, neutropenia and/or thrombocytopenia to ≥ Grade 3 during treatment with luspatercept without any other likely cause (eg, infectious event, trauma, etc.). **Worsening of Anemia** A ≥ 50% increase in transfusion burden from baseline in combination with an unexplained worsening from baseline of ≥ 2 grades[i] leukopenia, neutropenia and/or thrombocytopenia.	Dose delay[c] and repeat WBC, neutrophils and platelet counts weekly **for two consecutive weeks** • If WBC, neutrophils and platelet counts improve to baseline or ≤ Grade 1, resume treatment at the same/decreased dose. • If WBC, neutrophils and platelet counts do **not** improve as defined above, collect bone marrow and peripheral blood samples to assess MDS disease status. – If disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) is confirmed, discontinue treatment – If disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) is **not** confirmed, discuss future dosing with Medical Monitor

Abbreviations: AE = adverse event; CBC = complete blood count; CTCAE = Common Terminology Criteria for Adverse Events; Hgb = hemoglobin; IP = investigational product; IWG = International Working Group; MDS = myelodysplastic syndromes; RBC = red blood cell; WBC = white blood cell count.

[a] Possibly, probably or definitely related to IP.

[b] Includes systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 100 mmHg.

[c] If dose delay is > 12 consecutive weeks, treatment should be discontinued

[d] Predose Hgb value not being influenced by RBC transfusion (ie, Hgb result > 14 days after last RBC transfusion or within 3 days from next RBC transfusion); Hgb should be rechecked weekly during dose delay.

[e] Upper limit of normal > 10,000 total WBC/μL or as defined by institutional standards.

[f] Peripheral blood smear should be prepared for central pathology lab assessment.

[g] At the investigator's discretion, bone marrow samples may also be collected and analyzed centrally to assess MDS disease status (eg, cytomorphology) prior to making decision regarding treatment discontinuation. The central laboratory must also confirm < 5% bone marrow blasts prior to resumption of treatment.

[h] The investigator may contact the Medical Monitor prior to making decision regarding treatment discontinuation.

[i] Thrombocytopenia, leukopenia, and neutropenia toxicity grades as defined by CTCAE criteria.

[k] Every attempt should be taken to assess the blasts count in peripheral blood prior to dosing, however, in circumstances where results are not readily available at the time of planned dosing, the investigator may proceed with dosing provided there are no signs of clinical progression. In this case, results must be evaluated as soon as they become available (but no later than 3 days post dosing). If presence of ≥ 1% blasts in peripheral blood is observed, actions described in table above must be followed immediately.

Epoetin Alfa Dose Adjustment and Modification

Starting as soon as the W7D1 dosing visit (ie, Dose 7) of epoetin alfa and assessed by the investigator, subjects may have the dose level increased in a stepwise manner beyond the starting dose of 450 IU/kg to 787.5 IU/kg and 1,050 IU/kg (total dose 80,000 IU). Dose increases and decreases should be done one dosing level at a time (Table 33). A minimum of 4 weeks should elapse between dose increases.

Dose delay and/or reduction or discontinuation may be required due to increased Hb or adverse events. For details on dose modification guidance for epoetin alfa please refer to Table 34.

Table 33: Epoeitin alfa starting dose level with dose reductions and dose titration

Dose Level -1	Starting Dose Level	Dose Level +1	Dose Level +2
337.5 IU/kg (maximum total dose 40,000 IU)	450 IU/kg (maximum total dose 40,000 IU)	787.5 IU/kg (maximum total dose 80,000 IU)	1,050 IU/kg (maximum total dose 80,000 IU)

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.

Table 34: Epoeitin alfa dose modification: dose delay, dose reduction and discontinuation guidelines

Event at the Day of Dosing (Assessed prior to each IP administration at the respective visit[k])	Action
Any suspected related AE ≥ Grade 3[a,b]	Dose delay[c] until resolved to ≤ Grade 1 or baseline, and then reduce dose by one dose level according to Table 6.
> 2 dose reductions due to suspected related AE[a]	Discontinue treatment.
ΔHgb > 2.0 g/dL (1.2 mmol/L) over 4 weeks (not influenced by RBC transfusions[d])	Consider dose decrease by one dose level according to Table 6.
Predose Hgb ≥ 12.0 g/dL (7.5 mmol/L)	Dose delay until Hgb < 11.0 g/dL (6.8 mmol/L)[d]. Restart on same dose level or reduce by one dose level according to Table 6 (investigator judgement).
Loss of response or Hgb drop ≥ 1 g/dL (0.6 mmol/L) upon dose reduction	Increase by one dose level according to Table 6. A minimum of 4 weeks should elapse between dose increases.
≥ 50% increase in white blood cell count (WBC) compared to pre-dose WBC of previous treatment cycle and above upper limit of normal in the absence of an associated condition (eg, infection or concomitant corticosteroid use)[i]	Dose delay; recheck complete blood count (CBC), including WBC, at least weekly during dose delay. Treatment may be resumed if: WBC values below upper limit of normal[e] within 2 weeks
	If WBC remains above upper limit of normal[e] for ≥ 2 consecutive weeks in absence of an associated condition (eg, infection or concomitant corticosteroid use); continue dose delay and collect bone marrow/peripheral blood samples to assess MDS disease status. Treatment may be resumed if: Absence of disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) AND WBC values return below upper limit of normal Discontinue treatment if: Disease progression per IWG response criteria for altering natural history of MDS (Cheson, 2006) OR WBC remain above upper limit of normal[e]
Presence of ≥ 1% blasts in peripheral blood[j] (based on either local or central laboratory hematology sample)	Dose interruption; immediately prepare peripheral blood smear[f,g] for cytomorphology assessment by central pathology laboratory. • If central pathology laboratory cytomorphology assessment confirms ≥ 1% blasts in the peripheral blood; discontinue treatment[h] • If central pathology laboratory cytomorphology assessment determines < 1% peripheral blasts are present, repeat hematology assessment. – If presence of < 1% blasts in peripheral blood, treatment can be resumed at next scheduled epoetin alfa administration. – If presence of ≥ 1% blasts in peripheral blood; discontinue treatment[h]

Abbreviations: AE = adverse event; CBC = complete blood count; Hgb = hemoglobin; IP = investigational product; IWG = International Working Group; MDS = myelodysplastic syndromes; RBC = red blood cell; WBC = white blood cell count.

[a] Possibly, probably or definitely related to IP.

[b] Includes systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 100 mmHg.

[c] If dose delay is > 12 consecutive weeks, treatment should be discontinued.

[d] Predose Hgb value not being influenced by RBC transfusion (ie, Hgb result > 14 days after last RBC transfusion or within 3 days from next RBC transfusion); Hgb should be rechecked weekly during dose delay.

[e] Upper limit of normal > 10,000 total WBC/μL or as defined by institutional standards.

[f] Peripheral blood smear should be prepared for central pathology lab assessment.

[g] At the investigator's discretion, bone marrow samples may also be collected and analyzed centrally to assess MDS disease status (eg, cytomorphology) prior to making decision regarding treatment discontinuation. The central laboratory must also confirm < 5% bone marrow blasts prior to resumption of treatment.

[h] The investigator may contact the Medical Monitor prior to making decision regarding treatment discontinuation.

[i] Mandatory assessment only at 3-weekly visits (W4D1, W7D1, W10D1, etc.)

[k] Every attempt should be taken to assess the blasts count in peripheral blood prior to dosing, however, in circumstances where results are not readily available at the time of planned dosing, the investigator may proceed with dosing provided there are no signs of clinical progression. In this case, results must be evaluated as soon as they become available (but no later than 3 days post dosing). If presence of ≥ 1% blasts in peripheral blood is observed, actions described in table above must be followed immediately.

Prior and Concomitant Treatment

Prior treatments that were prohibited are listed among the exclusion criteria (section *Study Participants*). The following concomitant medications and procedures were either permitted or prohibited during the course of the study:

- Permitted: RBC transfusions, iron chelation therapy (if on a stable or decreasing dose for ≥ 8 weeks prior to randomization), corticosteroids (if on a stable or decreasing dose for ≥ 1 week prior to randomization for medical conditions other than MDS), attenuated vaccines (except a live COVID-19 vaccine), and phlebotomy (for emergency use only, if excessively high Hb levels occurred).
- Prohibited: ESAs other than the assigned study drug, other RBC hematopoietic growth factors, G-CSF and GM-CSF (except in cases of neutropenic fever), cytotoxic/chemotherapeutic/targeted or investigational agents/therapies, azacitidine, decitabine or other hypomethylating agents, lenalidomide, thalidomide and other immunomodulating drugs, hydroxyurea, androgens, oral retinoids, arsenic trioxide, and interferons and interleukins.

Objectives and endpoints

The study objectives and endpoints are provided in Table 35.

Tabe 35: Study ACE-536-MDS-002 objectives and endpoints

Objective	Endpoint	Endpoint Description
Primary		
To evaluate the efficacy of luspatercept on RBC-TI; for 12 weeks (84 days) with a concurrent mean Hgb increase ≥ 1.5 g/dL) compared with epoetin alfa	RBC-TI for 12 weeks (84 days) with a concurrent mean Hgb increase ≥ 1.5 g/dL	Proportion of subjects who were RBC transfusion-free for any 12-week period associated with a concurrent mean Hgb increase ≥ 1.5 g/dL compared to baseline. During Week 1 to 24.
Secondary (Included in the Statistical Testing Hierarchy)		
To assess the efficacy of luspatercept compared to epoetin alfa	HI-E per IWG ≥ 56 days	Proportion of subjects who achieved HI-E over any consecutive 56-day period. During Week 1 to 24.
	RBC-TI for 24 weeks	Proportion of subjects who were RBC transfusion-free from Week 1 to 24.
	RBC-TI for ≥ 12 weeks (84 days)	Proportion of subjects who were RBC transfusion-free over a consecutive 84-day period. During Week 1 to 24.
Other Secondary		
To assess the efficacy of luspatercept compared to epoetin alfa	Mean Hgb change over 24 weeks	Mean hemoglobin change over the 24-week period of Week 1 to 24 compared to baseline.
	Time to HI-E	Time from first dose to first onset of achieving HI-E. During Week 1 to 24.
	Duration of RBC-TI ≥ 12 weeks (84 days)	Maximum duration of RBC-TI for subjects who achieved RBC-TI ≥ 84 days. During Week 1 to EOT.
	Time to RBC-TI ≥ 12 weeks (84 days)	Time from first dose to first onset of RBC-TI ≥ 84 days. During Week 1 to 24.
	Time to first RBC transfusion	Time from first dose to first transfusion on treatment. During Week 1 to EOT.
To assess the safety and efficacy of luspatercept compared to epoetin alfa	RBC transfusion burden on treatment	Total number of RBC units transfused on treatment. During Week 1 to 24.
	RBC-TI for ≥ 8 weeks (56 days)	Proportion of subjects RBC transfusion-free over a consecutive 56-day period. During Week 1 to 24.
	RBC-TI for a consecutive 24-week period	Proportion of subjects RBC transfusion-free for a consecutive 24-week period in the first 48 weeks from first dose. During Week 1 to 48.
	Safety	Type, frequency, severity of AEs and relationship of AEs to luspatercept/epoetin alfa. Randomization through Week 48
	ADA (immunogenicity)	Frequency of antidrug antibodies. Randomization through 1 year post first dose.
	Progression to AML	Number and percentage of subjects progressing to AML; time to AML progression. Randomization through 5 years from first dose or 3 years from last dose (whichever occurred later)
	Overall survival	Time from date of randomization to death due to any cause. Randomization through 5 years from first dose or 3 years from last dose (whichever occurred later)
To assess HRQoL and anemia outcome measures (EORTC QLQ-C30, FACT-An) with luspatercept compared to epoetin alfa	HRQoL	Evaluation of EORTC QLQ-C30 score and FACT-An. Screening through Week 24.
To evaluate PK for luspatercept in MDS subjects	PK parameters	Serum luspatercept concentrations and PK parameters. Randomization through 1 year post first dose

Exploratory		
To evaluate the impact of luspatercept therapy on HCRU in both treatment arms	HCRU	Evaluation of healthcare resource use (eg, hospitalization) associated with IP during study. Screening through Week 24.
To evaluate overall HRQoL and treatment satisfaction in both treatment arms	HRQoL	Description of QUALMS-P and Treatment Satisfaction. Screening through Week 24.
To evaluate molecular and cellular markers in the bone marrow and/or in peripheral blood at baseline and during therapy that may provide: • further prognostic classification of MDS subtypes and potential impact on luspatercept efficacy • information on MOA (luspatercept) & on-therapy markers predictive of response or relapse	Molecular and cellular markers in the bone marrow and/or in peripheral blood	Evaluation of biomarkers that may potentially impact luspatercept efficacy, predict response or relapse, help to better understand the MOA and/or provide further prognostic classification of MDS subtypes. Baseline through EOT. Molecular markers (eg, SF3B1) include evaluation of MDS-associated gene mutations and their impact on drug efficacy, clinical response or relapse, drug MOA and prognostication of MDS. Baseline through EOT.
To evaluate exposure-response relationships for luspatercept in MDS subjects	Exposure-response relationship	Exposure-response relationship for selected endpoints of efficacy and safety. Randomization through 1 year post first dose.
To evaluate the safety of luspatercept in severe SARS-CoV-2 antibody positive subjects and to support potential health authority requests	SARS-CoV-2 serology	Measurements of anti-SARS-CoV-2 IgG or total antibody, from serum samples collected at baseline, D169, D337 and EOT, and impact on safety profile of luspatercept. Screening through 42 days post last dose.

The 14/3-day rule was applied to the Hb evaluations. Thereby, only Hb values that are at least 14 days after a transfusion was used unless there is another transfusion within 3 days after the Hb assessment. If this occurs, that Hb value was used despite being < 14 days after the previous transfusion. After applying the 14/3-day rule, the baseline Hb value is defined as the lowest Hb value that is within 56 days on or prior treatment. In case a subject is missing Hb records after the 14/3-day rule, a 7/3-day rule will be applied.

Sample size

A total sample size of approximately 350 subjects (175 in each arm) would have 90% power to detect a difference in the primary endpoint (RBC-TI for 12 weeks associated with a concurrent Hb increase) between the treatment arms (e.g., a response rate of 36% vs 20% for luspatercept vs epoetin alfa).

The first interim analysis (futility only) was planned when approximately 105 subjects completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment (30% of the information for primary endpoint). The Lan-DeMets (O'Brien-Fleming) spending function was used to calculate the futility boundary. The sample size calculation was based on a 1-sided alpha of 0.025 (test statistics on odds ratio of proportions using the EAST Version 6.4 software system).

The second interim analysis for superiority of the primary endpoint was planned when approximately 300 subjects completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment (85% of the information for primary endpoint). The addition of a second interim analysis did not alter the original sample size calculation. The overall study power remained at 90% with 350 subjects, and the Lan-DeMets spending function of the O'Brien-Fleming type was used to control the overall 1-sided Type I error rate at 0.025. The overall 1-sided Type I error rate for the second interim analysis was 0.015.

Randomisation

Eligible subjects were randomized by a central randomization procedure using integrated response technology (IRT) at a 1:1 ratio to either the Luspatercept or the epoetin alfa arm.

Randomization was stratified based on the following factors:

- RBC transfusion burden at baseline: < 4 vs ≥ 4 pRBC units/ 8 weeks
- RS status at baseline (with RS+ defined as RS ≥ 15% of erythroid precursors in bone marrow or ≥ 5% [but < 15%] if SF3B1 mutation was present): RS+ vs RS-
- Endogenous serum erythropoietin level at baseline: ≤ 200 vs > 200 to < 500 U/L
  (Subjects were required per protocol to have an endogenous sEPO level < 500 U/L.)

Blinding (masking)

The treatments in this study were open-label. The study center staff, study team, and the enrolled subjects were not blinded to treatment assignment. In order to prevent bias and objectively assess efficacy and safety, an external independent statistician prepared summaries of the unblinded aggregate efficacy and safety data for the DMC review. The Sponsor remained blinded to any aggregate analyses by treatment arm performed for the DMC.

This study was sponsored by BMS/Celgene Corporation (Celgene Corporation is a subsidiary of BMS) and the conduct of the study was outsourced to PPD, LLC (Wilmington, NC, US). The Sponsor's Clinical Trial Physician was responsible for the overall conduct of the study, including protocol development. Preparation of the statistical sections of the protocol and the statistical evaluation of the results was performed by BMS/Celgene; however, PPD created the datasets.

In addition, to avoid bias and to ensure comparability of the frequency and units of RBC transfusions administered in both treatment arms, for each subject a "pre-transfusion Hb threshold" for requiring transfusion during the study was determined based on transfusion history in the 8 weeks prior to the first dose of study drug. The baseline pre-transfusion Hb threshold was the mean of all documented pre-transfusion hemoglobin values during the 8 weeks prior to the first dose of study drug. This "pre-transfusion Hb threshold" was to be maintained throughout the Treatment Period when administering RBC transfusions. The primary endpoint combines RBC-TI of any 12 weeks between Week 1 and 24 (rolling 12-week period), with the additional requirement of a concurrent mean Hb increase of ≥ 1.5 g/dL.

Laboratory personnel were blinded to the treatment assignment of individual subjects. For stratification, sEPO results and RS status from the central laboratory were used. The site entered the sEPO results, RBC transfusion burden, and RS status in IRT.

Statistical methods

Analysis Sets

Intent-to-Treat Population (ITT) consists of all randomized subjects regardless of whether or not the subject received IP.

Safety population consists of all subjects who were randomized and received at least one dose of IP. Subjects will be included in the treatment arm corresponding to the IP they actually received.

HRQoL evaluable population consists of all subjects in the ITT population who completed the respective patient reported outcomes assessment at baseline and at least one post-baseline assessment visit.

PK population consists of all subjects who received at least one dose of Luspatercept and had at least one measurable Luspatercept serum concentrations.

All efficacy analyses were conducted based on the ITT population. Subjects were analysed based on randomized treatment arm.

Interim Analyses

Two interim analyses were planned. The first one is for futility only and the second one is for efficacy.

The first interim analysis to assess futility only was performed when approximately 105 subjects have completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment (30% information for primary endpoint). A non-binding β-spending function of the O'Brien-Fleming type (DeMets, 1994) was used to control the Type II error rate with overall one-sided β = 0.10.

The table below gives the nominal p-value for rejecting the alternative hypothesis corresponding to the O'Brien-Fleming boundary. (The interim bound is approximate and was re-calculated based on the amount of information available when the interim analysis is actually performed.)

Table 36: Futility Interim Boundaries for the First Interim Analysis

Analysis	Futility Bound (odds ratio)	Reject Alternative Hypothesis if p-value is greater than
Interim (30%)	0.632	0.844

Note: Nominal p-values for futility computed using the program East Version 6.4 (Cytel Statistical Software Company).

At the first interim analysis, CMH statistic was calculated and compared with the futility boundary. Thus, with a p-value greater than 0.844, the DMC could consider stopping the trial due to futility.

A second interim analysis was planned to test the superiority of the primary endpoint at about 85% of the information (when approximately 300 subjects have completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment). The Lan-DeMets spending function of the O'Brien-Fleming type was used to control the overall one-sided alpha level at 0.025. The table below summarizes alpha spent at each analysis.

Table 37: Summary of Alpha Spending

Analysis	Enrollment	One-sided alpha	Endpoint Assessment
Futility Interim	30% information for primary endpoint (105 subjects)	N/A	Efficacy not tested
Superiority Interim	85% information for primary endpoint (300 subjects)	0.015	Testing in order of: Primary endpoint HI-E response (Week 1 to 24) RBC-TI for 24 weeks (Week 1 to 24) RBC-TI ≥ 12 weeks (Week 1 to 24)
Superiority Final	100% information for primary endpoint (350 subjects)	0.021	Testing in order of: Primary endpoint HI-E response (Week 1 to 24) RBC-TI for 24 weeks (Week 1 to 24) RBC-TI ≥ 12 weeks (Week 1 to 24)

Considerations for the Second Interim Analysis

Primary efficacy endpoint analysis

For the primary efficacy endpoint (RBC-TI; for 12 weeks [84 days] with an associated concurrent mean Hb increase ≥ 1.5 g/dL) during Week 1 to 24, the response rate (number of responders divided by number of subjects in the ITT population for each treatment arm) with the corresponding 2-sided 95% CI, the common risk difference in the proportions between the 2 treatment arms with a corresponding 2-sided 95% CI, and an odds ratio with a corresponding 2-sided 95% CI, were calculated. The CMH test (stratified by baseline transfusion burden, RS status, and sEPO level) was used to compare the response rates between the treatment arms at a 1-sided significance level of 0.015 (p-value threshold).

Secondary efficacy endpoint analyses

At this interim analysis of the primary efficacy endpoint, a gate-keeping method was strictly implemented in order to control the 1-sided Type I error rate for 3 hierarchically tested secondary endpoints in the following order:

1. HI-E response (Week 1-24)
2. RBC-TI for 24 weeks (Week 1-24)
3. RBC-TI ≥ 12 weeks (Week 1-24)

Each of these secondary endpoints wastested for significance at the one-sided significance level of 0.021 only if the results for primary endpoint and previous secondary endpoint(s) according to the above order are all significant.

Other secondary endpoints were analysed without employing methods for controlling the Type I error rate. Any statistically significant treatment effect on these secondary endpoints cannot be interpreted as confirmatory, but rather as informatory (i.e., nominal).

Considerations for the Final Analysis

Final analysis was performed when all 350 subjects have completed 24 weeks of treatment or discontinued before 24 weeks. Additional follow-up analysis for efficacy and safety will be performed when all subjects have completed 48 weeks of treatment or discontinued before 48 weeks.

The Cochran–Mantel–Haenszel (CMH) test stratified by baseline transfusion burden, baseline RS status, and baseline sEPO level will be used to compare the response rates between treatment arm and control arm at a one-sided significance level of 0.021 at the final analysis with one planned interim analysis for superiority.

Baseline strata derived from data collected on CRF will be used for the CMH test instead of randomization strata from IRT.

The same hierarchically testing order as described above for the Second Interim Analysis will be implemented for the Final Analysis in order to control the 1-sided Type I error rate for 3 hierarchically tested secondary endpoints (HI-E response (Week 1-24), RBC-TI for 24 weeks (Week 1-24), and RBC-TI ≥ 12 weeks (Week 1-24)). Each of these secondary endpoints will be tested for significance at the one-sided significance level of 0.021 only if the results for primary endpoint and previous secondary endpoint(s) according to the above order are all significant.

Summaries will include the common risk difference in proportions between the two treatment arms with corresponding two-sided 95% CI and the odds ratio with corresponding two-sided 95% CI. Subject listings with supporting data will be provided.

Results

Participant flow

As of the clinical data cutoff date (31-Mar-2023), 679 subjects had completed screening; 363 subjects were randomized at 142 sites in 26 countries (Table 5.1-1). A total of 361 subjects were treated. The 2 subjects in the epoetin arm who were randomized and not treated withdrew consent prior to the first dose.

The ITT population (all subjects [N = 363] randomized up to the clinical data cutoff) was used for all of the efficacy analyses.

Table 38: Subject disposition: ITT population

Parameter	Luspatercept (N=182) n (%)	Epoetin Alfa (N=181) n (%)	Total (N=363) n (%)
Treatment Period			
Total Number of Subjects Treated (Safety Population)	**182**	**179**	**361**
Number of Subjects on Treatment [a]	**78 (42.9)**	**53 (29.6)**	**131 (36.3)**
Number of Subjects Discontinued from Treatment [a]	**104 (57.1)**	**126 (70.4)**	**230 (63.7)**
Subject's Status for the Treatment Period [a]			
Death	14 (7.7)	13 (7.3)	27 (7.5)
Adverse Event	9 (4.9)	5 (2.8)	14 (3.9)
Progressive Disease	9 (4.9)	7 (3.9)	16 (4.4)
Lack of Efficacy	41 (22.5)	68 (38.0)	109 (30.2)
Withdrawal by Subject	16 (8.8)	18 (10.1)	34 (9.4)
Lost to Follow-up	0 (0.0)	1 (0.6)	1 (0.3)
Study Terminated By Sponsor	1 (0.5)	2 (1.1)	3 (0.8)
Protocol Deviation	1 (0.5)	0	1 (0.3)
Physician Decision	5 (2.7)	5 (2.8)	10 (2.8)
Other	8 (4.4)	7 (3.9)	15 (4.2)
Discontinuation Reason Related to COVID-19 Pandemic [a] [b]			
Yes	1 (0.5)	1 (0.6)	2 (0.6)
No	94 (51.6)	117 (65.4)	211 (58.4)
Unknown	5 (2.7)	0 (0.0)	5 (1.4)
Missing	4 (2.2)	8 (4.5)	12 (3.3)
Follow-up Periods			
Number of Subjects Continued to 42-Day Follow-up [c]	**65 (35.7)**	**90 (49.7)**	**155 (42.7)**
Subject's Status for 42-Day Follow-up Period [c]			
Completed	52 (28.6)	72 (39.8)	124 (34.2)
Death	1 (0.5)	1 (0.6)	2 (0.6)
Progressive Disease	0 (0.0)	1 (0.6)	1 (0.3)
Withdrawal by Subject	2 (1.1)	1 (0.6)	3 (0.8)
Protocol Deviation	0 (0.0)	1 (0.6)	1 (0.3)
Physician Decision	0 (0.0)	4 (2.2)	4 (1.1)
Other	5 (2.7)	3 (1.7)	8 (2.2)
Alternative Treatment	2 (1.1)	6 (3.3)	8 (2.2)
Discontinuation Reason Related to COVID-19 Pandemic [b] [c]			
No	6 (3.3)	13 (7.2)	19 (5.2)
Unknown	1 (0.5)	1 (0.6)	2 (0.6)
Missing	3 (1.6)	3 (1.7)	6 (1.7)

Number of Subjects Continued to Long-term Follow-up [c]	**61 (33.5)**	**86 (47.5)**	**147 (40.5)**
Subject's Status for Long-term Follow-up Period [c]			
Death	19 (10.4)	22 (12.2)	41 (11.3)
Withdrawal by Subject	5 (2.7)	9 (5.0)	14 (3.9)
Lost to Follow-up	0	1 (0.6)	1 (0.3)
Physician Decision	0 (0.0)	1 (0.6)	1 (0.3)
Other	2 (1.1)	3 (1.7)	5 (1.4)
Discontinuation Reason Related to COVID-19 Pandemic [b] [c]			
No	23 (12.6)	36 (19.9)	59 (16.3)
Unknown	2 (1.1)	0 (0.0)	2 (0.6)
Missing	1 (0.5)	0 (0.0)	1 (0.3)
Entire Study			
Number of Subjects Discontinued from Study [c]	**67 (36.8)**	**77 (42.5)**	**144 (39.7)**
Primary Reason for Study Discontinuation [c]			
Death	39 (21.4)	38 (21.0)	77 (21.2)
Adverse Event	0 (0.0)	1 (0.6)	1 (0.3)
Withdrawal by Subject	17 (9.3)	25 (13.8)	42 (11.6)
Lost to Follow-up	0 (0.0)	2 (1.1)	2 (0.6)
Study Terminated By Sponsor	6 (3.3)	3 (1.7)	9 (2.5)
Physician Decision	3 (1.6)	2 (1.1)	5 (1.4)
Other	2 (1.1)	3 (1.7)	5 (1.4)
Transition To Commercially Available Treatment	0 (0.0)	3 (1.7)	3 (0.8)

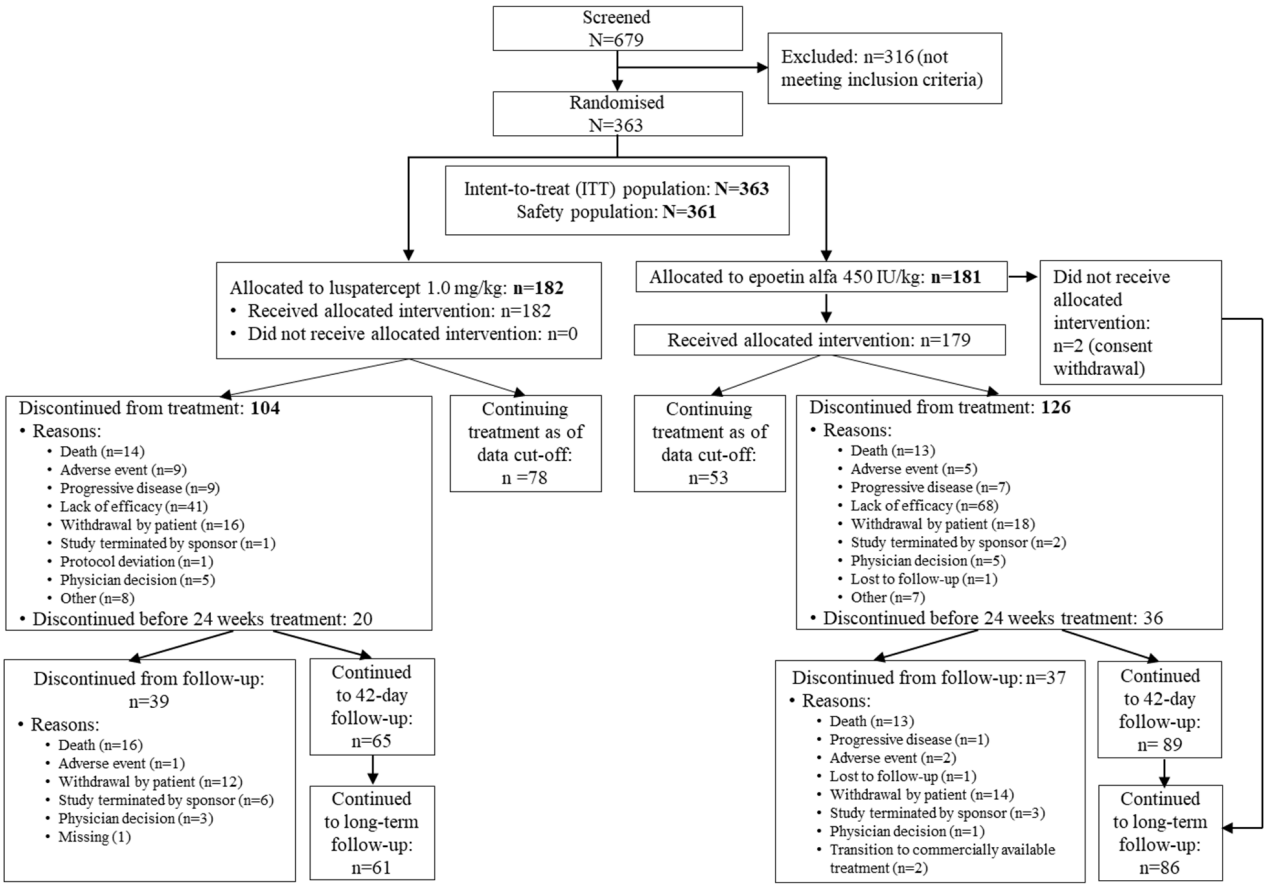
[a] Percentages are based on Safety population.

[b] Discontinuation Reason Related to COVID-19 Pandemic were completed for events that occurred after Nov 2019.

[c] Percentages are based on ITT population.

Upon request, the MAH provided a consort flow diagram, including subjects who discontinued treatment before the Week 24 disease assessment (Figure 18).

Figure 18: Consort Flow Diagram of ACE-536-MDS-002 and Subject Disposition



Recruitment

As of the clinical data cutoff (31-Mar-2023), 363 subjects were randomized at 142 sites in 26 countries: Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Japan, Korea, Lithuania, Netherlands, Poland, Portugal, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, UK, and US.

Table 39: Key dates and follow-up

First Subject Randomized Date	04-Feb-2019
Date Last Subject for the Primary Analysis was Randomized	29-Sep-2022
Clinical Data Cutoff Date	31-Mar-2023
Database Lock	23-May-2023
Median Follow-up (min, max)[a] months	
Luspatercept (N = 182)[b]	17.2 (1, 46)
Epoetin Alfa (N = 181)[b]	16.9 (0, 46)

[a] Median of the time from randomization date to death date or last known alive date.

[b] Number of randomized subjects as of the clinical data cutoff date (31-Mar-2023).

By the end of May 2022, the dispensing of drug was stopped at all 7 sites in Russia and all active Russian subjects (n = 9) were discontinued from the study by 17-Jun-2022. Recruitment was suspended at the Ukrainian sites as of the end of March 2022, but these sites remained open.

Conduct of the study

The original protocol was dated 03-May-2018. As of the clinical data cutoff (31-Mar-2023), there were a total of 4 global protocol amendments. The key changes are summarised below:

Amendment 1.0 (26-Feb-2019)

- Modified the primary endpoint from RBC-TI for 24 weeks from Week 1 - 24 to RBC-TI for 12 weeks (84 days) associated with a concurrent mean Hb increase ≥ 1.5 g/dL compared to baseline from randomization through Week 24.
- Added secondary endpoints to complement the new primary endpoint: RBC-TI (Week 1-24) and Mean Hb change over 24 weeks (Week 1-24)
- Added less stringent criteria for excluding subjects with prior ESAs treatment; up to 2 prior doses of epoetin alfa allowed
- Revised the definition of the "evidence of clinical benefit" evaluation at the MDS Disease Assessment visits. Clinical benefit simplified to transfusion reduction (≥ 2 pRBC units/8 weeks compared to baseline)
- Implemented a minimum percentage of subjects with an endogenous sEPO level of > 200 U/L (at least 25%)
- Clarified transfusion data collection and assessment; required mandatory confirmation with the subject of whether transfusions were received outside of the site before study drug administration
- Added dose delay and dose reduction guidelines for worsening of cytopenias as per FDA request
- Modified exclusion criteria #1. The exclusion of subjects who received prior G-CSF treatment was limited to 8 weeks prior to randomization

Amendment 2.0 (01-Aug-2019)

- Added additional criteria for luspatercept dose modification as requested by the US FDA

Amendment 3.0 (23-Feb-2021)

- Removed the enrollment cap for RS+ subjects (at least 40% but not more than 60% of subjects randomized)
- Added a gate-keeping method to control the overall Type I error rate for the following secondary endpoints in the order of:
    - HI-E response (Week 1 to 24)
    - RBC-TI for 24 weeks (Week 1 to 24)
    - RBC-TI ≥ 12 weeks (Week 1 to 24)
- Updated the language of the PK and ADA objectives and endpoints
- Removed the maximum total dose (168 mg) in the luspatercept arm to align with the luspatercept label
- Changed exclusion criteria: MDS/MPN-RS-T patients were eligible for recruitment
- Added the following time windows: for 42-Day Follow-up Visit (+ 3 days) for PK and ADA Post 24-Week MDS Disease Assessment Visit (± 14 days)
- Added severe acute respiratory syndrome coronavirus 2 testing

Amendment 4.0 (31-Mar-2022)

- Added a second interim analysis to test the superiority of the luspatercept arm
- Removed the requirement to enroll at least 25% of subjects with an endogenous sEPO level of > 200 U/L

Impact of COVID-19

This study was conducted during the COVID-19 pandemic: the first subject first visit was 02-Jan-2019 and the clinical data cutoff was 31-Aug-2022. The US FDA and EMA both issued guidelines on the management of clinical trials during the COVID-19 pandemic. In response to this public health emergency, BMS/Celgene developed overarching principles and guidance for the conduct of BMS/Celgene clinical research. The COVID-19 pandemic did not compromise the ability to collect both safety and efficacy data and did not significantly impact results of the study.

Overall, 17/356 (4.8%) of subjects had important protocol deviations related to COVID-19 between the onset of COVID related shutdowns and the database lock for the interim analysis. These protocol deviations had minimal impact on the quality of the data in this study (see Table 4.5.2-1).

Impact of the Russian/Ukrainian Political Crisis

Due to the Russian/Ukrainian political crisis, the dispensing of drug was stopped at all 7 sites in Russia by the end of May 2022. It was recommended that all active subjects at these sites complete the end of study activities and transition to local standard of care treatment. For the analysis of the primary endpoint, all 24 Russian subjects randomized had either completed Week 24 or discontinued early. All active Russian subjects (n = 9) were discontinued from the study by 17-Jun-2022. There were no important protocol deviations related to the closure of the Russian sites.

The 4 sites in Ukraine suspended recruitment as of the end of March 2022. At the time of the clinical data cutoff, all 10 subjects had either completed Week 24 or discontinued early and there were 6 active subjects. The Ukrainian sites remained open and all active subjects continued receiving treatment. Six Ukrainian subjects had important protocol deviations related to the Russian/Ukrainian political crisis. All 6 subjects had missing laboratory results at 1 or more visits mainly related to the shipment of laboratory samples to the central laboratory. No local tests were done for 2 of the 6 subjects. In addition, 2/6 subjects did not have PRO assessments at 1 or more study visits, 1/6 did not have an MDS disease assessment at Week 24; 1/6 had study procedures performed outside of the visit window for 1 visit, and 1/6 had a dose delay due to a personal reason.

Overall, the important protocol deviations related to the Russian/Ukrainian political crisis had minimal or no impact on the analysis of the primary efficacy endpoint and the safety data.

Table 40: Important protocol deviations: ITT population

Parameter	Luspatercept (N=182) n (%)	Epoetin Alfa (N=181) n (%)	Total (N=363) n (%)
Number of Subjects with ≥ 1 Important Protocol Deviation [a]	**117 (64.3)**	**112 (61.9)**	**229 (63.1)**
Laboratory tests/procedures	76 (41.8)	79 (43.6)	155 (42.7)
Investigational product issues/compliance	41 (22.5)	43 (23.8)	84 (23.1)
Other	16 (8.8)	13 (7.2)	29 (8.0)
Safety reporting	9 (4.9)	18 (9.9)	27 (7.4)
Inclusion/exclusion criteria	8 (4.4)	9 (5.0)	17 (4.7)
Investigational product withdrawal/study discontinuation criteria	6 (3.3)	8 (4.4)	14 (3.9)
Informed consent issues	3 (1.6)	0 (0.0)	3 (0.8)
Visit schedule	0 (0.0)	1 (0.6)	1 (0.3)
Concomitant medication	0 (0.0)	2 (1.1)	2 (0.6)
Number of Subjects with ≥ 1 COVID-19 Related Important Protocol Deviation [a]	**7 (3.8)**	**5 (2.8)**	**12 (3.3)**
Laboratory tests/procedures	6 (3.3)	5 (2.8)	11 (3.0)
Investigational product issues/compliance	1 (0.5)	0 (0.0)	1 (0.3)

[a] A subject was counted only once for multiple deviations within a deviation type.

Baseline data

Table 41: Demographics and baseline disease characteristics: ITT population

	Luspatercept (N=182)	Epoetin Alfa (N=181)	Total (N=363)
Age (years) [a]			
Median	74.0	74.0	74.0
Min, Max	46.0, 93.0	31.0, 91.0	31.0, 93.0
≤ 64, n (%)	27 (14.8)	25 (13.8)	52 (14.3)
65-74, n (%)	68 (37.4)	66 (36.5)	134 (36.9)
≥ 75, n (%)	87 (47.8)	90 (49.7)	177 (48.8)
Gender – n (%)			
Male	109 (59.9)	92 (50.8)	201 (55.4)
Female	73 (40.1)	89 (49.2)	162 (44.6)
Race – n (%)			
Asian	19 (10.4)	25 (13.8)	44 (12.1)
Black or African American	2 (1.1)	0 (0.0)	2 (0.6)
White	146 (80.2)	143 (79.0)	289 (79.6)
Not Collected or Unknown	15 (8.2)	13 (7.2)	28 (7.7)
Median Height (cm)	166.6	165.0	165.0
Min, Max	140.7, 190.0	124.4, 191.4	124.4, 191.4
Median Weight (kg)	73.0	70.0	70.0
Min, Max	33.0, 122.8	32.0, 127.0	32.0, 127.0
Median BMI (kg/m^2) [b]	25.5	25.3	25.4
Min, Max	14.8, 41.9	15.3, 43.5	14.8, 43.5
Regions			
US	8 (4.4)	9 (5.0)	17 (4.7)
Non-US	174 (95.6)	172 (95.0)	346 (95.3)
Regions [c]			
North America	14 (7.7)	14 (7.7)	28 (7.7)
Europe	111 (61.0)	108 (59.7)	219 (60.3)
Asia	16 (8.8)	23 (12.7)	39 (10.7)
Rest of World	41 (22.5)	36 (19.9)	77 (21.2)
Baseline Transfusion Burden (pRBC units) – n (%) [d]			
< 4	118 (64.8)	111 (61.3)	229 (63.1)
= 2	81 (44.5)	82 (45.3)	163 (44.9)
≥ 4	64 (35.2)	70 (38.7)	134 (36.9)
Mean (SD)	3.1 (1.47)	3.3 (1.74)	3.2 (1.61)
Median (Min, Max)	3.0 (1, 10)	3.0 (0, 14)	3.0 (0, 14)

MDS Classification WHO 2016 at Baseline - n (%)			
MDS-SLD	1 (0.5)	4 (2.2)	5 (1.4)
MDS-MLD	50 (27.5)	47 (26.0)	97 (26.7)
MDS-RS-SLD	2 (1.1)	6 (3.3)	8 (2.2)
MDS-RS-MLD	127 (69.8)	118 (65.2)	245 (67.5)
MDS/MPN-RS-T	2 (1.1)	5 (2.8)	7 (1.9)
Missing	0 (0.0)	1 (0.6)	1 (0.3)
IPSS-R Risk Classification at Baseline – n (%)			
Very Low	16 (8.8)	17 (9.4)	33 (9.1)
Low	130 (71.4)	133 (73.5)	263 (72.5)
Intermediate	34 (18.7)	29 (16.0)	63 (17.4)
High	1 (0.5)	0 (0.0)	1 (0.3)
Missing [e]	1 (0.5)	2 (1.1)	3 (0.8)
ECOG Performance – n (%)			
0	74 (40.7)	69 (38.1)	143 (39.4)
1	104 (57.1)	94 (51.9)	198 (54.5)
2	4 (2.2)	18 (9.9)	22 (6.1)
Time Since Original MDS Diagnosis (years) – n (%) [g][h]			
≤ 1	103 (56.6)	123 (68.0)	226 (62.3)
> 1 to ≤ 2	26 (14.3)	21 (11.6)	47 (12.9)
> 2 to ≤ 5	31 (17.0)	22 (12.2)	53 (14.6)
> 5	22 (12.1)	15 (8.3)	37 (10.2)
Median mo. [f][g]	7.97	5.13	6.05
Min, Max	-0.4, 243.1	-0.3, 171.6	-0.4, 243.1
Ring Sideroblasts Status (per WHO criteria)– n (%)			
RS+	133 (73.1)	130 (71.8)	263 (72.5)
RS-	49 (26.9)	50 (27.6)	99 (27.3)
Missing [h]	0 (0.0)	1 (0.6)	1 (0.3)
SF3B1 Mutation Status – n (%)			
Mutated	114 (62.6)	101 (55.8)	215 (59.2)
Non-mutated	65 (35.7)	72 (39.8)	137 (37.7)
Missing	3 (1.6)	8 (4.4)	11 (3.0)

[a] Age (years) = (Informed consent date – date of birth + 1)/365.25, then truncating.

[b] BMI (kg/m^2) = baseline weight (kg) / height (m^2)

[c] **North America:** Canada, US; **Europe:** Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, Ukraine, UK; **Asia:** Japan, Korea, Taiwan. **Rest of World:** Israel, Russia, Turkey, Australia

[d] Baseline transfusion burden: the number of RBC units received 8 weeks prior to or on the first dose date. 1 subject in the epoetin alfa arm did not have a prior transfusion history at baseline. This subject had received a prior transfusion of 2 pRBC units, but it was out of the 16-week window prior to randomization.

[e] IPSS-R risk score is based on 5 parameters. For 3 subjects (1 in the luspatercept arm and 2 in the epoetin alfa arm), 1 of the 5 parameters (cytogenetic score), yielded no results; therefore, the risk score could not be calculated.

[f] The number of months from the date of original diagnosis to the date of informed consent.

[g] The MDS diagnosis was made using the screening bone marrow evaluation for 2 subjects.1 subject had an original diagnosis date 28-Apr-2021 and an ICF date 23-Apr-2021. 1 subject had an original diagnosis date 15-Jul-2021 and an ICF date 07-Jul-2021.

[h] 1 subject in the epoetin alfa arm had a missing RS assessment. This subject had a bone marrow biopsy assessed by central lab with the diagnosis MDS-MLD; RS status was not provided. This subject was included in the ITT analyses as missing RS status. This subject was not included in the subgroup analyses by RS status.

Table 42: Baseline laboratory characteristics: ITT population

	Luspatercept (N=182)	Epoetin Alfa (N=181)	Total (N=363)
Platelet (10^9/L) – n (%) [a]			
< 100	26 (14.3)	20 (11.0)	46 (12.7)
100 - 450	149 (81.9)	148 (81.8)	297 (81.8)
> 450	6 (3.3)	13 (7.2)	19 (5.2)
Missing	1 (0.5)	0 (0.0)	1 (0.3)
Median Platelet counts (Min, Max) (10^9/L)	230.0 (38, 770)	236.0 (47, 715)	233.5 (38, 770)
ANC (10^9/L) – n (%)			
< 0.5	1 (0.5)	0 (0.0)	1 (0.3)
0.5 to < 1.0	14 (7.7)	16 (8.8)	30 (8.3)
≥ 1.0	167 (91.8)	165 (91.2)	332 (91.5)
Median ANC (Min, Max) (10^9/L)	2.410 (0.39, 9.14)	2.300 (0.50, 13.25)	2.340 (0.39, 13.25)
Hemoglobin (g/dL) – n (%) [b]			
< 8	110 (60.4)	108 (59.7)	218 (60.1)
≥ 8	72 (39.6)	73 (40.3)	145 (39.9)
Median Hemoglobin (Min, Max) (g/dL)	7.80 (4.7, 9.2)	7.80 (4.5, 10.2)	7.80 (4.5, 10.2)
Serum EPO (U/L) – n (%)			
≤ 200	145 (79.7)	144 (79.6)	289 (79.6)
≤ 100	103 (56.6)	106 (58.6)	209 (57.6)
> 100 and ≤ 200	42 (23.1)	38 (21.0)	80 (22.0)
> 200 to < 500 [c]	37 (20.3)	37 (20.4)	74 (20.4)
Median Serum EPO (U/L)	77.245	85.370	83.980
Min, Max	7.80, 495.77	4.61, 462.53	4.61, 495.77
eGFR (mL/min/1.73m^2) – n (%)			
< 60	48 (26.4)	49 (27.1)	97 (26.7)
60 - 90	84 (46.2)	78 (43.1)	162 (44.6)
> 90	50 (27.5)	54 (29.8)	104 (28.7)
Median eGFR (mL/min/1.73m^2)	72.75	72.30	72.40
Min, Max	29.5, 142.0	28.8, 164.4	28.8, 164.4
Serum Ferritin (µg/L) – n (%)			
< 1000	140 (76.9)	134 (74.0)	274 (75.5)
≥ 1000	42 (23.1)	47 (26.0)	89 (24.5)
Median Serum Ferritin (µg/L)	623.00	650.00	634.50
Min, Max	12.4, 3170.0	39.4, 6960.5	12.4, 6960.5

[a] Baseline platelet (efficacy) is defined as the lowest platelet value within 35 days of the first dose of study drug.

[b] After applying above 14/3-day rule, the baseline Hgb value (efficacy) is defined as the lowest Hgb value from the central, local laboratory, or pre-transfusion Hgb from transfusion records that is within 35 days on or prior to the first dose of study drug if it was available.

[c] Per protocol, all subjects had sEPO levels < 500 U/L.

The most frequently reported **medical history** conditions in the luspatercept and epoetin alfa arms, respectively, were hypertension (52.2% vs 45.3%), type 2 diabetes mellitus (22.0% vs 20.4%), benign prostatic hyperplasia (15.4% vs 11.6%), atrial fibrillation (12.6% vs 13.3%), insomnia (8.8% vs 12.2%), osteoarthritis (11.5% vs 10.5%) and gastroesophageal reflux disease (11.5% vs 10.5%).

Extent of exposure

A longer median duration of therapy was observed in the luspatercept arm compared with the epoetin alfa arm: 51.3 vs 37.0 weeks. A higher proportion of subjects in the luspatercept compared with the epoetin alfa arms completed 24 weeks of treatment: 89.0% and 79.3%, respectively. Likewise, a higher proportion of subjects in the luspatercept arm vs the epoetin alfa arm completed 48 weeks of treatment: 55.5% vs 42.5%, respectively.

Table 43: treatment exposure: safety population

	Luspatercept (N=182)	Epoetin Alfa (N=179)
Median Treatment Duration (weeks) (Min, Max) [a]	**51.3 (3, 196)**	**37.0 (1, 202)**
Median Number of Doses Received (Min, Max)	**16.5 (1, 60)**	**33.0 (1, 194)**
Total Number of Doses Received by Planned Dose Level, n (%) [b]	**2950 doses**	**6729 doses**
1.0 mg/kg	1298 (34.5)	--
1.33 mg/kg	765 (20.4)	--
1.75 mg/kg	1491 (39.7)	--
0.80 mg/kg	185 (4.9)	--
0.60 mg/kg	5 (0.1)	--
0.45 mg/kg	13 (0.3)	
450 IU/kg	--	1923 (23.1)
787.5 IU/kg	--	1883 (22.6)
1050 IU/kg	--	4024 (48.3)
337.5 IU/kg	--	504 (6.0)
Completed 24 Weeks of Treatment – n (%)	**162 (89.0)**	**142 (79.3)**
Completed 48 Weeks of Treatment – n (%)	**101 (55.5)**	**76 (42.5)**

[a] [(Treatment end date) – (the date of the first dose of IP) + 1]/7.
[b] Percentages based on the total number of doses received in each arm.

Dose escalations were common in both treatment arms (Table 44). The most common reason for dose escalation in luspatercept and epoetin alfa treated subjects was per protocol: 73.6% vs 75.4%.

Table 44: dose escalation: safety population

	Luspatercept (N = 182)	Epoetin Alfa (N = 179)
Number of Subjects with at Least One Dose Escalation – n (%)	**143 (78.6)**	**146 (81.6)**
Dose Escalated from 0.8 mg/kg to 1.0 mg/kg	7 (3.8)	0 (0.0)
Dose Escalated from 1.0 mg/kg to 1.33 mg/kg	139 (76.4)	0 (0.0)
Dose Escalated from 1.33 mg/kg to 1.75 mg/kg	113 (62.1)	0 (0.0)
Dose Escalated from 337.5 IU/kg to 450 IU/kg	0 (0.0)	8 (4.5)
Dose Escalated from 450 IU/kg to 787.5 IU/kg	0 (0.0)	144 (80.4)
Dose Escalated from 787.5 IU/kg to 1050 IU/kg	0 (0.0)	116 (64.8)
Reasons for Dose Escalation – n (%)		
Per Protocol	134 (73.6)	135 (75.4)
Loss of Response or Hgb Drop ≥ 1 g/dL upon Dose Reduction	0 (0.0)	11 (6.1)
Investigator Decision	26 (14.3)	18 (10.1)
Other	2 (1.1)	1 (0.6)
Missing	3 (1.6)	4 (2.2)
Time to First Dose Escalation (days)		
Median (Min, Max)	62.0 (41, 1144)	43.0 (37, 517)

Dose delays were common in both treatment arms, but were more frequent in luspatercept treated subjects compared with epoetin alfa treated subjects (60.4% vs 43.0%) (Table 45).

Table 45: Dose delay and dose reduction: safety population

	Luspatercept (N = 182)	Epoetin Alfa (N = 179)
Number of Subjects with at Least One Dose Delay – n (%)	**110 (60.4)**	**77 (43.0)**
Reasons for Dose Delay – n (%)		
Adverse Event	52 (28.6)	40 (22.3)
Predose Hgb ≥ 12.0 g/dL	44 (24.2)	22 (12.3)
Elevated White Blood Cell [a]	1 (0.5)	2 (1.1)
Presence of ≥ 1% Blasts in Peripheral Blood	3 (1.6)	5 (2.8)
Investigator Decision	6 (3.3)	4 (2.2)
Other	47 (25.8)	31 (17.3)
Median (Min, Max) Time to First Dose Delay (days)	180.5 (26, 1122)	105.0 (12, 827)
Time to First Dose Delay due to AE (days)	**n = 52**	**n = 40**
Median (Min, Max)	254.0 (29, 1122)	109.0 (12, 827)
Time to First Dose Delay due to Hgb > 12 g/dL (days)	**n = 44**	**n = 22**
Median (Min, Max)	247.5 (30, 800)	95.5 (36, 484)
Number of Subjects with at Least One Dose Reduction – n (%)	**25 (13.7)**	**28 (15.6)**
Dose Reduced from 1.75 mg/kg to 1.33 mg/kg	7 (3.8)	0
Dose Reduced from 1.33 mg/kg to 1.0 mg/kg	4 (2.2)	0
Dose reduced from 1.33 mg/kg to 0.8 mg/kg	1 (0.5)	0
Dose Reduced from 1.0 mg/kg to 0.8 mg/kg	15 (8.2)	0
Dose Reduced from 0.8 mg/kg to 0.6 mg/kg	1 (0.5)	0
Dose Reduced from 0.6 mg/kg to 0.45 mg/kg	1 (0.5)	0
Dose Reduced from 1050 IU/kg to 787.5 IU/kg	0	8 (4.5)
Dose Reduced from 787.5 IU/kg to 450 IU/kg	0	9 (5.0)
Dose Reduced from 450 IU/kg to 337.5 IU/kg	0	19 (10.6)
Reasons for Dose Reduction – n (%)		
Adverse Event	9 (4.9)	4 (2.2)
Increase in Hgb ≥ 2.0 g/dL Compared to Previous Pre-dose Hgb	11 (6.0)	0 (0.0)
Increase in Hgb ≥ 2.0 g/dL over 4 Weeks	0 (0.0)	7 (3.9)
Per Protocol	2 (1.1)	7 (3.9)
Investigator Decision	5 (2.7)	10 (5.6)
Other	1 (0.5)	2 (1.1)
Missing	0 (0.0)	2 (1.1)
Time to First Dose Reduction (days)	**n = 25**	**n = 28**
Median (Min, Max)	107.0 (22, 534)	98.5 (15, 1079)
Time to First Dose Reduction due to AE (days)	**n = 9**	**n = 4**
Median (Min, Max)	127.0 (64, 348)	67.0 (15, 113)
Time to First Dose Reduction due to Hgb Increase > 2 g/dL (days)	**n = 11**	**n = 7**
Median (Min, Max)	114.0 (22, 778)	58.0 (31, 869)

[a] Elevated white blood cell is defined as ≥ 50% increase in white blood cell count (WBC) compared to pre-dose WBC of previous study drug administration and above upper limit of normal.

Numbers analysed

Table 46: Analysis populations presented in this primary CSR

Population	Luspatercept	Epoetin Alfa	Total
Intent-to-Treat Population [a]	182	181	363
Safety Population [b]	182 (100.0)	179 (98.9)	361 (99.4)
HRQoL Evaluable Population - EORTC QLQ-C30 [c]	166 (91.2)	159 (87.8)	325 (89.5)
HRQoL Evaluable Population - FACT-An [c]	170 (93.4)	169 (93.4)	339 (93.4)
HRQoL Evaluable Population – QUALMS-P [c]	29 (15.9)	14 (7.7)	43 (11.8)

[a] ITT population: all randomized subjects regardless of whether or not the subject received study drug.

[b] Safety population: all subjects who were randomized and received at least 1 dose of study drug. The 2 subjects in the epoetin alfa arm who were randomized and not treated withdrew consent on the date of the first potential first dosing visit.

[c] HRQoL evaluable population: all subjects in the ITT population who completed the respective patient reported outcomes assessment at baseline and at least 1 post-baseline assessment visit.

Outcomes and estimation

Efficacy Summary

For this primary analysis (31-Mar-2023 clinical data cut-off), median follow-up was 17.2 months for the luspatercept arm and 16.9 months for the epoetin alfa arm. The analysis population for all efficacy endpoints was all randomized subjects who had completed 169 days (24 weeks) of treatment or discontinued early.

At the primary analysis (31-Mar-2023 clinical data cutoff), results for the primary efficacy endpoint and all 3 hierarchically tested secondary endpoints, as well as corresponding Week 1-48 endpoints, met the threshold for statistical significance (1-sided $p < 0.015$).

Table 47: Summary of efficacy – ACE-536-MDS-002-ITT population -primary analysis (weeks 1 to 24 endpoint assessment)

	Luspatercept (N=182)[a]	Epoetin Alfa (N=181)[a]
Primary Efficacy Endpoint		
RBC-TI for 12 weeks (84 days) with an associated concurrent mean Hgb increase ≥ 1.5 g/dL (Week 1 to 24)		
Response Rate (95% CI)	60.4 (52.9, 67.6)	34.8 (27.9, 42.2)
Common Risk Difference on Response Rate (%) (95% CI)[b]	25.4 (15.8, 35.0); p < 0.0001	
Odds Ratio (95% CI)[b]	3.1 (2.0, 4.8)	
Ad Hoc Analyses		
Median (95% CI) duration (wks) of RBC TI ≥ 12 weeks w/ concurrent mean Hgb increase ≥ 1.5 g/dL (Week 1-EOT)	N=110 71.9 (39.9, 83.9)	N=63 55.6 (39.9, 77.9)
Key Secondary Efficacy Endpoints		
HI-E per IWG for ≥ 56 days (Week 1 to 24)		
Response Rate (95% CI)	74.2 (67.2, 80.4)	53.0 (45.5, 60.5)
Common Risk Difference on Response Rate (%) (95% CI)[b]	21.5 (12.2, 30.7); p < 0.0001	
Odds Ratio (95% CI)[b]	2.8 (1.8, 4.5)	
RBC-TI for 24 weeks (Week 1 to 24)		
Response Rate (95% CI)	47.8 (40.4, 55.3)	30.9 (24.3, 38.2)
Common Risk Difference on Response Rate (%) (95% CI)[b]	16.3 (7.1, 25.4; 0.0003	
Odds Ratio (95% CI)[b]	2.3 (1.4, 3.7)	
RBC-TI for ≥ 12 weeks (84 days) (Week 1 to 24)		
Response Rate (95% CI)	68.1 (60.8, 74.8)	48.6 (41.1, 56.1)
Common Risk Difference on Response Rate (%) (95% CI)[b]	18.8 (9.5, 28.0); p <0.0001	
Odds Ratio (95% CI)[b]	2.5 (1.6, 4.0)	
Other Secondary Efficacy Endpoints		
RBC Transfusion-Related Secondary Endpoints		
Duration (weeks) of RBC-TI ≥ 12 weeks (84 days) (Week 1 to EOT)	N=124	N=88
Median (95% CI)	128.1 (108.3, NE)	89.7 (55.9, 157.3)
HR (95% CI)[c,d]	0.534 (0.330, 0.864); nominal p = 0.0096	
Time (days) to RBC-TI ≥ 12 weeks (Week 1 to 24)	N = 124	N = 88
Median (Min, Max)[e]	1.0 (1.0, 75.0)	1.0 (1.0, 85.0)

RBC-TI for ≥ 8 weeks (56 days) (Week 1 to 24)		
Response Rate (95% CI)	79.1 (72.5, 84.8)	64.6 (57.2, 71.6)
Common Risk Difference on Response Rate (%) (95% CI)[b]	13.7 (5.3, 22.2); nominal p = 0.0007	
Odds Ratio (95% CI)[b]	2.3 (1.4, 3.8)	
RBC Transfusion Burden on Treatment (Week 1 to 24)		
Mean Number of RBC Units (SD)	3.8 5.90	5.2 (6.36)
Median Number of RBC Units (Min, Max)	1.0 (0, 24.0)	3.0 (0, 37.0)
Time (days) to First RBC Transfusion (Week 1 to EOT)	N = 116	N = 137
Median (Min, Max)[f]	155.0 (80.0, 266.0)	42.0 (23.0, 55.0)
HR (95% CI)[c]	0.570 (0.437, 0.742); nominal p < 0.0001[d]	
Hematologic Improvement-Related Secondary Endpoints		
Mean Hgb Change (g/dL) over 24 weeks (Week 1 to 24)		
Mean (SD)	2.0 (1.14)	1.5 (1.12)
Time (days) to HI-E (Week 1 to 24)		
Median (Min, Max)	1.0 (1.0, 113.0)	6.0 (1.0, 108.0)
Key Exploratory Efficacy Endpoints (ad hoc analyses)		
Reduction in pRBC Units of at Least 50% (Week 1-EOT)		
At Least 12 Weeks		
Response Rate (95% CI)	83.0 (76.7, 88.1)	66.9 (59.5, 73.7)
Common Risk Difference (%) (95% CI)[b]	15.4 (6.9, 23.9); nominal p = 0.0002	
Odds Ratio (95% CI)[b]	2.5 (1.5, 4.1)	
At Least 24 Weeks		
Response Rate (95% CI)	72.5 (65.4, 78.9)	50.8 (43.3, 58.3)
Common Risk Difference (%) (95% CI)[b]	21.0 (11.6, 30.4); nominal p < 0.0001	
Odds Ratio (95% CI)[b]	2.7 (1.7, 4.3)	
Additional Secondary Endpoints		
Progression to AML[g]		
Number (%) of Subjects with AML Progression	5 (2.7)	6 (3.3)
Median Time (months) from Randomization[f]	NE	NE
Incidence Rate per 100 PY (95% CI)	1.70 (0.71, 4.08)	2.15 (0.97, 4.79)
HR (95% CI)[c,d]	0.913 (0.270, 3.082)	
Overall Survival[g]		
Number (%) of Subjects Alive (censored), n (%)	143 (78.6)	143 (79.0)
Number (%) of Subjects who Died	39 (21.4)	38 (21.0)
Median (months)	NE	42.8
(95% CI)[f]	(35.3, NE)	(42.8, NE)
HR (95% CI)[c,d]	1.089 (0.686, 1.728)	

[a] The analysis population is subjects who completed 169 days (24 weeks) of treatment or discontinued early.

[b] Based on CMH test stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L). 1-sided p-value is presented.

[c] HR calculated by Cox proportional hazard model stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L).

[d] p-value (1-sided) from log-rank test with by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L) as covariates.

[e] Time to RBC-TI ≥ 12 weeks was summarized only for subjects who achieved RBC-TI ≥ 84 days from Week 1 through Week 24. It was defined as the time between Week 1 and the date of the onset of first TI.

[f] Median is from unstratified Kaplan-Meier method.

[g] Randomization through 5 years from first dose or 3 years from last dose, whichever occurred later. The analysis population was ITT up to the clinical data cutoff date (with any treatment duration).

Table 48: summary of efficacy – week 1 to 48 assessment -ITT population – ACE-536-MDS-002 primary analysis

	Luspatercept (N=163)[a]	Epoetin Alfa (N=167)[a]
RBC-TI for 12 weeks (84 days) with an associated concurrent mean Hgb increase ≥ 1.5 g/dL (Week 1 to 48)		
Response Rate (95% CI)	66.9 (59.1, 74.0)	40.1 (32.6, 48.0)
Common Risk Difference on Response Rate (%) (95% CI)[b]	26.8 (16.6, 37.0); p < 0.0001	
Odds Ratio (95% CI)[b]	3.2 (2.0, 5.1)	
HI-E per IWG for ≥ 56 days (Week 1 to 48)		
Response Rate (95% CI)	77.3 (70.1, 83.5)	54.5 (46.6, 62.2)
Common Risk Difference on Response Rate (%) (95% CI)[b]	23.3 (13.7, 33.0); p < 0.0001	
Odds Ratio (95% CI)[b]	3.1 (1.9, 5.2)	
RBC-TI ≥ 24 weeks (Week 1 to 48)		
Response Rate (95% CI)	60.7 (52.8, 68.3)	39.5 (32.1, 47.4)
Common Risk Difference on Response Rate (%) (95% CI)[b]	20.7 (10.8, 30.6); p <0.0001	
Odds Ratio (95% CI)[b]	2.6 (1.6, 4.3)	
RBC-TI for ≥ 12 weeks (84 days) (Week 1 to 48)		
Response Rate (95% CI)	73.0 (65.5, 79.7)	52.7 (44.8, 60.5)
Common Risk Difference on Response Rate (%) (95% CI)[b]	19.8 (10.0, 29.6); p <0.0001	
Odds Ratio (95% CI)[b]	2.6 (1.6, 4.3)	

a Only subjects whose first dose date is at least 337 days from the cutoff date or discontinued early are included in this efficacy analysis.

b Based on CMH test stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L). 1-sided p-value is presented.

Source: Response to RSI-1 Major Objection Appendix MO2[1]: Table 14.2.30.b (RBC-TI >= 12 Weeks with Concurrent Mean Hemoglobin Increase ≥1.5g/dL, Week 1-48); Table 14.2.31.b (HI-E, Week 1-48), Table 14.2.12 (RBC-TI for 24 weeks. Week 1-48): Table 14.2.32.b (RBC-TI for ≥ 12 weeks. Week 1-48).

Ancillary analyses

Sensitivity analyses

Results for the 2 sensitivity analyses (Week 1 to 24) of RBC-TI at least 12 weeks with concurrent mean Hb increase at least 1.5 g/dL (primary endpoint) and of HI-E per IWG for ≥ 56 (1st hierarchically tested secondary endpoint) were consistent with those for the primary analyses:

- **Sensitivity Analysis 1:** included Hb measurements from the central laboratory, local laboratory, as well as pre-transfusion Hb from transfusion records.
    - **Primary endpoint:** Luspatercept vs epoetin alfa: 60.4% (95% CI: 52.9, 67.6) vs 35.4% (95% CI: 28.4, 42.8); common risk difference on response rate = 24.8 (95% CI: 15.2, 34.5); 1-sided stratified CMH test p-value < 0.0001.

- **1st hierarchically tested secondary endpoint:** Luspatercept vs epoetin alfa: 75.3% (95% CI: 68.3, 81.4) vs 51.9% (95% CI: 44.4, 59.4); common risk difference on response rate = 23.7 (95% CI: 14.4, 32.9); 1-sided stratified CMH test p-value < 0.0001.

- **Sensitivity Analysis 2:** central laboratory results only were used for all Hb measurements. If the Hb change from baseline was based on a single central laboratory measurement, then the subject was considered a non-responder, even if the Hb change met the response definition.
  - **Primary endpoint:** Luspatercept vs epoetin alfa: 60.4% (95% CI: 52.9, 67.6) vs 34.8% (95% CI: 27.9, 42.2); common risk difference on response rate = 25.4 (95% CI: 15.8, 35.0); 1-sided stratified CMH test p-value < 0.0001.
  - **1st hierarchically tested secondary endpoint:** Luspatercept vs epoetin alfa: 74.2% (95% CI: 67.2, 80.4) vs 51.4% (95% CI: 43.9, 58.9); common risk difference on response rate = 23.1 (95% CI: 13.8, 32.5); 1-sided stratified CMH test p-value < 0.0001.

Analysis of Epoetin Alfa Comparator Arm by Drug Product

In the subgroup with EPREX/ERYPO-treated subjects, demographics, baseline disease characteristics, and baseline laboratory characteristics were similar to those of the corresponding luspatercept-treated subgroup, as well as to those of the overall treatment arms and overall study population.

Efficacy results (response rate and durability) of the subgroup with EPREX/ERYPO-treated subjects were similar to those of the entire overall comparator arm (Table 49).

Table 49: Summary of key efficacy results -overall and Eprex/Erypo- treated subgroup- ACE-536-MDS-002

	Overall Population [a]		Non-US [a]	
	Luspatercept (N=182)	Epoetin Alfa (N=181)	Luspatercept (N=174)	Epoetin Alfa (EPREX/ERYPO) (N=172)
Primary Efficacy Endpoint				
RBC-TI for 12 weeks (84 days) with concurrent mean Hgb increase ≥ 1.5 g/dL (Week 1 to 24)				
Responder, n (%) [b]	110 (60.4)	63 (34.8)	104 (59.8)	61 (35.5)
Risk Difference (%) (95% CI) [c]	25.4 (15.8, 35.0)		24.30 (13.09, 34.52)	
Median (95% CI) duration (wks) of the primary endpoint (Week 1 to EOT) [d]	71.9 (39.9, 83.9)	55.6 (39.9, 77.9)	71.9 (48.1, 87.7)	57.9 (38.1, 79.1)
Hierarchically Tested Secondary Efficacy Endpoints				
HI-E per IWG (Week 1 to 24)				
Responder, n (%) [b]	135 (74.2)	96 (53.0)	129 (74.1))	94 (54.7)
Risk Difference (%) (95% CI) [c]	21.5 (12.2, 30.7)		19.49 (8.57, 29.41)	
RBC-TI for 24 weeks (Week 1 to 24)				
Responder, n (%) [b]	87 (47.8)	56 (30.9)	81 (46.6)	53 (30.8)
Risk Difference (%) (95% CI) [c]	16.3 (7.1, 25.4)		15.74 (4.83, 25.83)	
RBC-TI for ≥ 12 weeks (Week 1 to 24)				
Responder, n (%) [b]	124 (68.1)	88 (48.6)	117 (67.2)	84 (48.8)
Risk Difference (%) (95% CI) [c]	18.8 (9.5, 28.0)		18.40 (7.16, 28.54)	
Other Secondary Efficacy Endpoint				
Duration of RBC-TI for ≥ 12 weeks (Week 1 to EOT)				
Median (95% CI) [d]	128.1 (108.3, NE)	89.7 (55.9, 157.3)	126.6 (108.3, NE)	91.1 (62.9, NE)
HR (95% CI) [e]	0.534 (0.330, 0.864)		0.559 (0.341, 0.916)	

[a] Only subjects who completed 169 days of treatment or discontinued early are included in efficacy analysis.

[b] Response rate is calculated using the number of responders divided by number of subjects in each subgroup.

[c] Common risk difference is calculated based on luspatercept and epoetin alfa group from ACE-536-MDS-002. Based on Cochran-Mantel-Haenszel test stratified for average baseline RBC transfusion burden at baseline (<4, >=4 units), ring sideroblast status at baseline (RS+, RS-) and sEPO level at baseline (<=200, > 200 to < 500 U/L). Derived baseline stratifications are used.

[d] Median is from un-stratified Kaplan-Meier method.

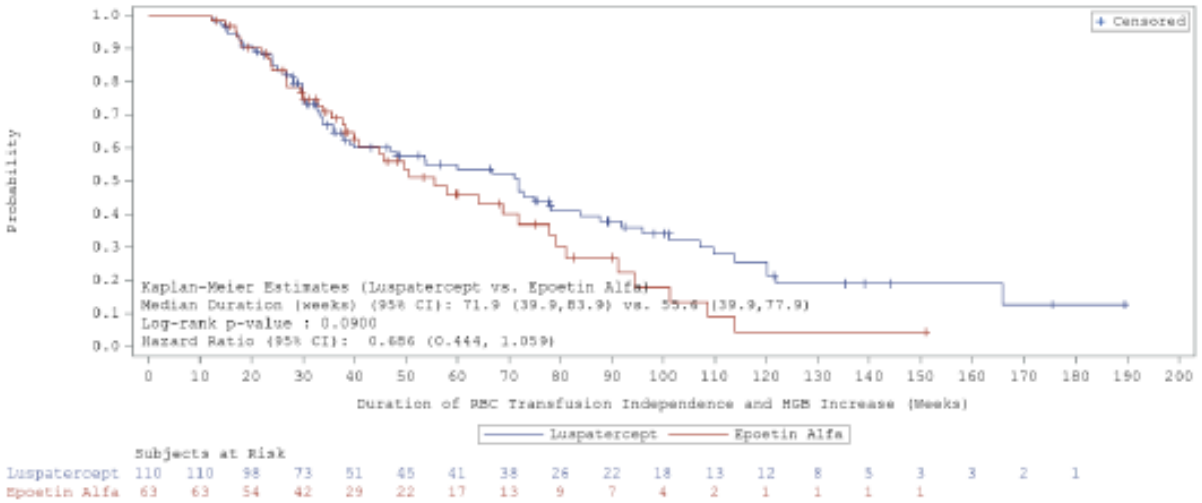
[e] Hazard ratio is calculated by Cox proportional hazard model stratified by RBC transfusion burden at baseline (<4, ≥4 units), ring sideroblast status at baseline, and sEPO level at baseline (<=200, > 200 U/L). Derived baseline stratifications are used.

Transfusion Independence and Transfusion Burden

A summary of the outcomes of the primary efficacy endpoint and secondary efficacy endpoints related to transfusion independence and transfusion burden is shown in Table 5 above.

In subjects who were **primary endpoint responders, the median duration** (of the longest single RBC TI period) during Week 1 to EOT (ad hoc analysis), was numerically longer in the luspatercept arm vs the epoetin alfa arm: 71.9 (95% CI: 39.9, 83.9) vs 55.6 (95% CI: 39.9, 77.9) weeks.

Figure 19: Kaplan-Meier curve of duration of RBC-TI at least 12 weeks with concurrent mean hemoglobin increase at least 1.5 g/dL (week 1 to EOT): primary endpoint responders in the ITT population



Only subjects who completed 169 days (24 weeks) of treatment or discontinued early were included in efficacy analysis.

Duration of RBC-TI ≥ 12 weeks with concurrent mean Hgb increase ≥ 1.5g/dL: the longest RBC-TI period with concurrent mean Hgb increase ≥ 1.5g/dL from Week 1 to EOT visit for subjects who are primary endpoint responders.

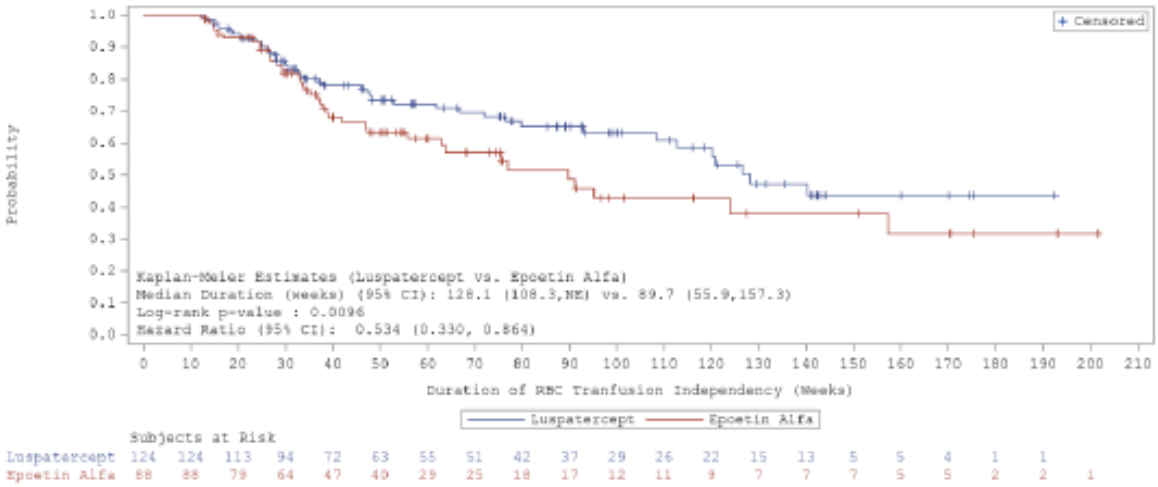
Median is from unstratified Kaplan-Meier method.

p-value is from log-rank test with RBC transfusion burden at baseline (< 4, ≥ 4 pRBC units), ring sideroblast status at baseline (RS+, RS-) and sEPO level at baseline (≤ 200, > 200 to < 500 U/L) as covariates. Derived baseline stratifications are used. 1-sided p-value is presented.

HR is calculated by Cox proportional hazard model stratified by RBC transfusion burden at baseline (< 4, ≥ 4 pRBC units), ring sideroblast status at baseline (RS+, RS-) and sEPO level at baseline (≤ 200, > 200 to < 500 U/L). Derived baseline stratifications are used.

The median **duration of the longest single RBC TI period** for subjects who achieved RBC TI ≥ 12 weeks (84 days) from Week 1 to EOT (3rd hierarchically tested secondary endpoint) was longer in the luspatercept arm vs the epoetin alfa arm: 128.1 (95% CI: 108.3, Not estimable) vs 89.7 (95% CI: 55.9, 157.3) weeks (Figure 7.3.1.2-1).

Figure 20: Kaplan-Meier curve of duration of RBC-TI≥12 weeks (week 1 to EOT): RBC-TI≥12 weeks (week 1 to 24) responders



Only subjects who completed 169 days (24 weeks) of treatment or discontinued early were included.

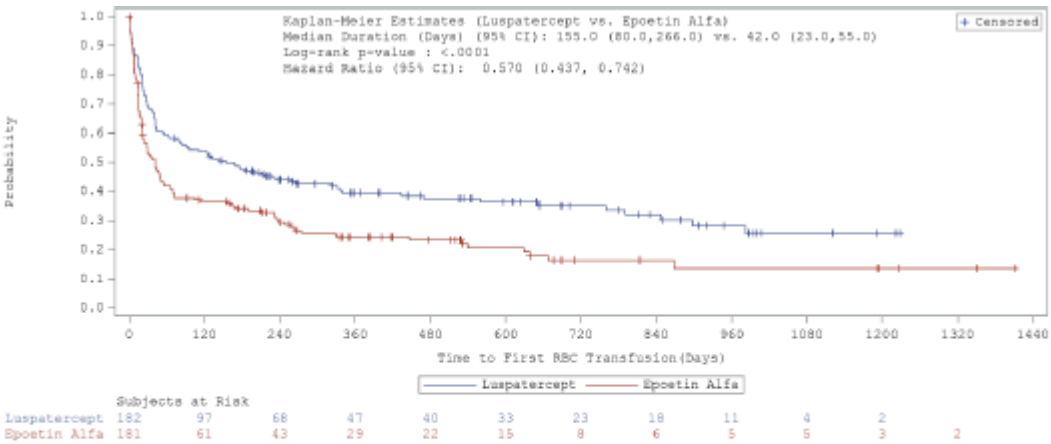
Median is from un-stratified Kaplan-Meier method.

p-value is from log-rank test with RBC transfusion burden at baseline (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L) as covariates. Derived baseline stratifications are used. 1-sided p-value is presented.

Hazard ratio is calculated by Cox proportional hazard model stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L). Derived baseline stratifications are used.

The median **time to first pRBC transfusion** (Week 1 to EOT) was longer in the luspatercept arm vs the epoetin alfa arm: 155.0 vs 42.0 days.

Figure 21: Kaplan-Meier curve to first RBC transfusion (week 1 EOT): ITT population



Only subjects who completed 169 days (24 weeks) of treatment or discontinued early were included.

Median is from un-stratified Kaplan-Meier method.

p-value is from log-rank test with baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L) as covariates. Derived baseline stratifications are used. 1-sided p-value is presented.

Hazard ratio is calculated by Cox proportional hazard model stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L). Derived baseline stratifications are used.

The median **duration of ≥ 50% reduction in pRBC units** for subjects who achieved a ≥ 50% reduction in pRBC units (over at least 12 weeks or over at least 24 weeks) from Week 1 to EOT, was longer in the luspatercept arm compared with the epoetin alfa arm:

- Over at least 12 weeks
  - Median (95% CI): 130.0 (120.6, Not estimable) vs 77.0 (54.9, 123.1) weeks
  - Hazard ratio: 0.479 (0.317, 0.723); log rank nominal p-value = 0.0004
- Over at least 24 weeks
  - Median (95% CI): 160.0 (135.0, Not estimable) vs 117.4 (80.1, Not estimable) weeks
  - Hazard ratio: 0.409 (0.236, 0.710); log rank nominal p-value = 0.0011

Hematologic Improvement

Erythroid response (HI-E) was defined as the proportion of subjects meeting the modified HI-E criteria per IWG sustained over any consecutive 56-day period in Week 1 to 24 as follows:

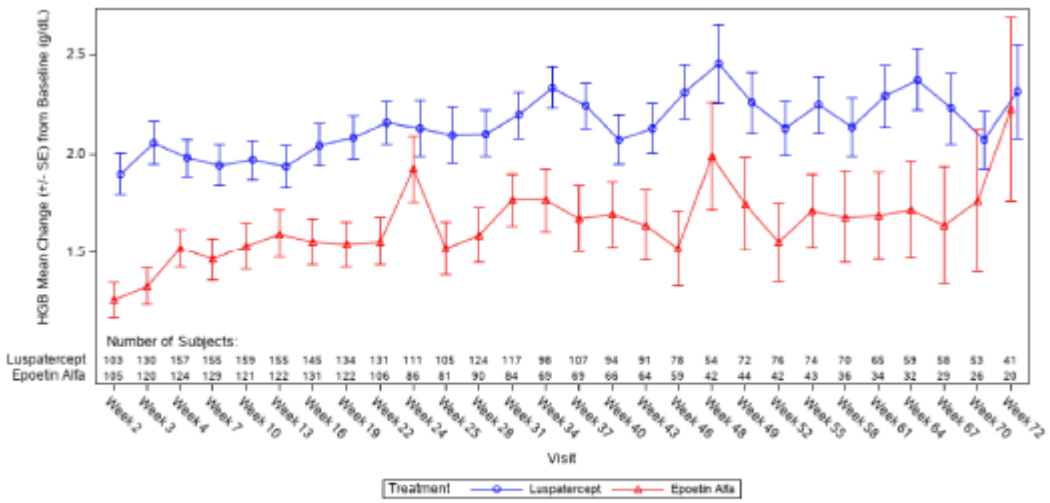
- Subjects with baseline transfusion burden of < 4 pRBC units/8 weeks: Hb increase of ≥ 1.5 g/dL in the absence of transfusions for any consecutive 56 days.
- Subjects with baseline transfusion burden of ≥ 4 pRBC units/8 weeks: a relevant reduction of pRBC units by an absolute number of at least 4 units compared with the baseline transfusion burden for any consecutive 56 days.

Central laboratory results only were used for Hb measurements for the primary analyses.

A summary of the outcomes of secondary efficacy endpoints related to HI-E is shown in Table 5 above.

The mean **Hb increase** from baseline during Week 1 to 24 for luspatercept-treated subjects was greater compared with epoetin alfa-treated subjects: 2.0 vs 1.5 g/dL.

Figure 22: Mean change (SE) from baseline for hemoglobin: ITT population



SE = Standard error.

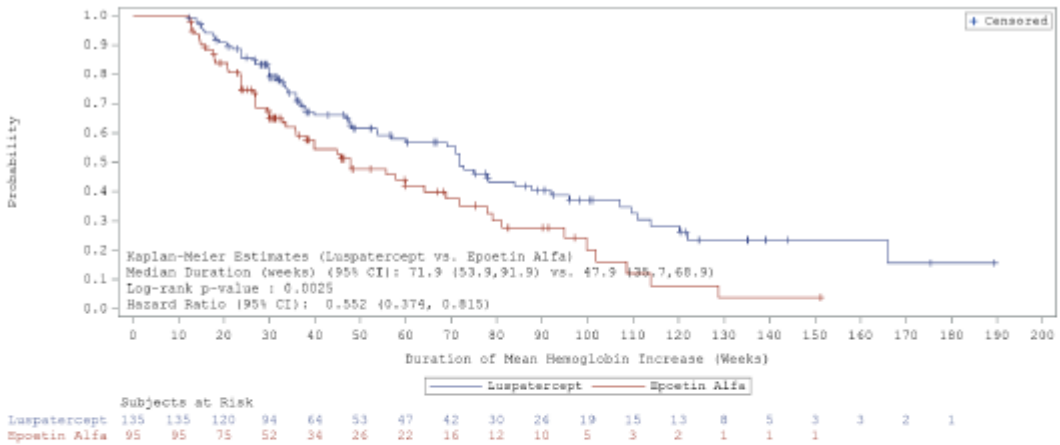
Excludes hemoglobin measurement within 14 days after a RBC transfusion unless within 3 days prior to another transfusion. Only central laboratory results were included.

A greater proportion of luspatercept-treated subjects than epoetin alfa-treated subjects had a **mean Hb increase ≥ 1.5 g/dL** during Week 1 to 24:

- Response rates: 74.2% vs 52.5%
- Common risk difference on response rate = 22.0% (95% CI: 12.3, 31.6)
- 1 sided stratified CMH test nominal p value < 0.0001.

In subjects with a Hb increase ≥ 1.5 g/dL, the median duration of the longest period where the mean Hb increase ≥ 1.5 g/dL was sustained during Week 1 to EOT was greater for luspatercept-treated subjects compared with epoetin alfa-treated subjects: 71.9 vs 47.9 weeks.

Figure 23: Kaplan-Meier curve of duration of mean hemglobin increase at least 1.5 g/dL (week 1 to EOT) - responders



Only subjects who completed 169 days (24 weeks) of treatment or discontinued early are included in efficacy analysis.

Duration of mean hemoglobin increase ≥ 1.5g/dL: longest period where mean hemoglobin increase ≥ 1.5g/dL is sustained from Week 1 through EOT visit for subjects who have mean hemoglobin increase ≥ 1.5g/dL compared to baseline for at least any consecutive 84 days in Week 1 to 24.

Median is from unstratified Kaplan-Meier method.

p-value is from log-rank test with RBC transfusion burden at baseline (< 4, ≥ 4 pRBC units), ring sideroblast status at baseline (RS+, RS-) and sEPO level at baseline (≤ 200, > 200 to 500 U/L) as covariates. Derived baseline stratifications are used. One-sided p-value is presented.

Hazard ratio is calculated by Cox proportional hazard model stratified by RBC transfusion burden at baseline (< 4, ≥ 4 pRBC units), ring sideroblast status at baseline (RS+, RS-) and sEPO level at baseline (≤ 200, > 200 to < 500 U/L). Derived baseline stratifications are used.

Neutrophil response (HI-N) was defined as the proportion of subjects meeting the modified HI-E criteria per IWG sustained over any consecutive 56-day period in Week 1 to 24 as follows: 100% increase and an absolute increase of > 0.5 x 10^9/L. Only central laboratory results were used and only subjects with a baseline neutrophil value < 1.0 x 10^9/L were eligible for HI-N evaluation (luspatercept arm: N = 15 and epoetin alfa arm: N = 16).

A numerically greater proportion of subjects in the luspatercept arm achieved HI-N per IWG during Week 1 to 24 (ad hoc analysis) compared with the epoetin arm:

- Response rates: 33.3% (95% CI: 11.8, 61.6) vs 25.0% (95% CI: 7.3, 52.4)
- Common risk difference on response rate = -8.4 (95% CI: -47.0, 30.2)
- 1-sided unstratified CMH test nominal p-value = 0.6604

For subjects with a baseline platelet value > 20 x 10^9/L, **platelet response** (HI-P) was defined as an absolute increase of ≥ 30 x 10^9/L. Only central laboratory results were used and only subjects with a baseline platelet value < 100 x 10^9/L were eligible for HI-P evaluation (luspatercept arm: N = 26 and epoetin alfa arm: N = 20).

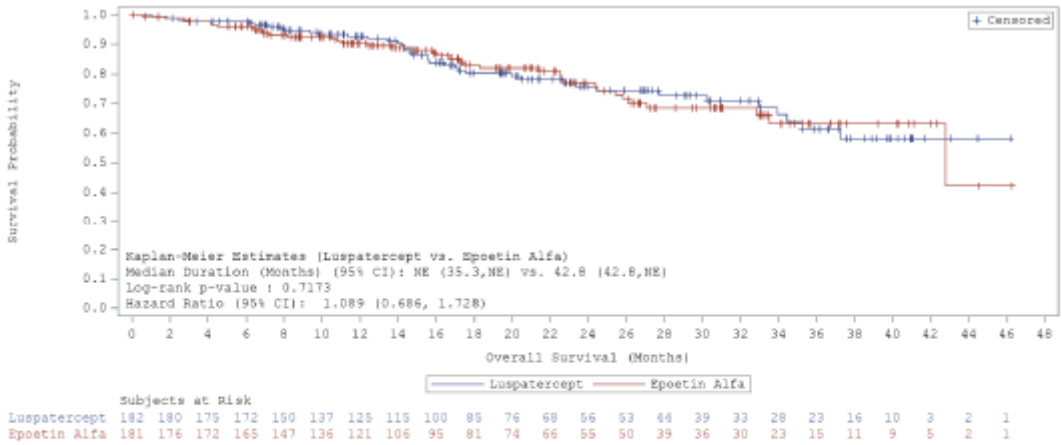
A numerically greater proportion of subjects in the luspatercept arm achieved HI-P per IWG during Week 1 to 24 (ad hoc analysis) compared with the epoetin arm:

- Response rates: 42.3% (95% CI: 23.4, 63.1) vs 30.0% (95% CI: 11.9, 54.3)
- Common risk difference on response rate = 13.7 (95% CI: -16.4, 43.8)
- 1-sided unstratified CMH test nominal p-value = 0.1952

Progression to Acute Myeloid Leukemia and Overall Survival

A summary of the outcome up to the clinical data cutoff for the primary analysis (31-Mar-2023) is shown in Table 23 above. The median time to progression to AML (Week 1 to EOT) was not estimable in either group. The proportion of deaths was balanced between treatment arms. See Safety Section for more information.

Figure 24: Kaplan-Meier curve of overall survival ITT population



Median is from un-stratified Kaplan-Meier method.

p-value is from log-rank test with by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L) as covariates. Derived baseline stratifications are used. 1-sided p-value is presented.

Hazard ratio is calculated by Cox proportional hazard model stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L). Derived baseline stratifications are used.

Patient-Reported Outcomes

EORTC QLQ-C30 (secondary objective) is a validated questionnaire composed of 30 items addressing 15 HRQoL domains. It includes a global health status score as well as scores for 5 functional scales (physical, role, emotional, cognitive and social), 3 symptom scales (fatigue, nausea/vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties).

A high score for global health status or a functional scale represents a high or healthy level of functioning; a high score for a symptom scale or item represents a high level of symptomatology or problems.

Completion rates at baseline and at Week 49 in the luspatercept and epoetin arms were 95.6% vs 95.0% and 84.0% vs 75.0%, respectively. The baseline characteristics (demographics and disease characteristics) for the HRQoL evaluable population for EORTC QLQ-C30 were generally balanced across the 2 treatment arms and were consistent with those for the ITT population. At baseline, there was some imbalance in mean EORTC QLQ-C30 scores for most domains, demonstrating better health status for subjects in the luspatercept arm than the epoetin alfa arm.

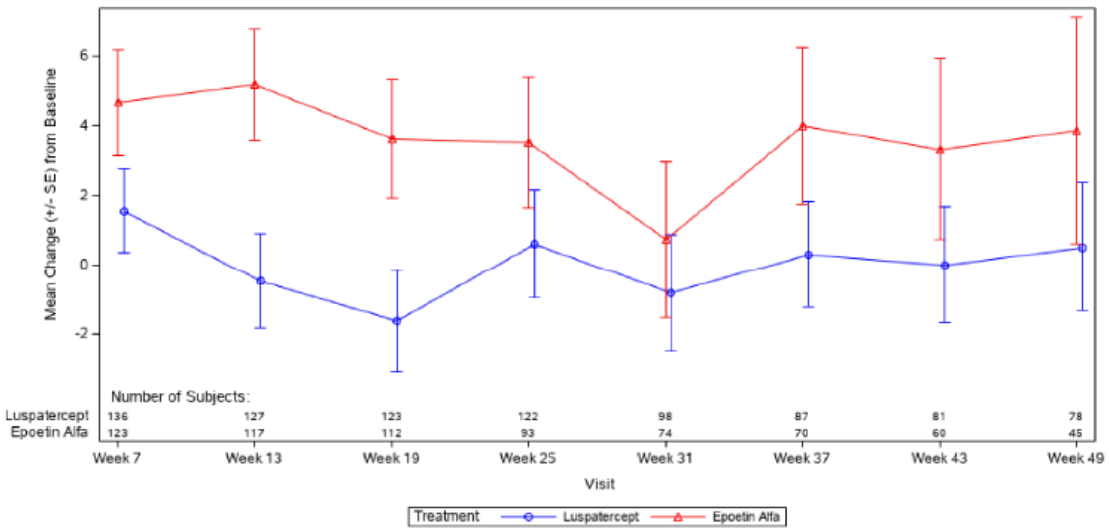
Global Health Status

In both treatment arms, there were small increases from baseline in the mean scores for global health status (indicating improvement) during the treatment period up to Week 25 which generally continued through Week 49. None of the changes in either arm reached the MID of 5 for improvement. At Week 49, the mean change from baseline was 3.1 in the luspatercept arm and 1.1 in the epoetin alfa arm.

Functional Scales

In the luspatercept arm, changes in physical functioning did not reach the MID threshold of 2 for improvement or deterioration. In the epoetin alfa arm, increases reached the MID of 2 (indicating improvement) at all timepoints during the treatment period up to Week 49 except Week 31.

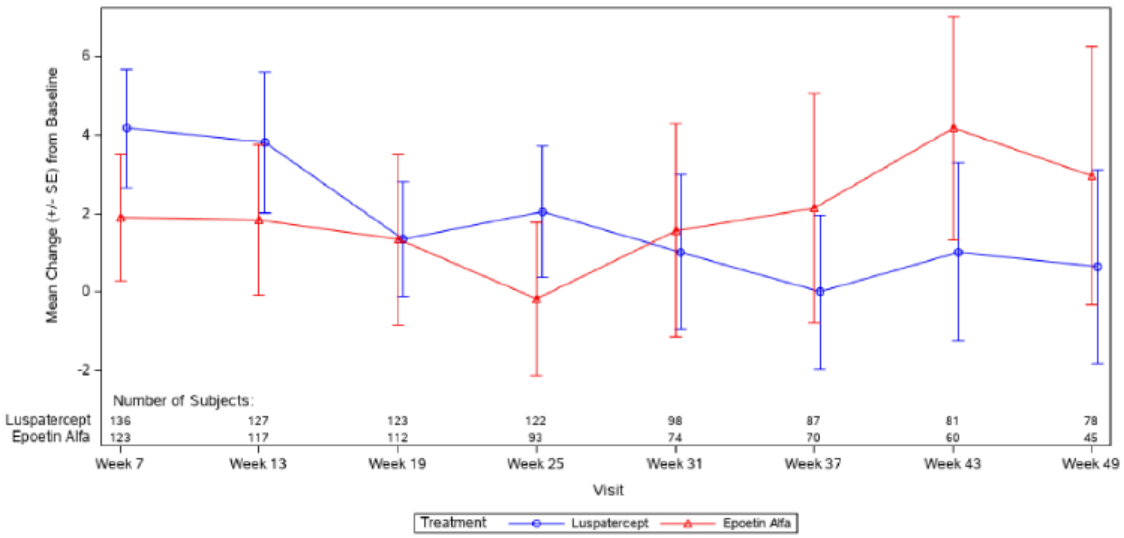
Figure 25: change from baseline in physical scores (HRQoL- evaluable population)



In both treatment arms, the mean scores for role functioning and emotional functioning did not reach the MID threshold for improvement of 6 at any timepoint.

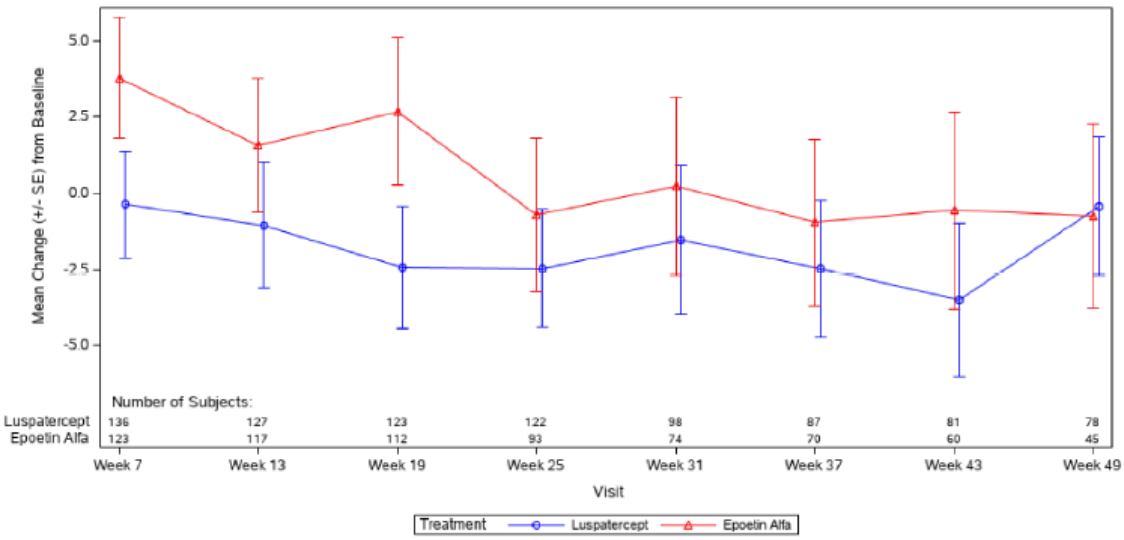
In both treatment arms, the mean scores for cognitive functioning generally increased from baseline (indicating improvement) up to Week 49. For the luspatercept arm, the mean changes from baseline exceeded the MID threshold of 3 at Weeks 7 and 13, then decreased to near baseline. For the epoetin arm, the mean changes from baseline were stable until Weeks 43 and 49 when they reached the MID for improvement of 3 (Figure 26).

Figure 26: Changes from baseline in cognitive functioning scores (HRQoL- evaluable population)



In the luspatercept arm, the mean scores for social functioning remained close to the baseline level during the treatment period up to Week 49 and did not reach the MID threshold for improvement of 3. In the epoetin alfa arm, the mean scores for social functioning increased from baseline (indicating improvement) during the treatment period through Week 19, with mean changes that exceeded the MID threshold of 3 at Week 7, then mean scores returned to near baseline (Figure 27).

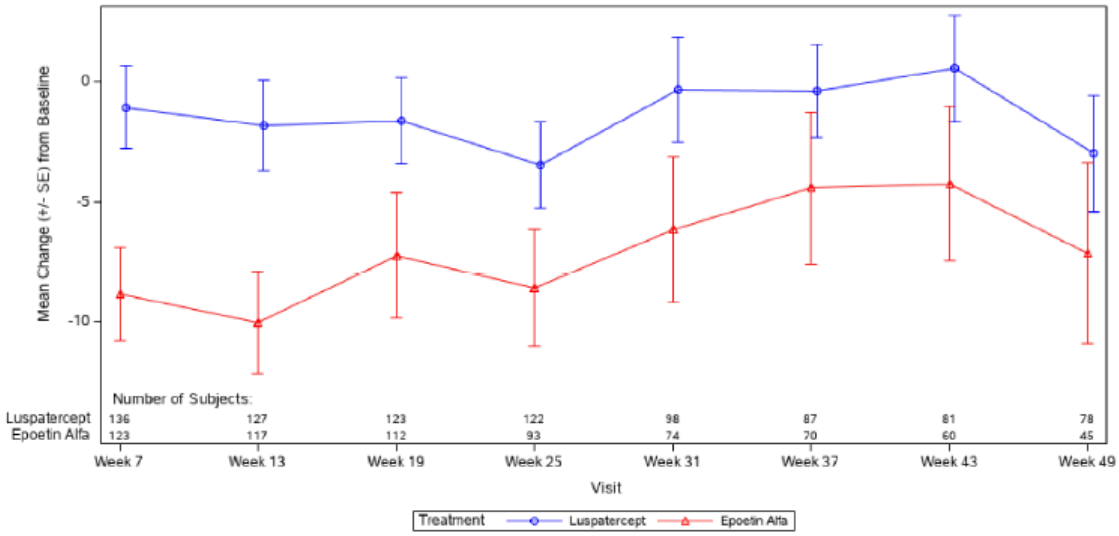
Figure 27: Changes from baseline in social functioning scores (HRQoL- evaluable population)



Symptom Scales

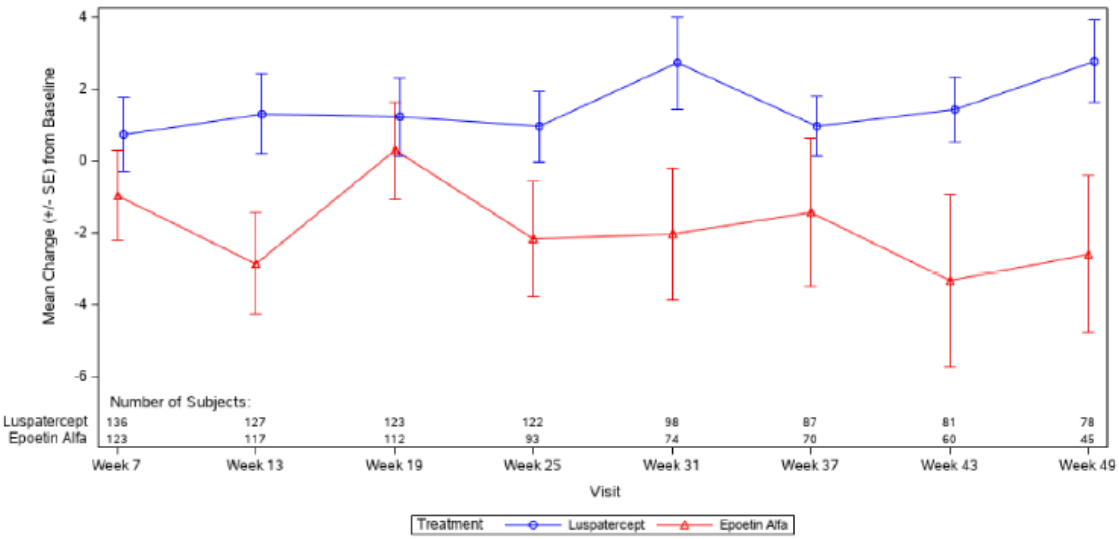
In both treatment arms, the mean scores for fatigue decreased from baseline (indicating improvement) during treatment up to Week 49. However, in the luspatercept arm, these improvements did not reach the MID threshold of -4. In contrast, the improvements in the epoetin alfa arm reached the MID threshold at every timepoint (Figure 28).

Figure 28: Changes from baseline in fatigue scores (HRQoL-evaluable population)



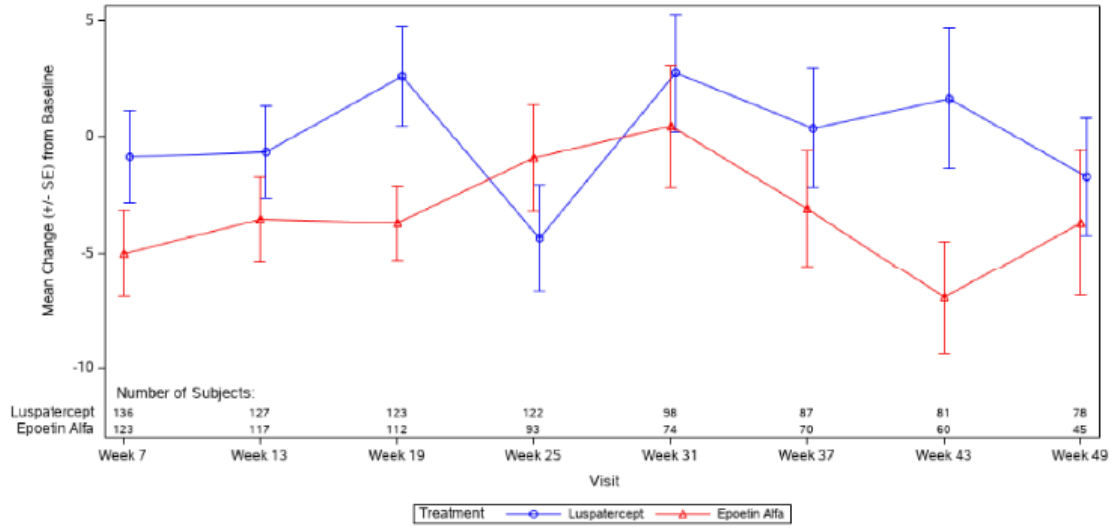
In the luspatercept arm, the mean scores for nausea and vomiting remained close to the baseline level during the treatment period up to Week 49 with small increases (indicating deterioration) in the luspatercept arm. These increases did not reach the MID threshold of 5 for deterioration. In the epoetin alfa arm, there were decreases (indicating improvement) from baseline; the Week 43 decrease met the MID threshold of -3 for improvement (Figure 29).

Figure 29: Changes from baseline in nausea and vomiting scores (HRQoL- evaluable population)



In the luspatercept arm, the mean scores for pain remained close to the baseline level during the treatment period up to Week 49 with both small increases (indicating deterioration) and decreases (indicating improvement). These increases did not reach the MID thresholds for either deterioration or improvement. The epoetin alfa arm mean scores generally decreased from baseline (indicating improvement) throughout the treatment period up to Week 49 (Figure 30). These mean changes met MID threshold of -5 for improvement at Weeks 7 and 43.

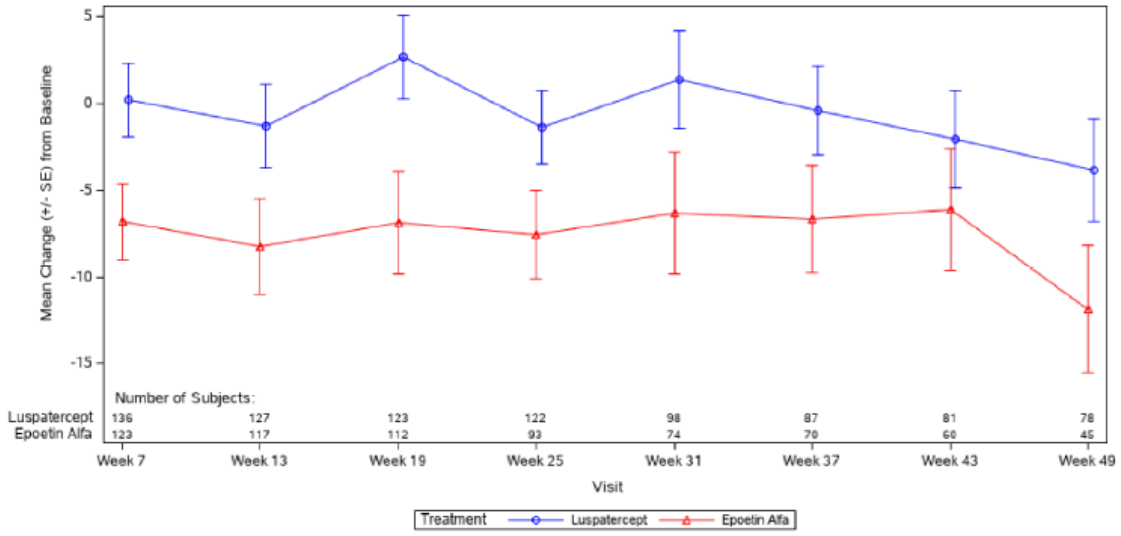
Figure 30: Changes from basline in pain scores (HRQoL-evaluable population)



Single Items

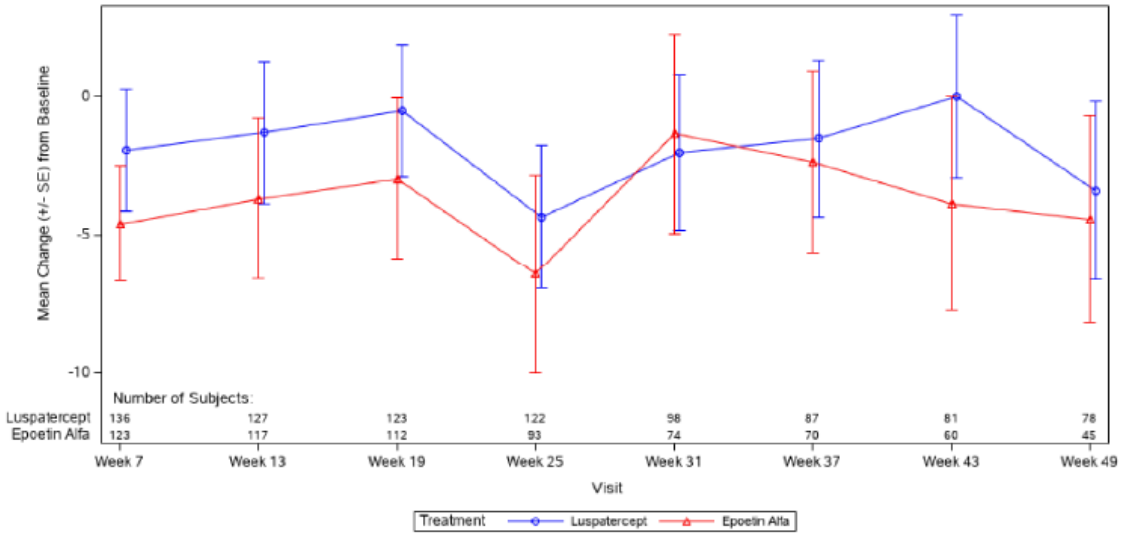
In the luspatercept arm, the mean scores for dyspnea were stable during treatment up to Week 31, then decreased (improved), with mean changes from baseline reaching the MID threshold of -2 for improvement at Weeks 43 and 49. The epoetin arm showed more improvement with the mean changes from baseline reaching the MID for improvement (-2) at all timepoints measured up to Week 49 (Figure 31).

Figure 31: Changes from baseline in dyspnea scores (HRQoL-evaluable population)



In both treatment arms, the mean scores for insomnia were similar, decreasing from baseline (indicating improvement) during the treatment period up to Week 49 (Figure 32). The mean changes reached the MID threshold of -5 for improvement in the epoetin alfa treatment arm only at Week 25.

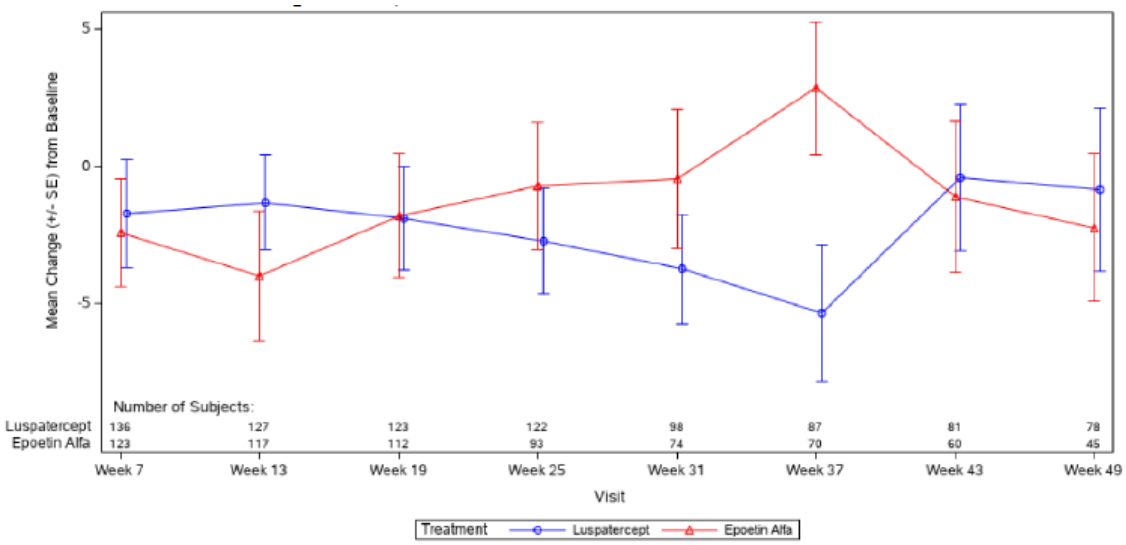
Figure 32: changes from baseline in insomnia scores (HRQoL-evaluable population)



In the luspatercept arm, the mean scores for appetite loss decreased from baseline (indicating improvement) during treatment up to Week 49; however, none of these decreases reached the MID threshold of -7. In the epoetin alfa arm, the mean scores initially decreased from baseline (indicating improvement) but then increased at later time points; none of these changes reached the MID thresholds for either improvement or deterioration.

In both treatment arms, the mean scores for constipation decreased from baseline (indicating improvement) during treatment up to Week 49 (with the exception of Week 37 in the epoetin alfa arm); Week 13 in the epoetin alfa arm and Week 37 in the luspatercept arm reached the MID threshold of -4 for improvement (Figure 33).

Figure 33: Changes from baseline in constipation scores (HRQoL-evaluable population)

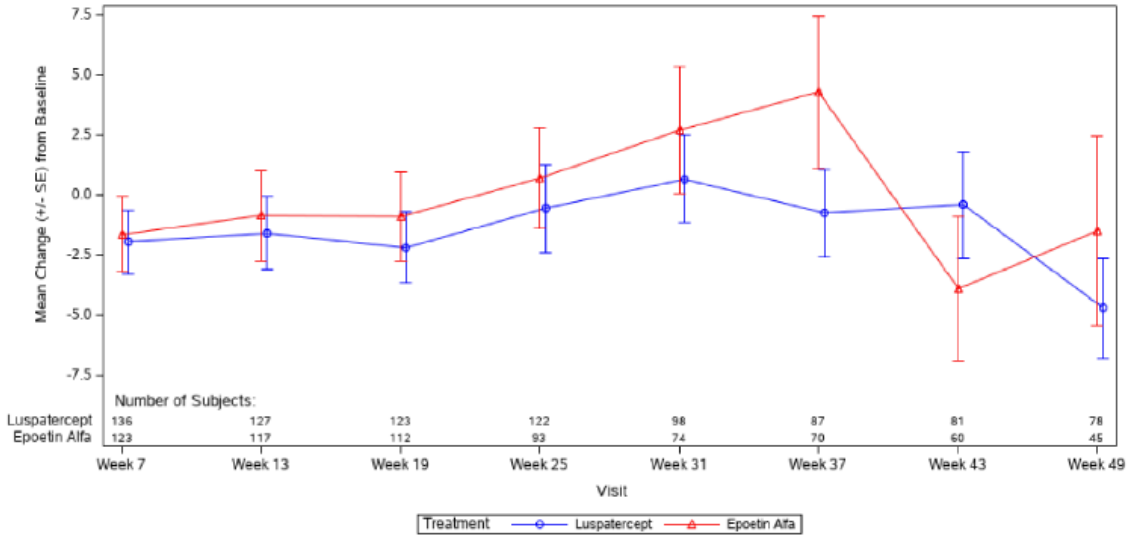


In both treatment arms, the mean scores for diarrhea remained close to the baseline level during the treatment period up to Week 49. Changes did not reach the MID threshold for improvement (-3) or deterioration (5).

In the luspatercept arm, the mean scores for financial difficulties decreased from baseline (indicating improvement) during treatment up to Week 49, exceeding the MID threshold of -3 at Week 49. In the

epoetin arm, the mean scores remained close to the baseline level during the treatment period up to Week 25, then increased at Weeks 31 and 37 (exceeding the MID threshold for deterioration of 2) and decreased below baseline at Weeks 43 and 49 (exceeding the MID for improvement (-3) at Week 43) (Figure 34).

Figure 34: Changes from baseline in financial difficulties scores (HRQoL-evaluable population)



The **FACT-An** (secondary objective) is a validated instrument specific for measuring HRQoL related anemia. The FACT-General Scale (FACT-G) includes 4 domains (physical well-being, social/family well-being, emotional well-being and functional well-being) and an Anemia subscale (which includes a fatigue subscale). The FACT-An total score is scored by summing up the 4 domains of the FACT-G and the Anemia Subscale.

For all FACT scales and symptom indices, the higher the score, the better the QoL. Meaningful change is defined only for the FACT-An total score (7 points) and the fatigue subscale score (3 points).

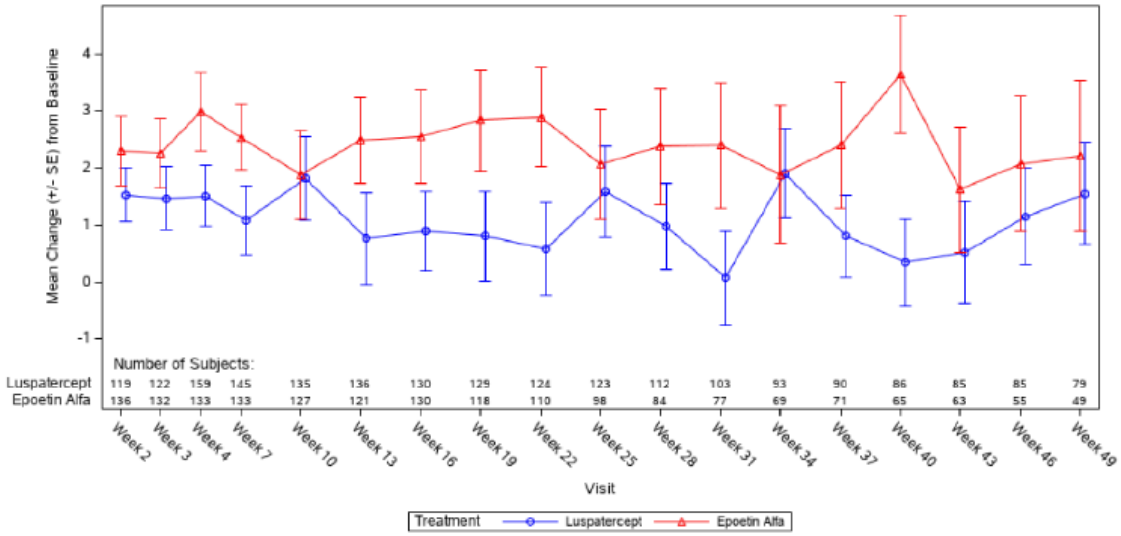
For this study, the scale scores for FACT-An total, fatigue subscale, and anemia subscale are the primary analyses of FACT-An; the FACT-G total and subscale scores are secondary analyses of FACT-An.

The completion rates at baseline and at Week 49 in the luspatercept and epoetin arms were 95.1% vs 95.6% and 85.1% vs 82.8%, respectively. The baseline characteristics (demographics and disease characteristics) for the HRQoL evaluable population for FACT-An were generally balanced across the 2 treatment arms and were consistent with those for the ITT population. Baseline FACT-An scores (FACT-An total, FACT-G total, FACT-G physical, social/family, emotional, and functional well-being, and the anemia and fatigue subscales) were higher in the luspatercept arm than the epoetin alfa arm, with subjects in the luspatercept arm demonstrating better quality of life across all domains.

In the luspatercept and epoetin alfa arms, there were mostly small increases from baseline in mean FACT-An total scores during the treatment period up to Week 49. In both treatment arms, these mean increases did not reach the MID threshold of 7 for improvement at any timepoint up to Week 49.

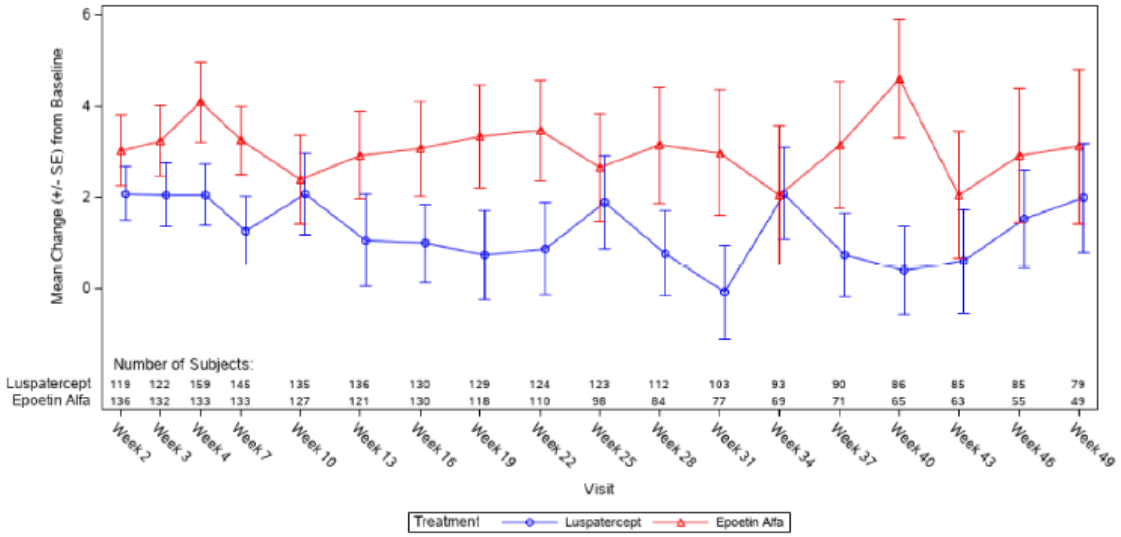
In both treatment arms, mean FACT-An fatigue subscale scores increased from baseline during the treatment period up to Week 49. In the luspatercept arm, increases did not reach the MID threshold of 3 at any timepoint up to Week 49. In the epoetin alfa arm, increases reached the MID threshold at Weeks 4 and 40 (Figure 35).

Figure 35: Mean changes from baseline in FACT-an Fatigue subscale score (HRQoL-evaluable population)



In both treatment arms, mean FACT-An anemia subscale scores increased from baseline during the treatment period up to Week 49 (Figure 36). No MID threshold is defined for this scale.

Figure 36: Mean changes from baseline in FACT-An anemia subscale score (HRQoL-evaluable population)



In both treatment arms, the mean FACT-An G total scores increased, but remained close to the baseline level during the treatment period up to Week 49. FACT-An G subscale scores physical well-being, social/family well-being, emotional well-being and functional well-being were stable with small increases or decreases from baseline up to Week 49 in both treatment arms.

The **QUALMS-P** (exploratory objective) is subscale of QUALMS, an MDS-specific HRQoL tool; the QUALMS-P subscale measures physical burden. Higher QUALMS-P scores mean better HRQoL. QUALMS-P was measured at 2 timepoints (baseline and at Day 169).

The overall completion rate was 38.6% and similar in both arms at baseline and 27.0% in the luspatercept group and 16.9% in the epoetin alfa group at Day 169. There was a limited number of translations available for the QUALMS-P questionnaire; therefore, it was used at sites in a limited number of countries.

Because the HRQoL evaluable population for the QUALMS-P was a much smaller subset of the ITT population than the other PROs, there were some notable differences from the ITT population. Overall, the QUALMS-P population had a larger proportion of subjects aged ≥ 75 than the ITT population (67.4% vs 48.8%). Additionally, while the overall proportion of subjects with low baseline transfusion burden (< 4 units) was similar between the QUALMS-P and ITT populations (62.8% vs 63.1%), within the QUALMS-P HRQoL evaluable population, a higher proportion of subjects in the luspatercept arm had a low transfusion burden compared with the epoetin alfa arm (72.4% vs 42.9%).

At baseline, mean QUALMS-P scores were higher in the luspatercept arm than the epoetin alfa arm, with subjects in the luspatercept arm demonstrating better quality of life across all domains. At Day 169, mean scores increased slightly from baseline in the luspatercept arm (2.7) and decreased from baseline in the epoetin alfa arm (-3.2). There are no MIDs for QUALMS-P scores.

Healthcare Resource Utilisation

Overall, healthcare resource utilization was generally consistent across the treatment arms with respect to doctor's office visits and emergency room visits, including the number of days in the ICU or CCU. In contrast, a higher proportion of subjects in the luspatercept arm compared with the epoetin arm were hospitalized (includes Day Hospital, Standard Unit, ICU, or CCU) and hospitalizations for AEs were higher in the luspatercept arm than the epoetin alfa arm (34.6% vs 23.8%). However, the number of days of hospitalization was similar across the treatment arms.

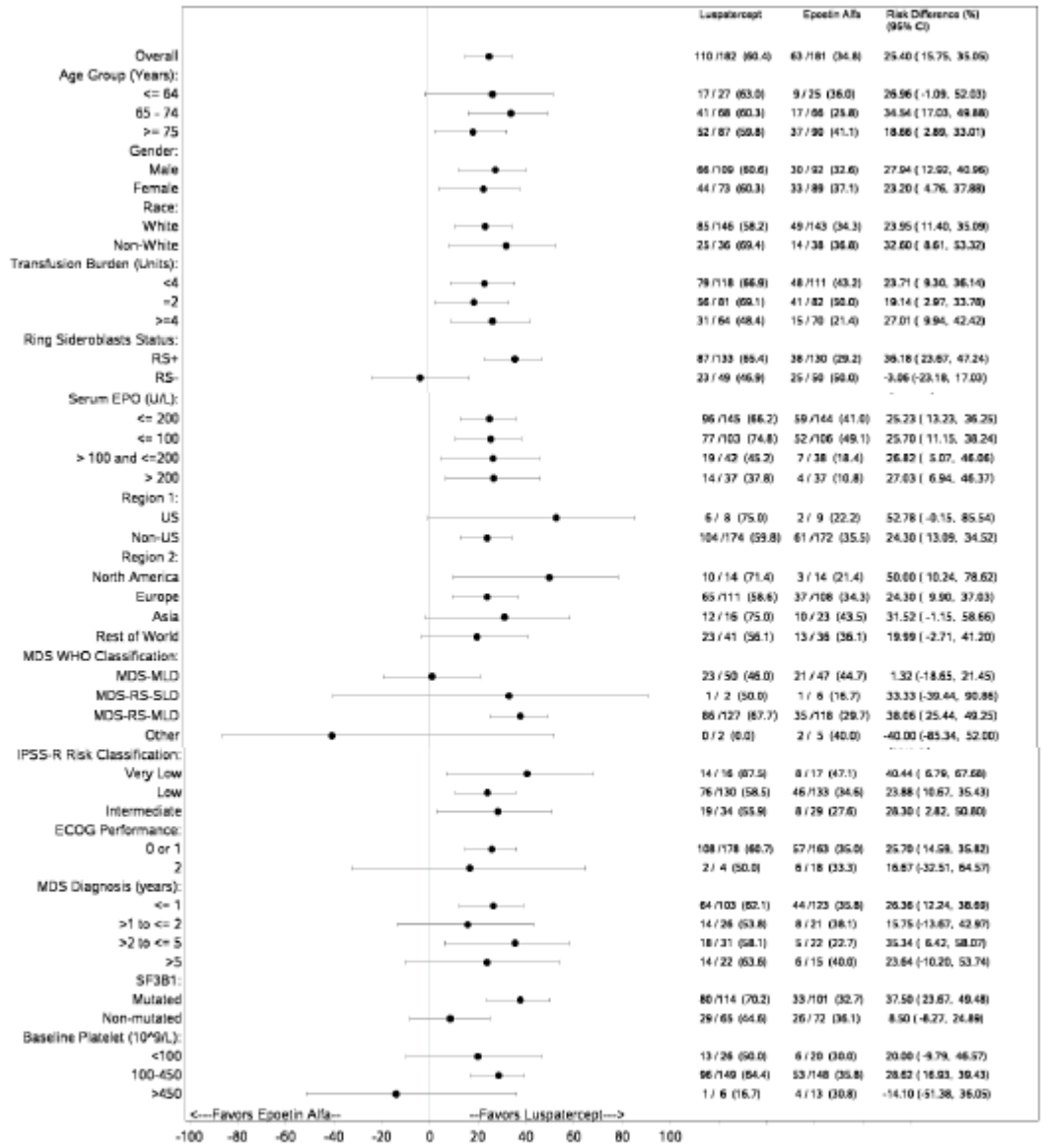
The median duration of treatment was longer in the luspatercept arm compared with the epoetin alfa arm: 51.3 vs 37.0 weeks, providing a longer reporting period for hospitalizations.

After adjusting for exposure, both hospitalizations and emergency room visits for any reason were balanced between the treatment arms. Hospitalizations due to an AE were reported at 34.3 in 100 PY for the luspatercept arm versus 27.2 in 100 PY for the epoetin alfa arm. Emergency room visits due to an AE were reported at 19.8 in 100 person-years (PY) for the luspatercept arm versus 16.7 in 100 PY for the epoetin alfa arm.

Subgroup analyses

The efficacy with respect to the **primary endpoint** favored luspatercept or was similar to epoetin alfa in all pre-defined subgroups, where there were sufficient numbers to make meaningful conclusions (Figure 37). Similar results were observed in subgroups with respect to **hierarchically tested secondary endpoints** RBC-TI for ≥ 12 weeks, RBC-TI for ≥ 24 weeks and HI-E for ≥ 56 days (not shown in this report).

Figure 37: Subgroup analysis RBC-TI≥ 12 weeks with concurrent mean hemoglobin increase ≥1.5g/dL (week 1 to 24) ITT population



Only subjects who completed 169 days (24 weeks) of treatment or discontinued early were included in efficacy analysis.

Stratified CMH test is used for the overall analysis. Unstratified CMH test is used for subgroup analysis.

Note that subgroups with less than 5 subjects in both arms are not included in the forest plots.

The **median duration of RBC-TI** (duration of the longest single RBC TI period) for subjects who achieved RBC TI for 12 weeks (Week 1 to EOT) was consistently longer in the luspatercept arm vs the epoetin alfa arm (with a point estimate of the HR < 1.0) in the following subgroups:

- Baseline transfusion burden:
  - < 4 pRBC units (median: not estimable vs 95.1 weeks: HR = 0.700)
  - ≥ 4 pRBC units (median: 112.7 vs 62.9 weeks; HR = 0.600)
- Ring sideroblast status at baseline:
  - RS+ (median: 120.9 vs 62.9 weeks: HR = 0.663)
  - RS- (median: not estimable vs not estimable weeks; HR = 0.508)

- sEPO level (U/L) at baseline:
  - ≤ 200 (median: 140.1 vs 89.7 weeks; HR = 0.635)
  - > 200 to < 500 (median: 52.9 vs 23.9 weeks; HR = 0.657)
- Baseline SF3B1:
  - mutated (median: 120.9 vs 77.0 weeks; HR = 0.687)
  - non-mutated (median: not estimable vs 123.9 weeks; HR = 0.690)

The results for ≥ **50% reduction in pRBC units** of at least 12 weeks or at least 24 weeks during Week 1 to EOT for luspatercept were better than or similar to epoetin alfa in subgroups by baseline transfusion burden (< 4, ≥ 4 pRBC units) and RS status (+, -).

Table 50: Subgroup analysis of≥ 50% reduction in RBC units at least 12 weeks during entire treatment phase ITT population

	Luspatercept			Epoetin Alfa			Difference in Response between Luspatercept and Epoetin Alfa		
Parameter	Total N	Responder n (%) [a]	95% CI on Response Rate	Total N	Responder n (%) [a]	95% CI on Response Rate	Diff. on Response Rate [a]	95% CI on Rate Diff.	Odds Ratio (95% CI) [b]
Baseline Transfusion Burden (units)									
< 4	118	105 (89.0)	81.9, 94.0	111	82 (73.9)	64.7, 81.8	15.1	3.7, 25.4	2.86 (1.40, 5.84)
= 2	81	74 (91.4)	83.0, 96.5	82	65 (79.3)	68.9, 87.4	12.1	1.1, 23.6	2.76 (1.08, 7.09)
>= 4	64	46 (71.9)	59.2, 82.4	70	39 (55.7)	43.3, 67.6	16.2	-0.4, 32.5	2.03 (0.99, 4.18)
Ring sideroblasts status									
RS+	133	115 (86.5)	79.5, 91.8	130	84 (64.6)	55.8, 72.8	21.9	10.9, 32.1	3.50 (1.89, 6.46)
RS-	49	36 (73.5)	58.9, 85.1	50	37 (74.0)	59.7, 85.4	-0.5	-18.2, 17.5	0.97 (0.40, 2.38)
RS status and baseline transfusion burden									
RS+ and < 4	85	77 (90.6)	82.3, 95.8	80	57 (71.3)	60.0, 80.8	19.3	6.1, 31.9	3.88 (1.62, 9.31)
RS+ and >=4	48	38 (79.2)	65.0, 89.5	50	27 (54.0)	39.3, 68.2	25.2	5.4, 42.8	3.24 (1.33, 7.89)
RS- and < 4	33	28 (84.8)	68.1, 94.9	31	25 (80.6)	62.5, 92.5	4.2	-15.5, 24.4	1.34 (0.36, 4.95)
RS- and >=4	16	8 (50.0)	24.7, 75.3	19	12 (63.2)	38.4, 83.7	-13.2	-45.6, 20.9	0.58 (0.15, 2.26)

[a] Defined as >= 50% RBC unit reduction sustained over any consecutive 84-day period compared to the 12-week baseline during entire treatment period.
[b] Based on unstratified CMH test.
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Data source: ADSL ADEFA ADBASE
Run date: 13JUN2023

Table 51: subgroup analysis of ≥50% reduction in RBC units over at least 24 weeks during entire treatment phase ITT population

	Luspatercept			Epoetin Alfa			Difference in Response between Luspatercept and Epoetin Alfa		
Parameter	Total N	Responder n (%) [a]	95% CI on Response Rate	Total N	Responder n (%) [a]	95% CI on Response Rate	Diff. on Response Rate [a]	95% CI on Rate Diff.	Odds Ratio (95% CI) [b]
Baseline Transfusion Burden (units)									
< 4	118	95 (80.5)	72.2, 87.2	111	67 (60.4)	50.6, 69.5	20.1	6.6, 32.0	2.71 (1.50, 4.91)
= 2	81	65 (80.2)	69.9, 88.3	82	52 (63.4)	52.0, 73.8	16.8	2.5, 30.7	2.34 (1.15, 4.76)
>= 4	64	37 (57.8)	44.8, 70.1	70	25 (35.7)	24.6, 48.1	22.1	4.1, 38.2	2.47 (1.23, 4.95)
Ring sideroblasts status									
RS+	133	105 (78.9)	71.0, 85.5	130	61 (46.9)	38.1, 55.9	32.0	20.2, 43.0	4.24 (2.47, 7.28)
RS-	49	27 (55.1)	40.2, 69.3	50	31 (62.0)	47.2, 75.3	-6.9	-26.2, 12.9	0.75 (0.34, 1.68)
RS status and baseline transfusion burden									
RS+ and < 4	85	73 (85.9)	76.6, 92.5	80	47 (58.8)	47.2, 69.6	27.1	12.9, 40.3	4.27 (2.01, 9.09)
RS+ and >=4	48	32 (66.7)	51.6, 79.6	50	14 (28.0)	16.2, 42.5	38.7	17.0, 56.1	5.14 (2.17, 12.16)
RS- and < 4	33	22 (66.7)	48.2, 82.0	31	20 (64.5)	45.4, 80.8	2.2	-21.5, 25.7	1.10 (0.39, 3.09)
RS- and >=4	16	5 (31.3)	11.0, 58.7	19	11 (57.9)	33.5, 79.7	-26.6	-56.6, 7.5	0.33 (0.08, 1.33)

[a] Defined as >= 50% RBC unit reduction sustained over any consecutive 168-day period compared to the prorated 24-week baseline based on 16-week baseline during entire treatment period.
[b] Based on unstratified CMH test.
Program path: /u02/projects/ace_536/ace_536_mds_002/deliverables/d018_primary_dbl_may2023/programs/tables/final/t_14_2_23_1.sas
Data Extraction Date: 17MAY2023
Data source: ADSL ADEFA ADBASE
Run date: 13JUN2023

The results for median **duration of ≥ 50% reduction in pRBC units** of at least 12 weeks or at least 24 weeks during Week 1 to EOT favored luspatercept over epoetin alfa (point estimate of the HR < 1.0) in the following subgroups:

- Baseline transfusion burden:
  - over at least 12 weeks
    - < 4 pRBC units (median: 129.9 vs 95.7 weeks; HR = 0.755)
    - ≥ 4 pRBC units (median: 164.0 vs 36.4 weeks; HR = 0.366)
  - over at least 24 weeks
    - < 4 pRBC units (median: not estimable vs 117.4 weeks; HR = 0.677)
    - ≥ 4 pRBC units (median: 160.0 vs 119.0; HR = 0.373)
- Ring sideroblast status at baseline:
  - over at least 12 weeks
    - RS+ (median: 129.9 vs 54.9 weeks; HR = 0.479)
    - RS- (median: not estimable vs 116.3 weeks; HR = 1.009)
  - over at least 24 weeks
    - RS+ (median: 160.0 vs 93.1; HR = 0.553)
    - RS- (median: not estimable vs 160.7 weeks; HR = 0.268)

Note that the median duration of ≥ 50% reduction in pRBC units of at least 12 weeks in the RS- subgroup had a HR of 1.009.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 52: Summary of Efficacy for study ACE-536-MDS-002

Title: A Phase 3, Open-Label, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) Versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low, Low or Intermediate Risk Myelodysplastic Syndromes (MDS) in ESA Naïve Subjects Who Require Red Blood Cell Transfusions			
Study identifier	Protocol number: ACE-536-MDS-002 EudraCT number: 2017-003190-34		
Design	Multi-center, active-controlled, open-label, randomized study		
	First subject first visit: Clinical data cutoff for the Primary CSR: Duration of Run-in phase: Duration of Extension phase:		02-Jan-2019 31-Mar-2023 not applicable not applicable
Hypothesis	Superiority of luspatercept vs epoetin alfa for 1L transfusion-dependent (TD) MDS		
Treatments groups	Luspatercept		Starting dose of 1.0 mg/kg subcutaneous (SC) injection every 3 weeks (N = 182)
	Epoetin alfa		Starting dose of 450 IU/kg (maximum total starting dose: 40,000 IU) SC weekly (N = 181)
Endpoints and definitions	*Primary/ Secondary/ Exploratory*	*Endpoint*	*Endpoint Description*
	Primary endpoint	Red blood cell-transfusion independence (RBC-TI) for 12 weeks with an associated concurrent mean hemoglobin (Hgb) increase ≥1.5 g/dL	Proportion of subjects who were RBC transfusion-free for any 12-week period associated with a concurrent mean Hgb increase ≥ 1.5 g/dL compared to baseline. During Week 1 to 24
	Key Secondary Endpoint 1 of the statistical testing hierarchy	Hematologic improvement -erythroid (HI-E) response (Week 1-24)	Proportion of subjects who achieved HI-E over any consecutive 56-day period. During Week 1 to 24.
	Key Secondary Endpoint 2 of the statistical testing hierarchy	RBC-TI for 24 weeks (Week 1-24)	Proportion of subjects who were RBC transfusion-free from Week 1 to 24.
	Key Secondary Endpoint 3 of the statistical testing hierarchy	RBC-TI ≥ 12 weeks (Week 1-24)	Proportion of subjects who were RBC transfusion-free over a consecutive 84-day period. During Week 1 to 24.

	Secondary endpoint (Efficacy)	Duration of RBC-TI ≥ 12 weeks (84 days)	Maximum duration of RBC-TI for subjects who achieved RBC-TI ≥ 84 days. During Week 1 to end of treatment (EOT).
	Secondary endpoint (Efficacy)	Time to RBC-TI ≥12 weeks (84 days)	Time from first dose to first onset of RBC-TI ≥ 84 days. During Week 1 to 24.
	Secondary endpoint (Efficacy)	RBC-TI for ≥8 weeks	Proportion of subjects who are RBC transfusion-free over a consecutive 56-day period. During Week 1 to 24.
	Secondary endpoint (Efficacy)	RBC transfusion burden on treatment	Total number of RBC units transfused on treatment. During Week 1 to 24.
	Secondary endpoint (Efficacy)	Time to first RBC transfusion	Time from first dose to first transfusion on treatment. During Week 1 to EOT.
	Secondary endpoint (Efficacy)	Mean Hgb change over 24 weeks	Mean Hgb change over the 24-week period of Week 1 to 24 compared to baseline.
	Secondary endpoint (Efficacy)	Time to HI-E	Time from first dose to first onset of achieving HI-E. During Week 1 to 24.
	Secondary endpoint (Efficacy)	RBC-TI for a consecutive 24-week period	Proportion of subjects who are RBC transfusion-free for a consecutive 24-week period in the first 48 weeks from first dose. During Week 1 to 48.
	Secondary endpoint (Efficacy)	Progression to acute myeloid leukemia (AML)	Number and percentage of subjects progressing to AML; time to AML progression. Randomization through 5 years from first dose or 3 years from last dose (whichever occurred later)
	Secondary endpoint (Efficacy)	Overall survival (OS)	Time from date of randomization to death due to any cause. Randomization through 5 years from first dose or 3 years from last dose (whichever occurred later)
Database lock	For primary analysis for superiority: 23-May-2023 (31-Mar-2023 data cutoff)		

Results and Analysis				
Analysis description	**Primary and Hierarchically Tested Secondary Endpoint Analysis**			
Analysis population and time point description	The analysis population for all efficacy endpoints was all randomized subjects who had a first dose date at least 169 days (24 weeks) from the clinical data cutoff date or discontinued early.			
Descriptive statistics and estimate variability	Treatment group		Luspatercept	Epoetin Alfa
	Number of subjects		182	181
	Primary endpoint: RBC-TI for 12 weeks (84 days) with an associated concurrent mean Hgb increase ≥ 1.5 g/dL (Week 1 to 24)			
	Response Rate		60.4	34.8
	95% CI		52.9, 67.6	27.9, 42.2
	Key Secondary Endpoint 1: HI-E per IWG for ≥ 56 days (Week 1 to 24)			
	Response Rate		74.2	53.0
	95% CI		67.2, 80.4	45.5, 60.5
	Key Secondary Endpoint 2: RBC-TI for 24 weeks (Week 1 to 24)			
	Response Rate		47.8	30.9
	95% CI		40.4, 55.3	24.3, 38.2
	Key Secondary Endpoint 3: RBC-TI for ≥ 12 weeks (84 days) (Week 1 to 24)			
	Response Rate		68.1	48.6
	95% CI		60.8, 74.8	41.1, 56.1
Effect estimate per comparison	*Primary endpoint*: RBC-TI for 12 weeks with an associated concurrent mean Hgb increase ≥1.5 g/dL (Week 1 to 24)	Comparison groups	Luspatercept vs Epoetin Alfa	
		Common Risk Difference on Response Rate (%)[a]	25.4	
		95% CI	15.8, 35.0	
		P-value	p < 0.0001	
		Odds ratio[a]	3.1	
		95% CI	2.0, 4.8	
	Key Secondary endpoint 1: HI-E per IWG for ≥ 56 days (Week 1 to 24)	Comparison groups	Luspatercept vs Epoetin Alfa	
		Common Risk Difference on Response Rate (%)[a]	21.5	
		95% CI	12.2, 30.7	
		P-value	p < 0.0001	
		Odds ratio[a]	2.8	
		95% CI	1.8, 4.5	
	Key Secondary Endpoint 2: RBC-TI for 24 weeks (Week 1 to 24)	Comparison groups	Luspatercept vs Epoetin Alfa	
		Common Risk Difference on Response Rate (%)[a]	16.3	
		95% CI	7.1, 25.4	
		P-value	p = 0.0003	
		Odds ratio[a]	2.3	
		95% CI	1.4, 3.7	
	Key Secondary Endpoint 3: RBC-TI for ≥12 weeks (84 days) (Week 1 to 24)	Comparison groups	Luspatercept vs Epoetin Alfa	
		Common Risk Difference on Response Rate (%)[a]	18.8	
		95% CI	9.5, 28.0	
		P-value	p < 0.0001	
		Odds ratio[a]	2.5	
		95% CI	1.6, 4.0	
Notes	[a] Based on CMH test stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L). 1-sided p-value is presented.			

Analysis description	**Other Secondary Efficacy Endpoint Analysis**		
Analysis population and time point description	The analysis population for all efficacy endpoints was all randomized subjects who had a first dose date at least 169 days (24 weeks) from the clinical data cutoff date or discontinued early.		
Descriptive statistics and estimate variability	Treatment group	Luspatercept	Epoetin Alfa
	Number of subjects	182	181
	Duration of RBC-TI ≥12 weeks (Week 1 to EOT) Responders (n) Median (weeks) 95% CI Hazard ratio (HR)[a,b] 95% CI Nominal P value	 81 128.1 108.3, NE 0.534 0.330, 0.864 p = 0.0096	 50 89.7 55.9, 157.3
	Time to RBC-TI ≥ 12 weeks[c] (Week 1 to 24) Median (days) Min, max	 1.0 1.0, 75.0	 1.0 1.0, 85.0
	RBC-TI for ≥ 8 weeks (56 days) (Week 1 to 24) Response Rate 95% CI Common Risk Difference on Response Rate (%)[d] 95% CI Nominal P-value Odds ratio[d] 95% CI	 79.1 72.5, 84.8 13.7 5.3, 22.2 p = 0.0007 2.3 1.4, 3.8	 64.6 57.2, 71.6
	RBC Transfusion Burden on Treatment (Week 1 to 24) Mean Number of RBC Units Standard deviation (SD) Median Number of RBC Units Min, Max	 3.8 5.90 1.0 0.0, 24.0	 5.2 6.36 3.0 0.0, 37.0
	Time (days) to First RBC Transfusion (Week 1 to EOT) Subjects with RBC Transfusion (n) Median[e] 95% CI HR[a] 95% CI Nominal P value	 116 155.0 80.0, 266.0 0.570 0.437, 0.742 p < 0.0001[b]	 137 42.0 23.0, 55.0
	Mean Hgb Change (g/dL) over 24 weeks (Week 1 to 24) Subjects with central lab results (n) Mean SD	 181 2.0 1.14	 176 1.5 1.12

Other Secondary Efficacy Endpoint Analysis *Continued*			
	Time to HI-E (Week 1 to 24)		
	Subjects with HI-E (Week 1-24) (n)	135	96
	Median (days)	1.0	6.0
	Min, Max	1.0, 113.0	1.0, 108.0
	RBC-TI for a consecutive 24-week period		
	Response Rate	60.7	39.5
	95% CI	52.8, 68.3	32.1, 47.4
	Common Risk Difference on Response Rate (%)	20.7	
	95% CI	10.8, 30.6	
	Nominal P-value	p < 0.0001	
	Odds ratio	2.6	
	95% CI	1.6, 4.3	
	Progression to AML[f]		
	Subjects with AML Progression, n (%)	5 (2.7)	6 (3.3)
	Median Time (months) from Randomization[e]	NE	NE
	Incidence Rate per 100 PY	1.70	2.15
	95% CI	(0.71, 4.08)	(0.97, 4.79)
	HR[b,c]	0.913	
	95% CI	0.270, 3.082	
	Overall Survival[f]		
	Number (%) of Subjects Alive (censored)	143 (78.6)	143 (79.0)
	Number (%) of Subjects who Died	39 (21.4)	38 (21.0)
	Median (months) (95% CI)[e]	NE (35.3, NE)	42.8 (42.8, NE)
	HR[b,c]	1.089	
	95% CI	0.686, 1.728	
Notes	[a] Based on CMH test stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L). 1-sided p-value is presented.		
	[b] HR calculated by Cox proportional hazard model stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L).		
	[c] p-value (1-sided) from log-rank test with by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 to < 500 U/L) as covariates.		
	[d] Time to RBC-TI ≥ 12 weeks was summarized only for subjects who achieved RBC-TI ≥ 84 days from Week 1 through Week 24. It was defined as the time between Week 1 and the date of the onset of first TI.		
	[e] Median is from unstratified Kaplan-Meier method.		
	[f] Randomization through 5 years from first dose or 3 years from last dose, whichever occurred later. The analysis population was ITT up to the clinical data cutoff date (with any treatment duration).		
	Clinical data cutoff: 31-Mar-2023. Median follow-up (median of the time from randomization date to death date or last known alive date) was 17.2 months for the luspatercept arm and 16.9 months for the epoetin alfa arm.		
	NE = not estimable		

Supportive studies

Supporting efficacy data are provided from select MDS subjects in Phase 2 Study A536-03, including available follow-up data from its extension study A536-05 and patients who subsequently rolled over into the Phase 3b long term safety Study ACE-536-LTFU-001. Studies A536-03/05 have been also part of the initial submission in MDS patients. At the time of initial submission both studies were ongoing, but are now completed. Study ACE-536-LTFU-001 is still ongoing. Only data relevant to the current submission are presented here.

A subset of the TD MDS cohort from the A536-03 study and/or its extension study A536-05 and/or ACE-536-LTFU-001 study to match the following baseline characteristics from the ACE-536-MDS-002 study population ("COMMANDS-like" population) was defined:

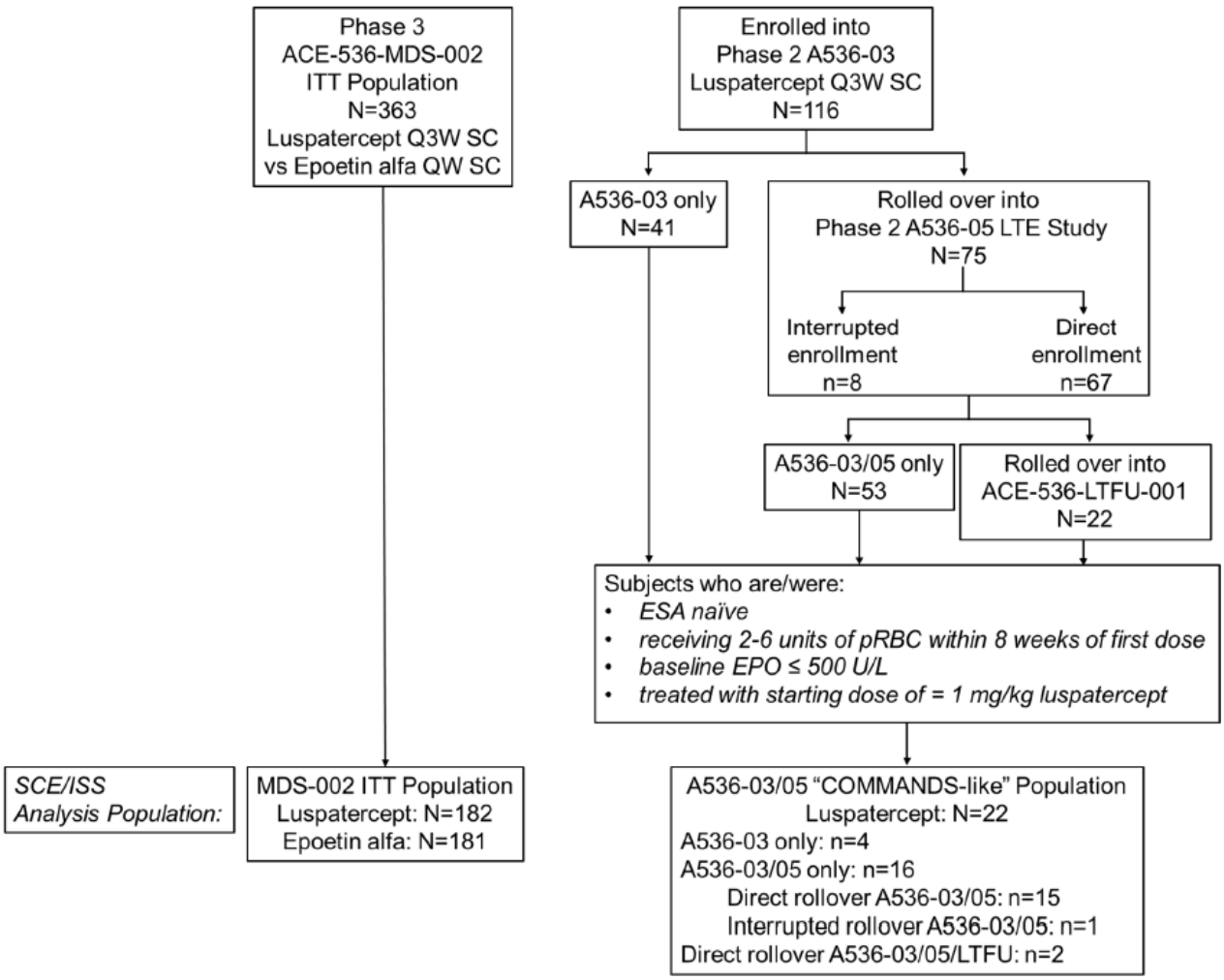
- ESA naïve
- Baseline transfusion burden: 2 to 6 units of pRBC units/8 weeks confirmed for a minimum of 8 weeks immediately preceding first dose
- Baseline endogenous sEPO level ≤ 500 U/L
- Starting dose of = 1 mg/kg of luspatercept in Study A536-03

Subjects from Study ACE-536-MDS-002 were not pooled with subjects from the supporting studies due to differences in study design and eligibility criteria. Subjects who participated in both A536-03/05 studies and ACE-536-LTFU-001 study, if applicable, were treated as one subject and counted only once in analyses.

From the Phase 2 studies, 3 types of subjects were included in the SCE analysis (Figure 1.2.2-1):

1) Direct rollover subjects: Data from A536-03, A536-05, and ACE-536-LTFU-001, if applicable, were combined and included in the analysis.
2) Interrupted rollover subjects:
    a. For demographic and baseline disease characteristics data from A536-03 was used.
    b. For subject population and disposition, data from A536-05 and ACE-536-LTFU-001, if applicable, was used.
    c. For efficacy related analysis, corresponding baselines (ie, baseline transfusion burden, baseline hemoglobin, etc.) were re-derived using A536-05 data.
    d. For overall presentation, efficacy results from A536-05 and ACE-536-LTFU-001, if applicable, are presented side by side with ACE-536-MDS-002 data.
3) No rollover subjects: Data from A536-03 will be used.

Figure 38: Subject disposition for studies supporting the proposed indication



Study A536-03

A536-03 was a Phase 2, open-label, multiple ascending dose study of luspatercept for the treatment of anemia in subjects with low or intermediate-1 risk MDS assessed via IPSS. The treatment duration was limited to 5 cycles (approximately 15 weeks) after which eligible subjects could enter the Phase 2 extension Study A536-05.

The dose levels of luspatercept were defined using a dose escalation scheme (0.125, 0.25, 0.50, 0.75, 1.0, 1.33, 1.75 mg/kg). Dose reductions were permitted for starting dose levels ≥ 0.5 mg/kg, and dose delays were permitted at any dose level based on Hb level and safety profile.

The primary objective was to evaluate the proportion of subjects who had erythroid response, defined as a Hb increase of ≥ 1.5 g/dL from baseline for ≥ 14 days (in the absence of RBC transfusions) in LTB subjects (defined as baseline RBC transfusion burden < 4 units/8 weeks), or a reduction of either ≥ 4 units or ≥ 50% of units of RBCs transfused compared to pretreatment in HTB subjects (defined as baseline RBC transfusion burden of ≥ 4 units/8 weeks).

Study A536-05

A536-05 was an open-label extension study to evaluate the long-term effects of luspatercept for the treatment of anemia in subjects with low or intermediate-1 risk MDS according to the IPSS who were previously enrolled in Study A536-03. Subjects received luspatercept treatment for up to 60 months, and were followed-up for a 3 year period.

Consenting subjects who met the A536-05 eligibility criteria at the EOT visit of Study A536-03 were permitted to roll over directly from Study A536-03 to Study A536-05 without treatment interruption. Subjects without treatment interruption continued treatment at the dose level administered for their last dose in Study A536-03. Transfusion status (baseline RBC transfusion burden < 4 units or ≥ 4 units/8 weeks) was carried over from Study A536-03.

Subjects who completed the EOS visit for Study A536-03 prior to C1D1 of Study A536-05 entered Study A536-05 after a treatment interruption. These subjects had a 28-day screening period to allow them to be reassessed for eligibility in Study A536-05 by meeting additional inclusion criteria. Subjects restarted treatment at a starting dose level of 1.0 mg/kg and had their baseline parameters reassessed. For all subjects in the extension study (regardless of treatment interruption), the dose level was titrated in subsequent cycles based on the change in Hb or transfusion burden.

The primary objective was to evaluate the long-term safety and tolerability of luspatercept in subjects previously enrolled in Study A536-03. Efficacy was a secondary objective and included evaluation of the proportion of subjects with an erythroid response, defined as a mean Hb increase ≥ 1.5 g/dL over an 8-week period as compared to baseline, not influenced by RBC transfusion, in LTB subjects and a decrease of ≥ 4 units or ≥ 50% of units of RBCs transfused over a period of 8 weeks, relative to the 8 weeks immediately prior to Day 1, in HTB subjects.

Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy results from "COMMANDS-like" subjects from Studies A536-03/05 were generally supportive of results from luspatercept-treated subjects from ACE-536-MDS-002, with the exception of the duration of RBC-TI for ≥ 12 weeks, despite a similar response rate (Table 53).

Table 53: Overall efficacy summary: study ACE-536-MDS-002 and studies A536-03/05

	ACE-536-MDS-002 [c]		A536-03/05 [g]
	Luspatercept (N=182)	Epoetin Alfa (N=181)	Luspatercept "COMMANDS-like" (N=22)
RBC-TI for 12 weeks (84 days) with concurrent mean Hgb increase ≥ 1.5 g/dL (Week 1 to 24)	*Primary Endpoint*		
Response Rate (95% CI) [a]	60.4 (52.9, 67.6))	34.8 (27.9, 42.2)	63.6 (40.7, 82.8)
Common Risk Difference on Response Rate (%) (95% CI) [b]	25.4 (15.8, 35.0); p < 0.0001		
Odds Ratio (95% CI) [b]	3.1 (2.0, 4.8)		
Median (95% CI) duration (wks) of RBC TI ≥ 12 weeks with concurrent mean Hgb increase ≥ 1.5 g/dL (Week 1 to EOT)	71.9 (39.9, 83.9)	55.6 (39.9, 77.9)	50.1 (21.9, 72.7)
HI-E per IWG for ≥ 56 days (Week 1 to 24)	*1st Key Secondary Endpoint*		
Response Rate (95% CI) [a]	74.2 (67.2, 80.4)	53.0 (45.5, 60.5)	81.8 (59.7, 94.8)
Common Risk Difference on Response Rate (%) (95% CI) [b]	21.5 (12.2, 30.7); p < 0.0001		
Odds Ratio (95% CI) [b]	2.8 (1.8, 4.5)		
RBC-TI for 24 weeks (Week 1 to 24)	*2nd Key Secondary Endpoint*		
Response Rate (95% CI) [a]	47.8 (40.4, 55.3)	30.9 (24.3, 38.2)	54.5 (32.2, 75.6)
Common Risk Difference on Response Rate (%) (95% CI) [b]	16.3 (7.1, 25.4); p = 0.0003		
Odds Ratio (95% CI) [b]	2.3 (1.4, 3.7)		
RBC-TI for ≥ 12 weeks (84 days) (Week 1 to 24)	*3rd Key Secondary Endpoint*		
Response Rate (95% CI) [a]	68.1 (60.8, 74.8)	48.6 (41.1, 56.1)	68.2 (45.1, 86.1)
Common Risk Difference on Response Rate (%) (95% CI) [b]	18.8 (9.5, 28.0); p < 0.0001		
Odds Ratio (95% CI) [b]	2.5 (1.6, 4.0)		
Other Secondary Efficacy Endpoints			
RBC Transfusion-related Secondary Endpoints			
RBC-TI for ≥ 8 weeks (56 days) (Week 1 to 24)			
Response Rate (95% CI) [a]	79.1 (72.5, 84.8)	64.6 (57.2, 71.6)	77.3 (54.6, 92.2)
Common Risk Difference on Response Rate (%) (95% CI) [b]	13.7 (5.3, 22.2); nominal p = 0.0007		
Odds Ratio (95% CI) [b]	2.3 (1.4, 3.8)		
Duration (weeks) of RBC-TI ≥ 12 weeks (84 days) (Week 1 to EOT)	N = 81	N = 50	N = 15 [f]
Median (95% CI) [d]	128.1 (108.3, NE)	89.7 (55.9, 157.3)	73.0 (35.9, 131.0)
HR (95% CI) [e],[h]	0.534 (0.330, 0.864); nominal p = 0.0096		

Time (days) to RBC-TI ≥ 12 weeks (84 days) (Week 1 to 24)	N = 124	N = 88	N = 15
Median (Min, Max) [f]	1.0 (1.0, 75.0)	1.0 (1.0, 85.0)	1.0 (1.0, 43.0)
Time (days) to First RBC Transfusion (Week 1 to EOT)	N = 116	N = 137	N = 18
Median (95% CI) [d]	155.0 (80.0, 266.0)	42.0 (23.0, 55.0)	252.0 (21.0, 512.0)
HR (95% CI) [e] [h]	0.570 (0.437, 0.742); nominal p <0.0001		
RBC Transfusion Burden on Treatment (Week 1 to 24)	N = 182	N = 181	N = 22
Mean Number of RBC Units (SD)	3.8 (5.90)	5.2 (6.36)	2.9 (4.48)
Median Number of RBC Units (Min, Max)	1.0 (0, 24.0)	3.0 (0, 37.0)	0.0 (0.0, 14.0)
Hematologic Improvement-related Secondary Endpoints			
Mean Hgb Change (g/dL) over 24 weeks (Week 1 to 24)	N = 181	N = 176	
Mean (SD)	2.0 (1.14)	1.5 (1.12)	2.6 (1.80)
Time (days) to HI-E (Week 1 to 24)	N = 135	N = 96	
Median (Min, Max)	1.0 (1.0, 113.0)	6.0 (1.0, 108.0)	1.0 (1.0, 43.0)
Additional Secondary Endpoints			
Progression to AML [i]			
Number (%) of subjects with AML Progression	5 (2.7)	6 (3.3)	
Median Time (months) from Randomization (95% CI) [d]	NE (NE, NE)	NE (NE, NE)	N/A [j]
Incidence Rate per 100 person-years (95% CI)	1.70 (0.71, 4.08)	2.15 (0.97, 4.79)	
HR (95% CI) [e] [h]	0.913 (0.270, 3.082); nominal p = 0.8827		
Overall Survival [i]			
Number (%) of Subjects Alive (censored)	143 (78.6)	143 (79.0)	17 (77.3)
Number (%) of Subjects who Died	39 (21.4)	38 (21.0)	5 (22.7)
Median (months) (95% CI) [d]	NE (35.3, NE)	42.8 (42.8, NE)	36.0 (28.9, NE)
HR (95% CI) [e] [h]	1.089 (0.686, 1.728); nominal p = 0.7173		

Key Exploratory Efficacy Endpoints			
Reduction in pRBC Units of at Least 50%			
At Least 12 Weeks			
Response Rate (95% CI)	83.0 (76.7, 88.1)	66.9 (59.5, 73.7)	
Common Risk Difference (%) (95% CI)[b]	15.4 (6.9, 23.9); nominal p = 0.0002		
Odds Ratio (95% CI)[b]	2.5 (1.5, 4.1)		NA [j]
At Least 24 Weeks			
Response Rate (95% CI)	72.5 (65.4, 78.9)	50.8 (43.3, 58.3)	
Common Risk Difference (%) (95% CI)[b]	21.0 (11.6, 30.4); nominal p < 0.0001		
Odds Ratio (95% CI)[b]	2.7 (1.7, 4.3)		

For Study ACE-536-MDS-002, median follow-up (median of the time from randomization date to death date or last known alive date) was 13.9 months for the luspatercept arm and 13.0 months for the epoetin alfa arm.

[a] Response rate is calculated using the number of responders divided by number of subjects in the efficacy analysis.

[b] Common risk difference, Odds ratio and P-value are calculated based on luspatercept and epoetin alfa group from ACE-536-MDS-002. Based on Cochran-Mantel-Haenszel test stratified for average baseline RBC transfusion burden at baseline (<4, >=4 units), ring sideroblast status at baseline (RS+, RS-) and sEPO level at baseline (<=200, > 200 to < 500 U/L). Derived baseline stratifications are used. One-sided p-value is presented.

[c] Only subjects who completed 169 days of treatment or discontinued early will be included in efficacy analysis.

[d] Median is from un-stratified Kaplan-Meier method.

[e] Hazard ratio is calculated by Cox proportional hazard model stratified by RBC transfusion burden at baseline (<4, >=4 units), ring sideroblast status at baseline (RS+, RS-) and sEPO level at baseline (<=200, > 200 to < 500 U/L).

[f] Time to RBC-TI ≥ 12 weeks was summarized only for subjects who achieved RBC-TI ≥ 84 days from Week 1 through Week 24. It was defined as the time between first dose date and the date onset of TI is first observed (i.e., Day 1 of 84 days without any RBC transfusions).

[g] Including data collected in the ACE-536-LTFU-001 study for 2 TD-MDS subjects who rolled over from study A536-05.

[h] P-value is from log-rank test with RBC transfusion burden at baseline (<4, >= 4 units), ring sideroblast status at baseline (RS+, RS-) and sEPO level at baseline (<=200, > 200 to < 500 U/L) as covariates. One-sided p-value is presented.

[i] Randomization through 5 years from first dose or 3 years from last dose, whichever occurred later. The analysis population was ITT up to the clinical data cutoff date (with any treatment duration).

[j] Not analyzed in the Phase 2 studies.

NE, not estimable.

Clinical data cutoff: 31-Mar-2023

2.4.2. Discussion on clinical efficacy

Luspatercept is currently approved for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts (RS), who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy. With this variation procedure, the MAH intends to extend the indication to use luspatercept as first-line therapy, without having considered prior erythropoietin-based therapy. In addition, also patients without RS (RS-) are proposed to be included.

Design and conduct of clinical studies

The overall study design of pivotal study ACE-536-MDS-002 (COMMANDS), an active-controlled, open-label, randomized Phase 3 study to compare luspatercept vs epoetin alfa in ESA naive subjects with anemia due to IPSS-R very low-, low-, or intermediate-risk MDS who require RBC transfusions, is acceptable. After 24 weeks of treatment, all patients were permitted to discontinue treatment early, if no clinical benefit (defined as decrease in RBC requirements) or progression of disease (per IWG criteria for altering natural history of MDS based on central morphological assessment of bone marrow, peripheral blood and cytogenetics results), death or unacceptable toxicity was experienced. Thus, the discontinuation rate as such provided information on efficacy and safety. The open-label design was accepted in EMA Scientific Advice (EMEA/H/SA/3671/2/2017/PA/II) due to different modalities in the administration of the active comparator. Nevertheless, knowledge of treatment assignment may influence the decision to transfuse or discontinue a patient. In this regard, adding Hb increase to the primary efficacy endpoint adds further objectivity and reduces potential bias of the endpoint compared with RBC-TI alone. The MAH clarified that investigators responsible for the evaluation of patients were not blinded due to different appearance and dosing modalities of the active and control treatments. This is acknowledged.

The study population of the pivotal study included adult patients with confirmed transfusion-dependent MDS (transfusion requirement of 2 to 6 pRBCs units/8 weeks) according to WHO 2016 classification meeting IPSS-R classification of very low, low, or intermediate risk disease. Patients were required to be erythropoietin treatment-naïve, i.e. having received no more than 2 doses of epoetin alfa no later than 8 weeks before randomization, and not having received darbepoetin at any time prior to randomization. No restriction regarding the presence of ring sideroblasts was included, but stratification by RS status (RS+ and RS-) and an enrolment cap for RS+ subjects was initially planned (max. 60%), to ensure a sufficient number of subjects without ring sideroblasts. However, the cap was removed with Amendment 3.0.

The proposed extended indication to use luspatercept as first-line therapy in transfusion-dependent patients may be justified, provided that a positive benefit risk balance is concluded for the overall study population and relevant subgroups. Initially, the MAH had intended to extend the indication to non-transfusion dependent MDS patients ("*patients…who may require RBC transfusions*"). As this patient population was excluded from study ACE-536-MDS-002, the indication was restricted to transfusion-dependent patients upon request. The status or outcome of planned study CA056-025, which was discussed during EMA Scientific Advice (EMA/SA/0000079737) aiming to assess the efficacy of luspatercept in NTD MDS patients, is ongoing and patients have started enrolling.

The criteria for dose adjustments for both treatment arms are based on the posology for epoetin alfa to maintain Hb concentrations within the target range of 10 to 12 g/dL (6.2 to 7.5 mmol/L), independent of transfusions. Accordingly, Section 4.2 of the SmPC has been aligned to reflect the study design and the Hb concentration target range of 10 to 12 g/dL (6.2 to 7.5 mmol/L) upon request. Although permitted and prohibited medications are overall acceptable, prohibiting G-CSF and GM-CSF may lead to lower efficacy of the ESA treatment arm compared to the routine clinical setting, potentially overestimating the

effect of luspatercept. Nevertheless, as ESA treatment is approved as monotherapy for the treatment MDS patients with low serum erythropoietin (< 200 mU/mL), the choice of epoetin alfa as comparator is acceptable, with some caveats (see below). Region-dependent use of different ESA (PROCRIT in the US and EPREX/ERYPO outside the US) is acknowledged. Subgroup analyses of discontinuation rates for both US and non-US active comparators have been provided upon request.

As primary efficacy endpoint, the proportion of subjects who were RBC transfusion-free for any 12-week period associated with a concurrent mean Hb increase ≥ 1.5 g/dL compared to baseline during Week 1 to 24, was defined. Since the effect of luspatercept on Hb levels is expected to occur earlier compared to ESA treatment, the assessment from Week 1-24 may be too early and favour the luspatercept treatment arm. Therefore, sensitivity analyses with a shifted time window, time-to response endpoints as well as secondary endpoints at Week 48 are important for the overall assessment, and totality of data need to demonstrate a clinical benefit of luspatercept. Although not preferred, the rolling 12-week period is acceptable, and the concurrent mean Hb increase ≥ 1.5 g/dL, which is also in line with IWG response criteria to demonstrate clinical benefit, adds objectivity to the primary efficacy endpoint.

The first hierarchically tested secondary endpoint was HI-E for ≥ 56 days, based on modified IWG HI-E criteria differentiating between subjects with baseline transfusion burden of < 4 and ≥ 4 pRBC units/8 weeks. Subjects with lower transfusion burden need an Hb increase of ≥ 1.5 g/dL in the absence of transfusions, while subjects with higher transfusion burden are required to have a minimum reduction of at least 4 pRBC units for any consecutive 56 days, in order to meet HI-E criteria. This and other secondary endpoints are overall acceptable. It is however noted that in regards of the three secondary endpoints included in the statistical testing hierarchy, the corresponding statistical analyses are performed using the same information retrieved from the patient. Hence, there is a strong correlation in the outcomes expected, in particular for the 3rd secondary endpoint (RBC-TI for ≥12 weeks).

Assessing the primary endpoint from Week 1 to 24 may be too early and overestimate the effect of luspatercept due to its rapid onset of efficacy compared to epoetin alfa. Indeed, as higher mean Hb increase after extended treatment, and longer time to HI-E was observed in the epoetin alfa arm (see below), potential responders may be discontinued too early in the epoetin arm to become responders. Therefore, upon request appropriate strategies to address intercurrent events were defined and sensitivity analyses as well as worst case/tipping point analyses were added to assess the robustness of the primary endpoint (see below).

Health-related quality of life (HRQoL) was assessed by the secondary endpoint EORTC QLQ-C30 scores using validated questionnaires. As requested during EMA Scientific Advice (EMEA/H/SA/3671/2/2017/PA/II), FACT-An scores and the MDS-specific HRQoL tool QUALMS-P, were assessed as additional endpoints.

From a technical perspective, the statistical analyses of the primary and hierarchically tested secondary efficacy endpoints are considered adequate. Overall, 350 subjects are planned for the final analysis, which is endorsed and will provide sufficient power, regardless of the second interim analysis for superiority and the applied Lan-DeMets spending function of the O'Brien-Fleming type to control the overall 1-sided Type I error rate. For the randomisation a central randomization procedure using integrated response technology (IRT) at a 1:1 ratio to either the Luspatercept or the epoetin alfa arm was used, stratified for RBC transfusion burden, RS status and endogenous serum erythropoietin level. The stratification factors are appropriate and were endorsed in EMA Scientific Advice (EMEA/H/SA/3671/2/2017/PA/II). The Cochran-Mantel-Haenszel (CMH) test including the stratification factors was used to compare the response rates between the treatment arms based on the ITT population, which is endorsed. From a statistical point of view, the two interim analyses were planned and conducted adequately and the applied Lan-DeMets spending function of the O'Brien-Fleming type is endorsed. A programmatic cut-off approach was adopted to ensure that the data were complete for the

pre-specified second interim analysis. Additionally, summaries are presented including the corresponding two-sided 95% CI as well as the two-sided CI received after alpha-correction based on the Lan-DeMets spending function of the O'Brien-Fleming type for the final analyses.

Changes in 4 global protocol amendments were overall acceptable except for the introduction of an IA with Amendment 4.0. Those included the implementation of Hb increase in the primary endpoint, and further secondary endpoints to complement the new primary endpoint. A minimum percentage of subjects (at least 25%) with an endogenous sEPO level of > 200 U/L was added in Amendment 1.0, but removed in Amendment 4.0. The rationale for adding and removing this requirement cannot entirely be followed, as data from previous clinical trials informing either decision were published already before the date of Amendment 1.0. Nevertheless, as in this subgroup the efficacy in the comparator arm is expected to be underestimated, no issue arises, if the minimum percentage is not reached. The basis for removing the enrolment cap for RS+ subjects (at least 40% but not more than 60% of subjects randomized) in Amendment 3.0 stems from the observation of subject recruitment in the study, presumably from the first interim analysis (futility only; clinical data cutoff 16-Sep-2020), where the proportion of RS+ subjects was 74%. The grounds to conduct the second interim analysis for superiority added during Amendment 4.0 were initially doubted, since Amendment 4.0 was done after conductance of the first interim analysis for futility. This concern was further aggravated by the open-label design, but concerns could be convincingly alleviated by the MAH.

Efficacy data and additional analyses

This report contains data from the primary analysis (clinical data cutoff: 31-Mar-2023).

At the primary clinical data cutoff (31-Mar-2023), the recruitment targets have been met, since 363 of 350 planned subjects were randomized. Based on the safety population, more patients had discontinued treatment in the epoetin alfa arm (126/179, 70.4%) compared to luspatercept (104/182, 57.1%). The most frequent status for the treatment period for discontinued patients in both treatment arms was lack of efficacy: 68/179 (38.0%) epoetin alfa and 41/182 (22.5%) luspatercept. Hence, the discontinuation rates suggest higher efficacy in the luspatercept arm. However, more patients discontinued due to an AE in the luspatercept arm (9/182, 4.9%) compared to epoetin alfa (5/179, 2.8%), which may suggest a worse safety profile of luspatercept (see Safety section). Due to the open-label design it cannot be excluded that the decision for discontinuation is at least partially driven by knowledge of treatment assignment. However, the response criteria for the multi-component primary endpoint are considered appropriate to minimise the risk of subjective decisions. The median duration of treatment was longer in the luspatercept arm compared to epoetin (51.3 vs 37.0 weeks), and a higher proportion of subjects completed 48 weeks of treatment (55.5% vs 42.5%), suggesting higher efficacy of luspatercept. On the other hand, dose delays were more frequent in luspatercept treated subjects compared with epoetin alfa treated subjects (60.4% vs 43.0%) and dose delay due to predose Hb ≥12.0 g/dL was almost 2 times more frequent in the luspatercept arm compared to epoetin alfa (44/182, 24.2% vs 22/179, 12.3%). This information was included in Section 4.8 of the SmPC upon request. Despite small number of US patients, overall more US patients compared to non-US patients discontinued the study, and treatment duration was longer and the proportion of subjects who completed 48 weeks of treatment was higher for the non-US subgroup vs the US subgroup in the epoetin alfa arm.

Demographics were overall balanced between treatment groups regarding median age, race, region, height and BMI. The overall high median age (74.0 years in both treatment groups) reflects the expected high age range of patients with MDS. More males were included in the luspatercept treatment arm compared to epoetin alfa (59.9% vs 50.8%), which may explain the slightly higher median height (166.6 vs 165.0 cm) and higher median weight (73.0 vs 70.0 kg). These differences are not expected to influence any outcome of the efficacy assessment.

At baseline, disease characteristics including transfusion burden (pRBC units), MDS WHO 2016 and IPSS-R risk classification, ring sideroblast status and SF3B1 mutation status were similar between treatment groups. Fewer patients with ECOG performance score of 2 were included in the luspatercept treatment group (2.2% vs 9.9%), hence more patients were in a better disease state (ECOG performance score of 0 and 1) at baseline. On the other hand, median time since MDS diagnosis was longer in the luspatercept group (7.97 vs 5.13 months), suggesting a more progressed disease at baseline. Approximately 3-fold higher mean values for disease duration in both treatment groups suggest exceptional cases of long intervals separating inclusion from diagnosis. Baseline laboratory characteristics including platelet count, ANC, Hb, serum EPO, eGFR and serum ferritin were balanced between treatment groups.

Among patients with single lineage dysplasia, only patients with anaemia (erythrocytopenia), but not patients with MDS or MDS-RS with neutropenia / thrombopenia were recommended to be included during EMA Scientific Advice (EMEA/H/SA/3671/2/2017/PA/II). Overall, few patients with single lineage dysplasia were included, and sensitivity analyses for the primary and three hierarchically tested secondary endpoints excluding 5 patients in the epoetin alfa arm, who were MDS-SLD or MDS-RS-SLD with baseline neutrophil count $<0.5 \times 10^9$/L or platelet count $<150 \times 10^9$/L, demonstrated robustness of the results favouring luspatercept (see below).

The main difference of the MDS population included in the current study ACE-536-MDS-002 compared to the population included in study ACE-536-MDS-001 for the initial market authorisation is the exclusion of previously ESA treated patients, which would suggest an overall less progressed disease. Indeed, in the current study more patients had low transfusion burden of <4 pRBC/8w at baseline (>60% vs 17% in ACE-536-MDS-001), and the mean transfusion burden was considerably lower in the 8 weeks prior to randomisation (3.2 vs 6.0 units in ACE-536-MDS-001). Further, more patients had a disease duration of less than 2 years (>70%) compared to study ACE-536-MDS-001 (26%), and the median time since MDS diagnosis was 6.05 vs 41.8 months.

The primary efficacy endpoint showed a significantly higher proportion of subjects with RBC-TI for 12 weeks with a concurrent mean Hb increase $\geq$ 1.5 g/dL (Week 1 to 24) in the luspatercept treatment arm compared with epoetin alfa: 60.4% (95% CI: 52.9, 67.6) vs 34.8% (95% CI: 27.9, 42.2); 1-sided stratified CMH test p-value < 0.0001. All 3 hierarchically tested secondary efficacy endpoints also showed a significantly higher response rate in luspatercept compared to epoetin alfa (Week 1 to 24): 74.2% (95% CI: 67.2, 80.4) vs 53.0% (95% CI: 45.5, 60.5)[p < 0.0001] achieved HI-E per IWG over any consecutive 56-day period, 47.8% (95% CI: 40.4, 55.3) vs 30.9% (95% CI: 24.3, 38.2)[p = 0.0003] achieved RBC-TI for 24 weeks, and 68.1% (95% CI: 60.8, 74.8) vs 48.6% (95% CI: 41.1, 56.1) [p < 0.0001] achieved RBC-TI for $\geq$12 weeks. As expected, due to some overlap in the hierarchically tested efficacy endpoints, responder rates were higher in both groups in the 3rd secondary endpoint compared to the primary and 2nd secondary endpoint. Of note, the HI-E (IWG 2006) response rate was higher in the epoetin alfa treatment arm in study ACE-536-MDS-002 (53.0%) compared to what would be expected from the registrational study of epoetin alfa (EPOANE3021 study: 31.8%), alleviating the concern of reduced efficacy in the epoetin alfa arm.

Regarding the overlap with discontinuation and responder rates for the hierarchically tested efficacy endpoints, frequencies of patients who are considered responders, but discontinued early, including reasons for discontinuations, were presented. Sensitivity analyses excluding those subjects from efficacy evaluation and worst case/tipping point analyses to assess the impact of early discontinued patients from the comparator arm demonstrate robustness of the beneficial effect of luspatercept. In addition, reasons for discontinuations before week 24 were presented upon request and suggest that the difference in discontinuations before week 24 (20 vs 36 for luspatercept vs epoetin alfa) is unlikely to have affected the primary endpoint.

Overall, superior efficacy of luspatercept compared to epoetin was formally demonstrated in the primary data set. As there is some redundancy among the hierarchically tested endpoints, other endpoints assessing the maintenance of treatment effect (i.e. up to Week 48), are considered to be of high relevance. Results for the secondary endpoint RBC-TI for 24 from Week 1-48 indicate a higher response rate in the luspatercept group: 60.7% (95% CI: 52.8, 68.3) vs 48.6% (95% CI: 41.1 vs 56.1) epoetin alfa [p<0.0001], alleviating the concern of underestimating the epoetin arm due to delayed treatment onset to some extent.

Sensitivity analyses of the primary efficacy endpoint and 1st hierarchically tested secondary endpoint, for which central laboratory results only were used, showed that the origin of Hb measurement (central, local laboratory, pre-transfusion Hb from transfusion records) had little impact on the outcomes, as results were similar and showed the same statistical significance level. Likewise, by excluding a responder, if relevant Hb increase was based on a single central laboratory measurement, the outcomes were highly similar. According to the revised IWG 2018 criteria, at least 2 consecutive Hb measurements ≥1.5 g/dL are required for a clinically meaningful response. Sensitivity analyses for the primary and first hierarchically tested secondary endpoints including only responders with at least 2 consecutive central laboratory Hb measurements ≥1.5 g/dL further demonstrated the robustness of the results. Results of the subgroup with subjects treated with EPREX/ERYPO (used outside of the US) were similar to those of the entire overall comparator arm and the inclusion of subjects treated with PROCRIT (used in the US) did not lead to results different from the overall analyses.

Other efficacy endpoints aimed to assess the **transfusion independence** in terms of duration of a response, or time to a response. An *ad hoc* analysis of the primary endpoint showed longer median duration of RBC TI ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL (Week 1 to EOT) in responders treated with luspatercept: 71.9 (95% CI: 39.9, 83.9) vs 55.6 (95% CI: 39.9, 77.9) weeks. Similarly, the median duration of the longest single RBC TI period for subjects who achieved RBC TI ≥ 12 weeks from Week 1 to EOT (3rd hierarchically tested secondary endpoint) was longer in the luspatercept arm: 128.1 (95% CI: 108.3, Not estimable) vs 89.7 (95% CI: 55.9, 157.3). The median time to RBC-TI ≥ 12 weeks was the same (1 day) in both treatment groups. Furthermore, median RBC transfusion burden (Week 1 to 24) was lower in the luspatercept group compared to epoetin alfa (1.0 vs 3.0 RBC units), and the time to first RBC transfusion (Week 1 to EOT) was significantly longer in the luspatercept group (median 155.0 vs 42.0 days; p < 0.0001). Thus, luspatercept treated patients had an overall higher rate of transfusion independence and lower transfusion burden as well as longer duration of responses. Of note, longer duration of responses is based on (early) RBC-TI responder during the first 24 weeks only. Time to transfusion independence was similarly short in both treatment groups, but time to first RBC transfusion was longer in patients treated with luspatercept.

In addition to an improved response regarding the 1st hierarchically tested secondary endpoint (HI-E for ≥ 56 days) **erythroid improvement** was also demonstrated by higher mean Hb change over time over 24 weeks in the luspatercept group compared to epoetin alfa: 2.0 vs 1.5 g/dL. At later time points, i.e. at weeks 70 and 72, Hb change in the epoetin alfa arm appears to have increased and to be similar compared to the luspatercept arm. However, due to considerably lower numbers of patients included and larger standard errors at later time points, these results need to be interpreted with caution, but highlight the importance of 48 week data. The median time to HI-E (Week 1 to 24) was shorter in the luspatercept group compared to epoetin alfa: 1.0 vs 6.0 days. Thus, sensitivity analyses investigating a shifted time window (i.e. week 5-28) were provided upon request, showing similar response rates as for the Week 1-24 period for the primary and hierarchically tested secondary endpoints. A significantly higher proportion of luspatercept-treated subjects than epoetin alfa-treated subjects (74.2% vs 52.5%) had a mean Hb increase ≥ 1.5 g/dL during Week 1 to 24, which was also sustained longer in the luspatercept treatment arm. Numerically greater proportions of subjects in the luspatercept arm achieved neutrophil or platelet

responses (HI-N and HI-P, respectively) during Week 1 to 24 compared with the epoetin arm. These results are however of limited value as only few patients were eligible for evaluation HI-N and HI-P.

No differences were observed in the number of subjects with **AML progression** (n=5 luspatercept vs n=6 epoetin alfa) or median time to progression to AML (not estimable in both groups). The **overall survival** was similar between treatment arms (39 deaths in the luspatercept arm vs 38 deaths in the epoetin alfa arm). Median time to death was not estimable in the luspatercept arm and 42.8 months for epoetin alfa, potentially suggesting longer survival in the luspatercept treatment group. However, data from a longer observation period would be necessary to draw any final conclusions on AML progression and overall survival.

At baseline, there was some imbalance in most mean **HRQoL** scores, suggesting better health status for subjects in the luspatercept arm compared to epoetin alfa, which is in line with a higher proportion of subjects with better ECOG performance scores of 0-1 at baseline. Therefore, less room for improvement regarding HRQoL may be expected in the luspatercept arm. After it was concluded that EORTC QLQ-C30 and FACT-An scores provided little support to demonstrate superior efficacy of luspatercept, the MAH provided additional analyses on the interim data accounting for relevant intercurrent events, which is in principle acceptable. However, the treatment groups still appeared similar regarding PRO domain scores, with few domains favouring luspatercept. As these post-hoc analyses were based on the interim data cut-off (31-Aug-2022), used different thresholds for clinically meaningful changes compared to the original protocol, and since anemia-related domains (physical functioning, fatigue, dyspnoea) rarely showed a beneficial effect of luspatercept, it was concluded that there was still little support from PRO data to show a clinically relevant benefit of luspatercept relative to epoetin alfa. Yet, due to the open-label study design, PRO data are overall considered of limited value, and as the primary and hierarchically tested secondary endpoints show a benefit of luspatercept, this issue was not further pursued. The completion rate for QUALMS-P was low (38.6% at baseline), since it was not used in all countries due to a limited number of translations available. This is acknowledged, but the results suggesting better performance in the luspatercept arm are of limited value. Hospitalisations and emergency room (ER) visits due to an AE were more frequent in the luspatercept treatment arm after adjusting for exposure (hospitalization: 34.3 vs 27.2 EAIR/100 PY; ER visit: 19.8 vs 16.7 EAIR/100 PY, luspatercept vs epoetin alfa, respectively). This is in line with the non-negligible safety profile of luspatercept.

If sufficient numbers per subgroup were available, the majority of **subgroup analyses** showed similar results with respect to the primary and hierarchically tested secondary efficacy endpoints, which showed a superior efficacy of luspatercept compared to epoetin alfa as of Week 24. Of particular interest is the subgroup of subjects with baseline endogenous sEPO levels 200-500 U/L, as the comparator epoetin is expected to show limited to no efficacy in this subgroup, which may favour the luspatercept arm. Reassuringly, efficacy in this subgroup was observed in both treatment groups, albeit at lower responder rates compared to the subgroup of sEPO <200 U/L (primary efficacy endpoint: 37.8% vs 66.2% luspatercept and 10.8% vs 41.0% epoetin alfa). The treatment difference in response between luspatercept and epoetin alfa was similar across sEPO subgroups (<200 U/L and 200-500 U/L), showing superior efficacy of luspatercept in both subgroups. Discontinuation rates were lower in the luspatercept arm compared to the epoetin alfa arm for both the baseline sEPO < 200 U/L and 200–500 U/L subgroups. The proportion of subjects discontinued from treatment in the sEPO 200-500 U/L subgroup was generally higher than in the sEPO < 200 U/L subgroup, with 88.9% (32/36) subjects discontinued in the sEPO 200-500 U/L subgroup treated with epoetin alfa. Nevertheless, the difference (luspatercept vs epoetin alfa) in proportion of discontinued subjects with lack of efficacy status during treatment was similar in both subgroups, indicating that baseline sEPO 200-500 U/L did not lead to lower efficacy specifically in the epoetin alfa arm.

Analyses of primary and hierarchically tested secondary endpoints in the **RS- subgroup** did not demonstrate superior efficacy of luspatercept compared to epoetin alfa. At the time of the primary

analysis, 46.9% (23/49) of RS- subjects receiving luspatercept were primary endpoint responders. The response rates for the primary and hierarchically tested secondary endpoints are similar compared to the response rates in epoetin alfa treated RS- MDS patients (50.0%, 25/50 for the PEP). Yet, even if the benefit is comparable to epoetin alfa for the responder endpoints, a clinically relevant response after luspatercept treatment is evident also for the RS- subgroup, and other benefits of luspatercept over epoetin alfa were observed, such as increased durability of response and continued benefit with longer follow-up. As discussed by the MAH upon request, at baseline the RS+ subgroup showed a higher percentage of erythroid precursors in the bone marrow compared to the RS- subgroup, whereas RS- subjects showed higher baseline levels of reticulocytes in peripheral blood compared to RS+ subjects, suggesting maturation block may occur earlier during erythropoiesis in RS+ compared to RS- patients. Consistent and sustained increases among these pharmacodynamic markers in the luspatercept arm suggest that luspatercept treatment leads to gradual improvements in erythropoiesis in both subgroups, which may partially explain a delayed onset of treatment effect with luspatercept in RS- patients, in particular when compared to epoetin alfa. In fact, the higher clinical response rate in epoetin alfa treated RS- patients (compared to RS+) may be a result of epoetin alfa acting exclusively on early bone marrow erythroid precursors, while luspatercept acts at various stages of erythroid maturation, independent of RS status. Thus, it can be agreed not to restrict the indication to RS+ subjects, since information on missing or limited efficacy data in section 5.1 of the SmPC was included upon request. Although the evidence of a beneficial effect in RS- patients in the previously approved second line setting is very limited, as no RS- patients were included in the pivotal MEDALIST (ACE-536-MDS-001) study, long-term efficacy results from Phase 2 (A536-03/05) indeed indicate a treatment benefit also in RS- patients, albeit again lower compared to RS+ patients. Therefore, the combined indication wording covering both first and second line treatment for MDS is considered appropriate.

It is furthermore agreed that the RS- subgroup is rather heterogeneous and that using genetic characterisation is a similarly relevant determinant in disease phenotype in MDS patients. A meta-analysis of mutation subgroups provided some evidence that treatment benefit is seen across most mutations, except in patients with *CBL* gene mutations, added in Section 5.1 of the SmPC.

To compare efficacy across studies, efficacy endpoints as defined in pivotal Study ACE-536-MDS-002 were evaluated, and similar responder rates in the luspatercept arm of study ACE-536-MDS-002 and in the COMMANDS-like population from **supportive A536-03/05 studies** were observed. A considerably shorter median duration of RBC-TI ≥12 weeks (for responders Week 1-24) was observed (73.0 weeks vs 128.1 weeks in the luspatercept arm of the pivotal study), being lower compared to the epoetin alfa comparator arm of the pivotal study (89.7 weeks). This may indicate a decrease of efficacy over time after extended treatment, as subjects in supportive extension study A536-05 overall have a higher median duration of exposure (552 days, i.e. 78.9 weeks vs 51.3 weeks in the luspatercept arm of pivotal study ACE-536-MDS-002). Upon request, the MAH highlighted the small number of responders in supportive A536-03/05 studies (n=15), hampering a clinically meaningful conclusion.

2.4.3. Conclusions on the clinical efficacy

The clinical superiority of luspatercept over epoetin alfa in patients with anemia due to IPSS-R very low-, low-, or intermediate-risk MDS who require RBC transfusions could be demonstrated for the primary efficacy endpoint (RBC transfusion-free for any 12-week period associated with a concurrent mean Hb increase ⩾ 1.5 g/dL compared to baseline during Week 1 to 24), as well as for several secondary endpoints. As high discontinuation rates may have affected the outcomes, several sensitivity analyses have been conducted, further supporting the efficacy of luspatercept. Limitations of the study include the open-label design, little support from PRO data and a considerably lower efficacy in RS- subjects compared to RS+ subjects.

2.5. Clinical safety

Introduction

This SCS provides safety data to support the use of luspatercept for treatment of anemia in ESA-naïve adult patients with very low- to intermediate-risk MDS who benefit from RBC transfusions.
The submitted safety database submitted in the summary of clinical safety (SCS) for the MDS population includes subjects from 1 pivotal Phase 3 study, 4 supporting clinical studies and one long-term follow-up study (Pivotal study: ACE-536-MDS-002, Supportive studies: A536-03, A536-05, ACE-536-MDS-001, ACE-536-MDS-004, Long-term follow-up study: ACE-536-LTFU-001; see Table 54 below for more details regarding study designs including primary objectives as well as specifics on the study population and applied dosing).

Table 54: Summary of Clinical Safety Studies Supporting the Safety of Luspatercept (ACE-536) in First-Line Transfusion-Dependent Lower-risk MDS

Study	Design/ Primary Objective	No. Treated Subjects	Population	Regimen and Dose	Study Status
ACE-536-MDS-002 Pivotal Study	Open-label randomized, Phase 3 study to compare the efficacy and safety of ACE-536 versus epoetin alfa for the treatment of anemia due to IPSS-R very low, low, or intermediate-risk MDS	361	ESA-naive subjects with very low, low, or intermediate-risk MDS who require red blood cell transfusions	luspatercept at a starting dose of 1.0 mg/kg SC Q3W or epoetin alfa at a starting dose of 450 IU/kg QW for up through at least the first 24 calendar weeks of the study unless the subject experiences unacceptable toxicities, disease progression, withdraws consent, or meets any other discontinuation criteria.	Ongoing
A536-03 Supportive Study	Open-label, ascending dose, Phase 2 study of ACE-536 in patients with low or intermediate-1 risk MDS	Total: 116 TD: 80	Subjects with low or intermediate-1 risk MDS (Only TD subjects will be included in the SCS)	luspatercept 0.125 mg/kg - 1.75 mg/kg SC Q3W for up to 15 weeks	Completed
A536-05 Supportive Study	Open-label, Phase 2 extension study of long-term effects of ACE-536 in patients with low or intermediate -1 risk MDS previously enrolled in study A536-03	Total: 75 TD: 43	Subjects with low or intermediate-1 risk MDS previously enrolled in study A536-03 (Only TD subjects will be included in the SCS)	luspatercept SC Q3W for up to 60 months Subjects rolling over from A536-03 with no interruption continued at the same dose level as in A536-03; those with an interruption in dosing were given a starting dose of 1.0 mg/kg	Completed
ACE-536-MDS-001 Supportive Study	Double-blind randomized, Phase 3 study to compare the efficacy and safety of ACE-536 versus placebo for the treatment of anemia due to IPSS- R very low, low, or intermediate risk MDS	229	ESA-refractory/ineligible subjects with very low, low, or intermediate risk MDS and ring sideroblasts who require red blood cell transfusions	luspatercept at a starting dose of 1.0 mg/kg or placebo SC Q3W until unacceptable toxicity, disease progression, withdrawal of consent, or subject met any other discontinuation criteria.	Completed
ACE-536-MDS-004 Supportive Study	Single-arm, multicenter, Phase 2 bridging study to evaluate the efficacy, pharmacokinetics and safety of luspatercept for the	13	ESA-refractory/ineligible Chinese and Japanese subjects with very low, low, or intermediate risk MDS and	luspatercept at a starting dose of 1.0 mg/kg until the subject experienced unacceptable toxicities, disease progression withdraws	Ongoing
Study	Design/ Primary Objective	No. Treated Subjects	Population	Regimen and Dose	Study Status
	treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS		ring sideroblasts who require red blood cell transfusions	consent, or meets any other discontinuation criteria.	
ACE-536-LTFU-001	Phase 3b, open-label, single-arm rollover study to evaluate long-term safety in subjects who have participated in other luspatercept Sponsor-initiated clinical trials which include A536-05 and ACE-536-MDS -001	Total: 78 A536-05: 5 ACE-536-MDS-001: 73	TD MDS subjects who rolled over from the ACE-536-MDS-001 and A536-05 studies to continue treatment or follow up	The same dose and schedule of luspatercept in this study as the last dose and schedule in the parent luspatercept study (A536-05 or ACE-536-MDS-001).	Ongoing

Source: ACE-536-MDS-002 Primary CSR[1], ACE-536-MDS-001 CSR[2], A536-03 CSR[3], A536-05 CSR[4]

Safety narratives for deaths, SAEs, AEs leading to discontinuation, AEs leading to dose reduction or dose interruption, pregnancy, and AESIs are provided for the above-mentioned studies.
Safety narratives only for malignancy events from ACE-536-MDS-003 are included with this submission to provide additional and current information for malignancy AESIs in ongoing MDS studies. If a subject from ACE-536-MDS-003 had another qualifying event (i.e. malignancy including progression to high risk MDS/AML or transformation to blast phase and solid tumors) in addition to a malignancy event, information on the other qualifying event is included with the malignancy narrative.

Table 55: Pivotal and Supporting Study Data Cutoff and Database Lock Dates for the Summary of Clinical Safety

	536-MDS-002 (Initial SCS - Feb-2023)	536-MDS-002 (Updated SCS - Dec-2023)	A536-03	A536-05	536-MDS-001	536-MDS-004 (Initial SCS - Feb-2023)	536-MDS-004 (Updated SCS - Dec-2023)	536-LTFU-001 (Initial SCS - Feb-2023)	536-LTFU-001 (Updated SCS - Dec-2023)
Clinical Cutoff/ LPLV	31-Aug-2022	31-Mar-2023	26-Nov-2020	19-Mar-2020	26-Nov-2020	10-Jul-2022	02-Jan-2023	10-Jul-2022	02-Jan-2023
CDL	09-Oct-2022	17-May-2023	30-Mar-2021	20-May-2020	30-Mar-2021	14-Sep-2022	15-Feb-2023	23-Sep-2022	17-Feb-2023

CDL: Clinical Database Lock

Subject Characteristics
Subjects included in the submitted SCS had baseline diagnoses of very low, low, or intermediate-risk MDS. MDS risk was assessed in ACE-536-MDS-001, ACE-536-MDS-002, and ACE-536-MDS-004 using the revised International Prognostic Scoring System (IPSS-R), which provides a discriminatory risk factor assessment for evaluating clinical outcomes for MDS patients. In ACE-536-03/05, MDS risk was determined using the original IPSS scale and thus includes a more heterogeneous patient population. For the purpose of this SCS, subjects with IPSS-R very low, low, and intermediate risk or IPPS low and intermediate-1 risk MDS will be referred to as lower-risk MDS. To be eligible for entry into ACE-536-MDS-001, ACE-536-MDS-002, and ACE-536-MDS-004, all subjects must have required RBC transfusions, i.e. transfusion-dependent (TD). A536-03 and A536-05 enrolled both TD and non-TD subjects; only TD subjects from A536-03 and A536-05 are included in the submitted SCS.

Safety Data

Scope of the proposed analyses in TD MDS: The integrated safety evaluations included disposition, demographics and baseline characteristics, medical history, concomitant medications, overall extent of exposure to study treatment, aEs (TEAEs, SAEs, and deaths), clinical laboratory data, and vital signs.

Analysis Population
All analyses were performed on the TD MDS Safety Population, which included all TD subjects who received at least 1 dose of study drug from any of the studies mentioned above. The TD MDS pooled group includes all luspatercept-treated subjects from the TD MDS Safety Population. Subjects who participated in both A536-03 (base study) and A536-05 (extension study) were treated as 1 subject and counted only once in the integrated analyses. Subjects who rolled over to ACE-536-LTFU-001 from A536-05 or ACE-536-MDS-001 were treated as 1 subject and counted only once in the integrated analyses.
All safety analyses are descriptive in nature with no formal statistical inference. Summary statistics consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, standard deviation, minimum, and maximum for continuous variables.

Analyses of Adverse Events

For the analyses of AEs and marked abnormalities for each of the data pools and for each of the analysis time periods, the following point estimates are summarised:

- Subject incidence (ie, percent used in a frequency summary) was defined as the number of subjects with the specific event divided by the number of subjects included in the analysis. Subjects with multiple AE occurrences in the specific analysis period were counted only once in the numerator.
- The exposure-adjusted incidence rate (EAIR) per 100 subject-years was defined as 100 times the number of subjects with the specific event divided by the total exposure time (in years) among subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period were counted only once in the numerator. The exposure time for a subject without the specific event was the treatment duration, whereas the exposure time for a subject with the specific event was the treatment duration up to the start date (inclusive) of the first occurrence of the specific event. The total exposure time in years was calculated by dividing the sum of exposure time in days over all subjects included in the analysis by 365. The EAIR per 100 subject-years is interpreted as the expected number of subjects with at least 1 occurrence of the specific event per 100 subject-years of exposure to the IP.

The rationale for providing EAIRs is to account for the differences in exposure between the placebo or epoetin alfa treatment arm and the luspatercept treatment arm. Exposure-adjusted incidence rate information adds value, as the exposure-time is considerably shorter for placebo or epoetin alfa. Exposure-adjusted incidence rate is useful when the event risk is evenly distributed over time but has limited utility when, for example, an event mainly is observed at treatment initiation. Such events will be noted if there is a potential impact on interpretation.

In addition to EAIR, safety data at 24 weeks when similar proportion of subjects in the luspatercept and epoetin alfa arms completed 24 weeks of treatment (71.3% and 67.0%, respectively) is included.

For progression to AML, and malignancies the total follow-up time was calculated in addition to the EAIR, the rationale being that malignancy may be diagnosed after treatment exposure.

Adverse Events of Special Interest

AESIs were selected based on based upon pre-specified events identified in the clinical development program across all indications, including malignancies, premalignant disorders, kidney injury, liver toxicity, thromboembolic events, immunogenicity-type reactions, hypertension, asthenia, and EMH mass.

<u>Malignancies</u>

Based on findings from a juvenile toxicity study, new malignancies or premalignant lesions were considered AESIs in Phase 2 and Phase 3 luspatercept studies.

- The PTs used to evaluate the malignancy AESI category were all based on the MedDRA narrow scope of sub-SMQs for malignancy-related conditions; malignancy-related therapeutic and diagnostic procedures; hematological malignant tumors; nonhematological malignant tumors; hematological tumors of unspecified malignancy; nonhematological tumors of unspecified malignancy; and tumor markers.

MDS disease progression and premalignant disorders

- The risk of progression to AML and high-risk MDS must be considered in the context of the underlying disease biology. For MDS, the risk of progression to AML is a recognized part of the natural history of the disease. In addition, the literature has reported that the risk of diagnosis of primary solid tumor malignancy in adult patients with de novo MDS is significantly higher compared to the general population. However, malignancies, including progression to AML or high-risk MDS, were considered AEs of interest in the MDS studies, based on findings from a juvenile toxicity study. For all subjects who received at least 1 dose of IP, continuation of monitoring for progression to AML and other malignancies/premalignancies was to occur in the follow-up period for at least 5 years from the date of first dose of IP.
- The PTs used to evaluate the premalignant disorder AESI category were all based on the MedDRA narrow scope of sub-SMQs for blood premalignant disorders; gastrointestinal premalignant disorders; premalignant disorders, general conditions and other site-specific disorders; reproductive premalignant disorders; and skin premalignant disorders.

Embolic and thrombotic events

- The embolic and thrombotic events AESI category was initially identified based on a numerical imbalance in thromboembolic events observed in subjects treated with luspatercept in the Phase 3 β-thalassemia study ACE-536-B-THAL-001 and the clinical relevance. For the purpose of this review, embolic and thrombotic events are defined by the MedDRA narrow scope of sub-SMQs for embolic and thrombotic events: Arterial embolic and thrombotic events, Venous embolic and thrombotic events, Vessel type unspecified and mixed arterial and venous, MedDRA broad scope of SMQ thrombophlebitis.
- These SMQs include terms that may not necessarily indicate the presence of a vascular occlusion or clinical thromboembolism (ie, device occlusion, transient ischemic attack).
- Clinically, an embolic and thromboembolic event is defined as a formation of a thrombus in a blood vessel that breaks loose and is carried by the blood stream to obstruct a secondary vessel, or the formation of the thrombus in situ (ie, deep vein thrombosis). Therefore, thromboembolic events include either the diagnosis of a vessel occlusion or embolism and exclude events in which the presence of a vessel clot has been ruled out. It excludes catheter obstructions, which are common occurrence for such devices, as well as ischemic conditions (such as transient ischemic attack, angina pectoris and peripheral arterial ischemia) in which a vessel occlusion or thrombus was ruled out. To better understand the etiology and risk factors, embolic and thrombotic events were further categorized into arterial and venous embolic and thromboembolic events based on vessel type affected and/or its anatomic location of the clot.

Kidney injury

- Kidney injury was selected based on nonclinical data. The PTs used to evaluate this EOI category were based on the MedDRA broad scope of SMQ acute renal failure. A comprehensive assessment of kidney injury also included an evaluation of creatinine clearance. In addition, albumin/creatinine ratio data for the Phase 2 and Phase 3 studies were analyzed for the potential of nephron damage. The albumin/creatinine ratio data are presented separately for the Phase 2 and Phase 3 studies due to the different visit schedules between these studies.

Hypertension

- Hypertension was selected because hypertension has been observed with the use of agents that increase hemoglobin and has been reported in the luspatercept clinical program studies. The PTs

used to evaluate this EOI category were based on the MedDRA narrow scope of SMQ hypertension.

Liver Toxicity

- The liver toxicity AESI category was selected based on the importance of liver injury when assessing safety in the context of populations that may or may not be subject to regular blood transfusion and consequent iron overload. The PTs used to evaluate this EOI category was Broad scope of Sub-SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions, Broad scope of Sub-SMQ Hepatitis, non-infectious. In addition, liver laboratory parameters of potential Hy's law cases regardless of PT is provided. There are no data to indicate a risk of drug-induced liver injury in luspatercept studies.

Immunogenicity-type Reactions

- The Immunogenicity-type reactions AESI category was selected based on nonclinical data and the potential for immunogenicity and hypersensitivity due to the protein nature of the drug. As with all biologics, there is the potential for ADA formation that may impact drug clearance, lead to loss of efficacy due to neutralizing antibodies, and/or cause hypersensitivity reactions. The PTs used to evaluate hypersensitivity-type reactions within this category were based on the high-level term of angioedemas, the high-level term of anaphylactic and anaphylactoid responses, and other selected PTs. Injection-site, local reactions were also included in this category.

Asthenia

- The asthenic conditions AESI category was selected based on safety results of MDS clinical studies. The PTs used to evaluate this category were based on the high-level term of asthenic conditions.

EMH Mass

- EMH mass was initially identified as an AESI based on the numerical imbalance observed in subjects treated with luspatercept in the Phase 2 β-thalassemia Study ACE-536-B-THAL-002 and the identification of EMH masses as significant safety finding in patients with transfusion dependent and non-transfusion dependent β-thalassemia. The PTs used to evaluate this AESI category were cutaneous extramedullary hematopoiesis and extramedullary hematopoiesis. The clinical significance in indications other than β-thalassemia where EMH masses are considered as part of the underlying disease remains to be proven.

Subject Disposition

The TD MDS Pool included 441 subjects with lower-risk MDS from the pooled studies listed above who received at least 1 dose of luspatercept. Of the 441 total subjects in the TD MDS Pool, the largest cohort was from pivotal study ACE-536-MDS-002 (182 luspatercept-treated subjects). A total of 255 subjects received at least 1 dose of comparator drug (179 subjects) or placebo (76 subjects). At the time of the data cut-off, treatment was ongoing for 24.0% of subjects in the TD MDS Pool, with lack of efficacy being the most common reason for discontinuing treatment both in the pooled population and across studies.

In those studies with a comparator arm (ACE-536-MDS-001 and ACE-536-MDS-002), discontinuation of treatment due to lack of efficacy was observed less frequently in the luspatercept arm than in the comparator arm. In the TD MDS Pool, 51.2% of subjects had discontinued from the study, with death

being the most common reason for study discontinuation both in the pooled population and across studies.

Table 56: TD MDS Subject Disposition - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N=182 N (%)	Epoetin alfa N=179 N (%)	Luspatercept N=153 N (%)	Placebo N=76 N (%)	Luspatercept TD N=80 N (%)	Luspatercept N=26 N (%)	Luspatercept N=441 N (%)
Analysis Population							
Safety Population	182 (100.0)	179 (100.0)	153 (100.0)	76 (100.0)	80 (100.0)	26 (100.0)	441 (100.0)
Completed Treatment[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	23 (28.8)	0 (0.0)	23 (5.2)
Treatment Ongoing	78 (42.9)	53 (29.6)	11 (7.2)	0 (0.0)	1 (1.3)	16 (61.5)	106 (24.0)
Subjects Discontinued Treatment	104 (57.1)	126 (70.4)	142 (92.8)	76 (100.0)	56 (70.0)	10 (38.5)	312 (70.7)
Adverse Event	9 (4.9)	5 (2.8)	18 (11.8)	4 (5.3)	0 (0.0)	2 (7.7)	29 (6.6)
Death	14 (7.7)	13 (7.3)	2 (1.3)	0 (0.0)	5 (6.3)	0 (0.0)	21 (4.8)
Lack of Efficacy	41 (22.5)	68 (38.0)	74 (48.4)	50 (65.8)	8 (10.0)	2 (7.7)	125 (28.3)
Lost to Follow-up	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Physician Decision	5 (2.7)	5 (2.8)	2 (1.3)	0 (0.0)	9 (11.3)	0 (0.0)	16 (3.6)
Presence of ≥ 1% Blasts in Peripheral Blood	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	2 (0.5)
Progressive Disease	9 (4.9)	7 (3.9)	9 (5.9)	2 (2.6)	5 (6.3)	1 (3.8)	24 (5.4)
Protocol Deviation	1 (0.5)	0 (0.0)	2 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	4 (0.9)
Study Terminated by Sponsor	1 (0.5)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Transition to Commercially Available Treatment	0 (0.0)	0 (0.0)	3 (2.0)	0 (0.0)	2 (2.5)	0 (0.0)	5 (1.1)
Withdrawal by Subject	16 (8.8)	18 (10.1)	19 (12.4)	10 (13.2)	10 (12.5)	1 (3.8)	46 (10.4)
Other	8 (4.4)	7 (3.9)	13 (8.5)	10 (13.2)	14 (17.5)	4 (15.4)	39 (8.8)
Completed Study	0 (0.0)	0 (0.0)	16 (10.5)	27 (35.5)	42 (52.5)	0 (0.0)	58 (13.2)
Study Ongoing	115 (63.2)	104 (58.1)	19 (12.4)	0 (0.0)	1 (1.3)	22 (84.6)	157 (35.6)
Subjects Discontinued Study	67 (36.8)	75 (41.9)	118 (77.1)	49 (64.5)	37 (46.3)	4 (15.4)	226 (51.2)
Adverse Event	0 (0.0)	1 (0.6)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Death	39 (21.4)	38 (21.2)	57 (37.3)	27 (35.5)	11 (13.8)	0 (0.0)	107 (24.3)
Lost to Follow-up	0 (0.0)	2 (1.1)	5 (3.3)	1 (1.3)	2 (2.5)	1 (3.8)	8 (1.8)
Physician Decision	3 (1.6)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)
Study Terminated by Sponsor	6 (3.3)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.4)
Transition to Commercially Available Treatment	0 (0.0)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Subject	17 (9.3)	23 (12.8)	40 (26.1)	14 (18.4)	10 (12.5)	1 (3.8)	68 (15.4)
Other	2 (1.1)	3 (1.7)	15 (9.8)	7 (9.2)	14 (17.5)	2 (7.7)	33 (7.5)

Source: Appendix 1 Table 14.1.1

[a] Includes data collected in the Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

[b] Completed treatment only applies to ACE-536-03/05 subjects.

Patient exposure

Overall Extent of Exposure

Treatment duration was longer with luspatercept when compared to active or placebo controls, demonstrating tolerability. In the TD MDS Pool, numerical differences in treatment duration and number of luspatercept doses were noted according to baseline transfusion burden (higher in subjects with

baseline transfusion burden < 4 units), ring sideroblast status (higher in RS+ subjects), baseline serum EPO levels (higher in subjects with baseline serum EPO ≤ 200 U/L), and SFB1 mutational status (higher in SFB1-mutated subjects).

Study Therapy

Study drug exposure was approximately 1.5 to 2 times longer in the luspatercept arms in ACE-536-MDS-002 and ACE-536-MDS-001 compared with the control arms. The median duration of treatment with luspatercept in ACE-536-MDS-002 was 51.64 (3.0, 195.6) weeks, compared with 37.00 (1.0, 201.7) weeks for epoetin alfa. A similar proportion of subjects in the luspatercept and epoetin alfa arms completed 24 weeks of treatment: 89% and 79.3%, respectively. In ACE-536-MDS-001, median duration of treatment with luspatercept was 50.86 (5.9, 332.9) weeks, compared with 24.00 (9.0, 103.0) weeks for placebo. The total exposure for the TD MDS Pool was 613.47 PY, and the median duration of treatment was 46.43 (0.7, 417.3) weeks. Most subjects in TD Pool were luspatercept dose-escalated at least once on study.

Table 57: Summary of Exposure - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002[a]		Supportive Study ACE-536-MDS-001[b]		Supportive Studies A536-03/05[b]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N =182	Epoetin alfa N = 179	Luspatercept N = 153	Placebo N = 76	Luspatercept TD N = 80	Luspatercept N = 26	Luspatercept N = 441
Total Person Year[c]	230.80	178.15	279.30	46.21	90.36	13.02	613.47
Treatment Duration (weeks)							
Mean	66.17	51.93	95.25	31.73	58.93	26.12	72.59
SD	45.426	43.550	94.853	18.184	80.064	24.394	74.154
Median	51.64	37.00	50.86	24.00	27.14	17.07	46.43
Min, Max	3.0, 195.6	1.0, 201.7	5.9, 332.9	9.0, 103.0	3.0, 417.3	0.7, 88.1	0.7, 417.3
Number of Doses Received							
Mean	20.6	46.6	30.1	10.5	17.7	8.7	22.7
SD	14.33	39.35	29.82	5.94	23.28	8.12	23.01
Median	16.5	33.0	17.0	8.0	9.0	6.0	14.0
Min, Max	1, 60	1, 194	2, 108	3, 34	1, 137	1, 29	1, 137
Number of Doses Received Category (%)							
1 - 4	13 (7.1)	12 (6.7)	8 (5.2)	3 (3.9)	14 (17.5)	11 (42.3)	46 (10.4)
5 - 8	18 (9.9)	6 (3.4)	48 (31.4)	47 (61.8)	25 (31.3)	8 (30.8)	99 (22.4)
9 - 16	60 (33.0)	9 (5.0)	19 (12.4)	17 (22.4)	18 (22.5)	2 (7.7)	99 (22.4)
17 - 24	32 (17.6)	30 (16.8)	16 (10.5)	5 (6.6)	7 (8.8)	3 (11.5)	58 (13.2)
25 - 36	29 (15.9)	40 (22.3)	18 (11.8)	4 (5.3)	3 (3.8)	2 (7.7)	52 (11.8)
> 36	30 (16.5)	82 (45.8)	44 (28.8)	0 (0.0)	13 (16.3)	0 (0.0)	87 (19.7)

Maximum Dose Level Received (%)							
Luspatercept							
0.125 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	2 (0.5)
0.25 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.2)
0.5 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	2 (0.5)
0.75 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (5.0)	0 (0.0)	4 (0.9)
1.0 mg/kg	43 (23.6)	0 (0.0)	22 (14.4)	5 (6.6)	18 (22.5)	9 (34.6)	92 (20.9)
1.33 mg/kg	26 (14.3)	0 (0.0)	24 (15.7)	7 (9.2)	14 (17.5)	6 (23.1)	70 (15.9)
1.75 mg/kg	113 (62.1)	0 (0.0)	107 (69.9)	64 (84.2)	39 (48.8)	11 (42.3)	270 (61.2)
Epoetin Alfa							
450 IU/kg	0 (0.0)	35 (19.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
787.5 IU/kg	0 (0.0)	28 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1050 IU/kg	0 (0.0)	116 (64.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Average Number of Days per Dose (days)[d]							
Mean	23.05	8.44	22.09	21.16	22.28	20.60	22.43
SD	6.382	6.522	2.825	0.665	3.404	3.570	4.767
Median	21.22	7.03	21.17	21.00	21.12	21.00	21.15
Min, Max	14.0, 67.0	5.5, 70.8	20.2, 42.8	19.6, 23.9	20.7, 41.7	5.0, 25.5	5.0, 67.0

Source: Appendix 1 Table 14.3.1

[a] Dosing frequency was Q3W for luspatercept and QW for epoetin alfa.

[b] Includes data collected in the Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

[c] Total person-years is defined as the sum of treatment duration in years for all subjects in the treatment arm.

[d] The average number of days per dose is defined as: [(the treatment end date) - (the date of the first dose of IP) + 1] / (the total number of doses received).

Exposure by Subgroup

In the TD MDS Pool, differences in exposure by baseline transfusion burden, ring sideroblast status, baseline serum EPO levels, and baseline SF3B1 mutational status were observed. Age: No differences in exposure by age were noted in the TD MDS Pool. Sex: No differences in exposure by sex were noted in the TD MDS Pool. Race: The difference between the number of White (n=333) and non-White (n=49) subjects limits the interpretability of potential differences in exposure by race. Baseline Transfusion Burden: Median treatment duration and median number of luspatercept doses were greater in subjects with baseline transfusion burden < 4 units in the TD MDS Pool, in the luspatercept arms in ACE-536-MDS-001 and ACE-536-MDS-002, and in supportive studies A536-03/05 compared with subjects with baseline transfusion burden ≥ 4 units. Ring Sideroblasts status: Median treatment duration and median number of luspatercept doses were greater in ring sideroblast-positive subjects in the TD MDS Pool, ACE-536-MDS-002, and in supportive studies A536-03/05 compared with ring sideroblast-negative subjects. Baseline Serum EPO: Median treatment duration and median number of luspatercept doses were greater in subjects with baseline serum EPO ≤ 200 U/L in the TD MDS Pool, ACE-536-MDS-001, ACE-536-MDS-002, and in supportive studies A536-03/05 compared with subjects with baseline serum EPO > 200 U/L. Baseline eGFR: No differences in exposure by baseline eGFR were noted in the TD MDS Pool. Baseline SF3B1 Mutational Status: Median treatment duration and median number of luspatercept doses were greater in SF3B1 mutated subjects in the TD MDS Pool, in the luspatercept arms in ACE-536-MDS-001 and ACE-536-MDS-002, and in supportive studies A536-03/05 compared with SF3B1 nonmutated subjects. Geographic Region: The difference between the number of non-US (n=408) and US (n=33) subjects limits the interpretability of potential differences in exposure by region.

Demographics and Other Characteristics of Study Population

Baseline characteristics in all studies were representative of the target/disease population (adult patients with anemia due to very low, low, and intermediate-risk MDS or MDS/MPN-RS-T who required RBC transfusions). In studies with active (ACE-536-MDS-002) or placebo (ACE-536-MDS-001) comparator arms, demographics and baseline disease characteristics were generally balanced between arms. In the TD MDS Pool, baseline demographics and baseline laboratory values were similar to those seen in the pivotal study ACE-536-MDS-002.

Demographics and Baseline Characteristics

Baseline demographics were similar across studies and generally balanced across treatment arms in ACE-536-MDS-002 and ACE-536-MDS-001. Most subjects in the TD MDS Pool were male (60.5%), White (75.5%) and enrolled from non-US countries (92.5%). The median age of the TD MDS Pool was 72.0 (27.0, 95.0) years.

Table 58: Subject Demographics - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05 [a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182	Epoetin alfa N = 179	Luspatercept N = 153	Placebo N = 76	Luspatercept TD N = 80	Luspatercept N = 26	Luspatercept N = 441
Age (years)							
Median	74.00	74.00	71.00	72.00	72.00	65.50	72.00
Min, Max	46.0, 93.0	31.0, 91.0	40.0, 95.0	26.0, 91.0	27.0, 90.0	27.0, 79.0	27.0, 95.0
Age Category (%)							
< 65	27 (14.8)	25 (14.0)	29 (19.0)	16 (21.1)	18 (22.5)	11 (42.3)	85 (19.3)
65 - 74	68 (37.4)	65 (36.3)	72 (47.1)	29 (38.2)	35 (43.8)	12 (46.2)	187 (42.4)
≥ 75	87 (47.8)	89 (49.7)	52 (34.0)	31 (40.8)	27 (33.8)	3 (11.5)	169 (38.3)
Gender (%)							
Male	109 (59.9)	90 (50.3)	94 (61.4)	50 (65.8)	50 (62.5)	14 (53.8)	267 (60.5)
Female	73 (40.1)	89 (49.7)	59 (38.6)	26 (34.2)	30 (37.5)	12 (46.2)	174 (39.5)
Region (%)							
US	8 (4.4)	9 (5.0)	25 (16.3)	11 (14.5)	0 (0.0)	0 (0.0)	33 (7.5)
Non-US	174 (95.6)	170 (95.0)	128 (83.7)	65 (85.5)	80 (100.0)	26 (100.0)	408 (92.5)
Ethnicity (%)							
Hispanic or Latino	11 (6.0)	12 (6.7)	3 (2.0)	4 (5.3)	0 (0.0)	0 (0.0)	14 (3.2)
Not Hispanic or Latino	155 (85.2)	154 (86.0)	115 (75.2)	52 (68.4)	70 (87.5)	25 (96.2)	365 (82.8)
Not Reported	16 (8.8)	11 (6.1)	35 (22.9)	20 (26.3)	9 (11.3)	1 (3.8)	61 (13.8)
Unknown	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.2)
Race (%)							
Asian	19 (10.4)	25 (14.0)	0 (0.0)	0 (0.0)	0 (0.0)	26 (100.0)	45 (10.2)
Black or African American	2 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)
White	146 (80.2)	141 (78.8)	107 (69.9)	51 (67.1)	80 (100.0)	0 (0.0)	333 (75.5)
Not Collected or Unknown	15 (8.2)	13 (7.3)	44 (28.8)	24 (31.6)	0 (0.0)	0 (0.0)	59 (13.4)
Other	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.2)
Weight (kg)							
Median	73.00	69.80	76.00	75.00	77.75	60.10	74.00
Min, Max	33.0, 122.8	32.0, 127.0	46.0, 124.2	51.0, 153.0	48.0, 118.2	41.7, 79.0	33.0, 124.2
Body Mass Index (kg/m^2)							
Median	25.49	25.22	26.23	27.07	26.56	22.75	25.72
Min, Max	14.8, 41.9	15.3, 43.5	17.1, 40.4	19.6, 48.3	18.6, 35.4	16.4, 27.4	14.8, 41.9
Body Mass Index Category (kg/m^2) (%)							
< 18.5	5 (2.7)	2 (1.1)	2 (1.3)	0 (0.0)	0 (0.0)	2 (7.7)	9 (2.0)
18.5 - < 25	72 (39.6)	82 (45.8)	53 (34.6)	27 (35.5)	29 (36.3)	18 (69.2)	172 (39.0)
25 - < 30	66 (36.3)	62 (34.6)	68 (44.4)	29 (38.2)	35 (43.8)	6 (23.1)	175 (39.7)
≥ 30	33 (18.1)	33 (18.4)	29 (19.0)	19 (25.0)	15 (18.8)	0 (0.0)	77 (17.5)
Missing	6 (3.3)	0 (0.0)	1 (0.7)	1 (1.3)	1 (1.3)	0 (0.0)	8 (1.8)

Source: Appendix 1 Table 14.1.2

[a] Includes data collected in Study LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05

Baseline Disease Characteristics

For entry into ACE-536-MDS-002, subjects must have had anemia due to IPSS-R very low, low, or intermediate risk MDS been ESA-naive, and required RBC transfusions (i.e. 2 to 6 pRBC units in the 8 weeks before randomization). The majority of subjects were RS+. Baseline disease characteristics and baseline laboratory values were generally balanced across arms in ACE-536-MDS-002.

Subjects in Study ACE-536-MDS-001 were all RS+ (per protocol). Because subjects were required to have failed or been refractory to an ESA prior to study entry, they had a longer time since their original MDS diagnosis than subjects in ACE-536-MDS-002 (approximately 75% of subjects had an MDS diagnosis of > 2 years before entering the ACE-536-MDS-001 study) and a higher transfusion burden at baseline.

Baseline disease characteristics and baseline laboratory values were generally balanced across arms in ACE-536-MDS-001. Baseline disease characteristics of subjects in ACE-536-MDS-004 were similar to those in ACE-536-MDS-001, as subjects were all RS+ and were required to have failed or been refractory to an ESA prior to study entry. Subjects included in the TD MDS Pool had diagnoses of low-to intermediate risk (A536-03/05) or very low, low, or intermediate risk MDS.

However, in the Phase 2 A536-03/05 study, lower-risk MDS was defined by the IPSS categorization (low and intermediate-1 IPSS), and thus included a more heterogeneous population according to IPSS-R risk (very low to very high risk IPSS-R) than the Phase 3 studies ACE-536-MDS-001, ACE-536-MDS-002, and the Phase 2 study ACE-536-MDS-004 (very low to intermediate IPSS-R). A536-03/05 included 7 subjects with high-risk IPSS-R and 1 subject with very high-risk IPSS-R. The majority of subjects were RS+ (81.6% in the TD MDS Pool). Median time from the original MDS diagnosis in the TD MDS Pool was 23.62 (-0.4, 420.6) months and subjects had a median transfusion history of 4.0 (1.0, 16.0) units prior to study start.

Table 59: Baseline Disease Characteristics - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182	Epoetin alfa N = 179	Luspatercept N = 153	Placebo N = 76	Luspatercept TD N = 80	Luspatercept N = 26	Luspatercept N = 441
Baseline Transfusion Burden (units)[b]							
Median	3.0	3.0	6.0	6.0	4.0	4.0	4.0
Min, Max	1, 10	0, 14	2, 16	0, 16	2, 16	2, 14	1, 16
Baseline Transfusion Burden Category (units)[b]							
< 4	118 (64.8)	109 (60.9)	28 (18.3)	11 (14.5)	29 (36.3)	9 (34.6)	184 (41.7)
≥ 4	64 (35.2)	70 (39.1)	125 (81.7)	65 (85.5)	51 (63.8)	17 (65.4)	257 (58.3)
Ring Sideroblasts Status (%)							
RS +	133 (73.1)	128 (71.5)	153 (100.0)	76 (100.0)	48 (60.0)	26 (100.0)	360 (81.6)
RS -	49 (26.9)	50 (27.9)	0 (0.0)	0 (0.0)	30 (37.5)	0 (0.0)	79 (17.9)
Missing	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	2 (0.5)
IPSS-R Risk Classification (%)							
Very low	16 (8.8)	17 (9.5)	18 (11.8)	6 (7.9)	5 (6.3)	0 (0.0)	39 (8.8)
Low	130 (71.4)	131 (73.2)	109 (71.2)	57 (75.0)	38 (47.5)	17 (65.4)	294 (66.7)
Intermediate	34 (18.7)	29 (16.2)	25 (16.3)	13 (17.1)	29 (36.3)	9 (34.6)	97 (22.0)
High	1 (0.5)[c]	0 (0.0)	1 (0.7)	0 (0.0)	7 (8.8)	0 (0.0)	9 (2.0)
Very High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.2)
Missing	1 (0.5)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
ECOG Performance (%)							
0	74 (40.7)	69 (38.5)	54 (35.3)	33 (43.4)	37 (46.3)	8 (30.8)	173 (39.2)
1	104 (57.1)	92 (51.4)	91 (59.5)	32 (42.1)	43 (53.8)	18 (69.2)	256 (58.0)
2	4 (2.2)	18 (10.1)	8 (5.2)	11 (14.5)	0 (0.0)	0 (0.0)	12 (2.7)
Time Since Original MDS Diagnosis (months)							
n	182	179	153	76	80	26	441
Median	7.97	4.93	44.02	36.07	23.85	27.32	23.62
Min, Max	-0.4, 243.1	-0.3, 171.6	2.8, 420.6	4.4, 193.3	0.2, 162.4	1.4, 178.0	-0.4, 420.6
Time Since Original MDS Diagnosis Category (years) (%)							
≤ 1	103 (56.6)	121 (67.6)	14 (9.2)	10 (13.2)	22 (27.5)	9 (34.6)	148 (33.6)
> 1 - ≤ 2	26 (14.3)	21 (11.7)	26 (17.0)	9 (11.8)	18 (22.5)	4 (15.4)	74 (16.8)
> 2 - ≤ 5	31 (17.0)	22 (12.3)	62 (40.5)	34 (44.7)	28 (35.0)	11 (42.3)	132 (29.9)
> 5	22 (12.1)	15 (8.4)	51 (33.3)	23 (30.3)	12 (15.0)	2 (7.7)	87 (19.7)
SF3B1 Mutation (%)							
Mutated	114 (62.6)	100 (55.9)	141 (92.2)	65 (85.5)	35 (43.8)	22 (84.6)	312 (70.7)
Non-mutated	65 (35.7)	71 (39.7)	12 (7.8)	10 (13.2)	35 (43.8)	0 (0.0)	112 (25.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (12.5)	0 (0.0)	10 (2.3)
Missing	3 (1.6)	8 (4.5)	0 (0.0)	1 (1.3)	0 (0.0)	4 (15.4)	7 (1.6)

Source: Appendix 1 Table 14.1.2

[a] Includes data collected in Study LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

[b] Baseline transfusion burden is defined as the number of RBC transfusion per 8-week period on or prior to first dose date.

[c] At screening, the central pathology lab confirmed MDS diagnosis with the IPSS-R risk score as intermediate for 1 subject. At the 24-week MDS disease assessment, bone marrow was collected for this subject. The central lab provided the report on IPSS-R risk score as high and stated that high risk score should have been provided at screening as well.

Table 60: Baseline Laboratory Values - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182	Epoetin alfa N = 179	Luspatercept N = 153	Placebo N = 76	Luspatercept N = 80	Luspatercept N = 26	Luspatercept N = 441
Platelets (10^9/L)							
n	182	179	153	76	80	26	441
Median	253.50	257.00	256.00	245.00	181.00	155.00	239.00
Min, Max	38.0, 987.0	47.0, 937.0	59.0, 930.0	60.0, 741.0	31.0, 1792.0	56.0, 891.0	31.0, 1792.0
Platelets Category (10^9/L) (%)							
< 100	21 (11.5)	18 (10.1)	5 (3.3)	5 (6.6)	18 (22.5)	6 (23.1)	50 (11.3)
100 - 450	151 (83.0)	146 (81.6)	133 (86.9)	67 (88.2)	56 (70.0)	18 (69.2)	358 (81.2)
> 450	10 (5.5)	15 (8.4)	15 (9.8)	4 (5.3)	6 (7.5)	2 (7.7)	33 (7.5)
Absolute Neutrophil Count Category (10^9/L) (%)							
< 0.5	1 (0.5)	0 (0.0)	1 (0.7)	0 (0.0)	7 (8.8)	1 (3.8)	10 (2.3)
0.5 to < 1.0	14 (7.7)	16 (8.9)	14 (9.2)	10 (13.2)	12 (15.0)	4 (15.4)	44 (10.0)
≥ 1.0	167 (91.8)	163 (91.1)	138 (90.2)	66 (86.8)	61 (76.3)	21 (80.8)	387 (87.8)
Absolute Neutrophil Count (10^9/L)[b]							
n	182	179	153	76	80	26	441
Median	2.41	2.31	2.33	2.18	1.82	1.64	2.17
Min, Max	0.4, 9.1	0.5, 13.3	0.3, 15.6	0.6, 12.0	0.1, 8.4	0.5, 7.2	0.1, 15.6
Hemoglobin (g/dL)[c]							
n	182	179	153	76	80	26	441
Median	8.90	8.90	8.80	8.90	8.60	6.35	8.70
Min, Max	5.1, 11.4	6.3, 11.2	6.4, 12.1	6.1, 10.6	5.2, 11.9	3.4, 10.1	3.4, 12.1
Hemoglobin Category (g/dL) (%)							
< 8	36 (19.8)	29 (16.2)	35 (22.9)	16 (21.1)	23 (28.8)	20 (76.9)	114 (25.9)
≥ 8	146 (80.2)	150 (83.8)	118 (77.1)	60 (78.9)	57 (71.3)	6 (23.1)	327 (74.1)
Serum EPO (U/L)							
N	182	179	153	76	80	13	428
Median	77.25	84.87	117.38	107.02	214.80	486.29	109.74
Min. Max	7.8, 495.8	4.6, 462.5	10.4, 2454.3	14.7, 1685.6	0.3, 2433.0	47.4, 3074.6	0.3, 3074.6
Serum EPO (U/L) Category (%)							
0 - < 100	103 (56.6)	106 (59.2)	69 (45.1)	34 (44.7)	28 (35.0)	1 (3.8)	201 (45.6)
100 - 200	42 (23.1)	37 (20.7)	34 (22.2)	21 (27.6)	11 (13.8)	3 (11.5)	90 (20.4)
> 200	37 (20.3)	36 (20.1)	50 (32.7)	21 (27.6)	41 (51.3)	22 (84.6)	150 (34.0)
eGFR (mL/min/1.73 m^2)							
N	182	179	129	63	80	26	417
Median	72.75	72.40	75.20	73.00	70.27	94.25	74.50
Min. Max	29.5, 142.0	28.8, 164.4	29.0, 157.8	45.5, 162.9	32.0, 116.2	57.8, 151.5	29.0, 157.8
eGFR Category (mL/min/1.73 m^2) (%)							
< 60	48 (26.4)	48 (26.8)	32 (20.9)	13 (17.1)	22 (27.5)	1 (3.8)	103 (23.4)
60 - 90	84 (46.2)	77 (43.0)	54 (35.3)	33 (43.4)	44 (55.0)	9 (34.6)	191 (43.3)
> 90	50 (27.5)	54 (30.2)	43 (28.1)	17 (22.4)	14 (17.5)	16 (61.5)	123 (27.9)
Missing	0 (0.0)	0 (0.0)	24 (15.7)	13 (17.1)	0 (0.0)	0 (0.0)	24 (5.4)

[a] Includes data collected in Study LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

[b] Absolute Neutrophils Count is derived using segmented and band Neutrophils for MDS-001, MDS-002 and MDS-004 and using Neutrophils only for A536-03/05.

[c] Baseline value is defined as the last value measured on or before the date and time of the first dose of IP.

Source: Appendix 1 Table 14.1.2

Medical History

The reported medical history in the TD MDS Pool was consistent with the disease population, the age of the patient population, and the known disease comorbidities. Based on published data, the most frequent age- and disease-related comorbidities are cardiac diseases, followed by solid tumors, diabetes and pulmonary, renal, and hepatic diseases.

The most frequently reported medical history events in the TD MDS Pool (≥ 30%) were in the SOCs of Metabolism and Nutrition Disorders (56.0%), Vascular Disorders (54.4%), Musculoskeletal and Connective Tissue Disorders (43.5%), Cardiac Disorders (39.7%), Gastrointestinal Disorders (39.0%), Respiratory, Thoracic and Mediastinal Disorders (32.9%). Overall, the most frequently reported PT was hypertension, which occurred in 45.8% of subjects in the TD MDS Pool. Other medical history PTs occurring in >10% of subjects in the TD MDS Pool included Type 2 diabetes mellitus (15.9%), benign prostatic hyperplasia (14.1%), anemia (11.8%), atrial fibrillation (11.1%), fatigue (11.3%), iron overload (11.6%), gastroesophageal reflux disease (10.2%), and hypothyroidism (10.2%).

Prior and Concomitant Medications

All subjects had a transfusion history of RBCs during the 16 weeks prior to randomization, most commonly for the treatment of anemia. Per protocol, subjects in ACE- 536-MDS-001 and ACE-536-MDS-004 must have received a prior ESA to be eligible for the study.

In the TD MDS Pool, the most frequently reported class of medications (> 40% in the TD MDS Pool) were antibacterials (51.2%), analgesics (50.8%), drugs for acid-related disorders (50.3%), and antithrombotic agents (45.8%). The most common concomitant medications (PTs) used by >10% of subjects in the TD MDS Pool included paracetamol (36.5%), deferasirox (30.2%), tozinameran (24.3%), furosemide (25.1%), acetylsalicylic acid (22%), folic acid (19.0%), colecalciferol (15.0%), allopurinol (15.0%), omepramole (14.3%), pantoprazole (14.3%), bisoprolol (11.3%), metformin (11.1%), ciprofloxacin (10.9%), amoxicillin (10.7%), ibuprofen (10.7%), ramipril (10.4%), and pantoprazole sodium sesquihydrate (10.0%).

Adverse events

The safety profile of luspatercept observed in the TD MDS pool, pivotal ACE-536-MDS-002 study, and supportive studies was similar overall and consistent with the known safety profile of luspatercept in the currently approved MDS population.

No new safety concerns or new types of clinically important events were identified with luspatercept.

Table 61: Overview of Treatment-Emergent Adverse Events - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182 n (%)	Epoetin alfa N = 179 n (%)	Luspatercept N = 153 n (%)	Placebo N = 76 n (%)	Luspatercept TD N = 80 n (%)	Luspatercept N = 26 n (%)	Luspatercept N = 441 n (%)
Subjects with at Least 1 TEAE	178 (97.8)	165 (92.2)	151 (98.7)	70 (92.1)	74 (92.5)	22 (84.6)	425 (96.4)
Subjects with at Least 1 Treatment-Related TEAE	61 (33.5)	36 (20.1)	72 (47.1)	26 (34.2)	33 (41.3)	11 (42.3)	177 (40.1)
Subjects with at Least 1 Serious TEAE	82 (45.1)	71 (39.7)	72 (47.1)	23 (30.3)	42 (52.5)	6 (23.1)	202 (45.8)
Subjects with at Least 1 Treatment-Related Serious TEAE	1 (0.5)	3 (1.7)	7 (4.6)	0 (0.0)	3 (3.8)	2 (7.7)	13 (2.9)
Subjects with at Least 1 TEAE with CTCAE Grade 3 or 4	107 (58.8)	88 (49.2)	88 (57.5)	34 (44.7)	46 (57.5)	6 (23.1)	247 (56.0)
Subjects with at Least 1 Treatment-Related TEAE with CTCAE Grade 3 or 4	14 (7.7)	4 (2.2)	14 (9.2)	3 (3.9)	7 (8.8)	1 (3.8)	36 (8.2)
Subjects with at Least 1 TEAE with CTCAE Grade 5	15 (8.2)	14 (7.8)	10 (6.5)	4 (5.3)	5 (6.3)	0 (0.0)	30 (6.8)
Subjects with at Least 1 Treatment-Related TEAE with CTCAE Grade 5	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Subjects with at Least 1 TEAE Leading to Dose Interruption	61 (33.5)	51 (28.5)	42 (27.5)	4 (5.3)	17 (21.3)	5 (19.2)	125 (28.3)
Subjects with at Least 1 TEAE Leading to Dose Reduction	7 (3.8)	6 (3.4)	9 (5.9)	0 (0.0)	2 (2.5)	0 (0.0)	18 (4.1)
Subjects with at Least 1 TEAE Leading to Permanent Study Drug Discontinuation	21 (11.5)	13 (7.3)	24 (15.7)	6 (7.9)	16 (20.0)	2 (7.7)	63 (14.3)

MedDRA Version 25.1 is used for coding.

CTCAE version 4.03 is used for A536-03/05, ACE-536-MDS-001 and ACE-536-MDS-002; CTCAE version 5.0 is used for ACE-536-MDS-004 and LTFU-001.

Treatment-Emergent Adverse Events are defined as any new AE or AE that worsened in severity on or after the first dose of investigational product (IP) until 42 days after the last dose of IP, as well as serious AEs made known to the Investigator at any time thereafter that are suspected to be related to the IP.

Source: Appendix 1 Table 14.3.2

[a] Includes data collected in Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Table 62: Frequently Reported (≥ 10% of Subjects in the TD MDS Pool) TEAEs by SOC and PT - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182	Epoetin alfa N = 179	Luspatercept N = 153	Placebo N = 76	Luspatercept TD N = 80	Luspatercept N = 26	Luspatercept N = 441
System Organ Class	n (%),	n (%),	n (%),	n (%),	n (%),	n (%),	n (%), 95% CI
Preferred Term	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY
Subjects with at least 1 specific event	178 (97.8) 608	165 (92.2) 413.5	151 (98.7) 900.6	70 (92.1) 879.2	74 (92.5) 566.9	22 (84.6) 598.3	425 (96.4) (94.2, 97.9) 677
General Disorders and Administration Site Conditions	97 (53.3) 67.6	77 (43.0) 64.3	125 (81.7) 142.9	39 (51.3) 140.5	43 (53.8) 83.4	7 (26.9) 64.7	272 (61.7) (57.0, 66.2) 92.7
Fatigue	32 (17.6) 15.7	13 (7.3) 7.7	47 (30.7) 22.1	11 (14.5) 27.1	20 (25.0) 24.1	0 (0.0) 0	99 (22.4) (18.6, 26.6) 19.3
Oedema peripheral	26 (14.3) 12.5	14 (7.8) 8.3	40 (26.1) 17.6	13 (17.1) 32	12 (15.0) 15.3	3 (11.5) 24.5	81 (18.4) (14.9, 22.3) 15.4
Asthenia	25 (13.7) 12.1	29 (16.2) 19	41 (26.8) 18.8	9 (11.8) 21.4	4 (5.0) 4.7	1 (3.8) 8	71 (16.1) (12.8, 19.9) 13.6
Infections and Infestations	96 (52.7) 63.9	83 (46.4) 66.9	92 (60.1) 81.4	31 (40.8) 90.6	49 (61.3) 120.8	14 (53.8) 151.5	251 (56.9) (52.1, 61.6) 80.2
Urinary tract infection	15 (8.2) 7	9 (5.0) 5.2	24 (15.7) 10.3	4 (5.3) 8.9	11 (13.8) 13.4	1 (3.8) 7.9	51 (11.6) (8.7, 14.9) 9.4
Nasopharyngitis	8 (4.4) 3.5	2 (1.1) 1.1	18 (11.8) 7.2	4 (5.3) 9	18 (22.5) 26.2	0 (0.0) 0	44 (10.0) (7.3, 13.2) 7.9
Gastrointestinal Disorders	83 (45.6) 53.5	72 (40.2) 58.2	104 (68.0) 91.3	26 (34.2) 75.9	32 (40.0) 53.9	6 (23.1) 65	225 (51.0) (46.2, 55.8) 66.6
Diarrhoea	32 (17.6) 16	25 (14.0) 15.7	47 (30.7) 23.5	8 (10.5) 18.4	13 (16.3) 17	3 (11.5) 29	95 (21.5) (17.8, 25.7) 19.5
Nausea	26 (14.3) 12.5	15 (8.4) 9	36 (23.5) 17.1	6 (7.9) 13.7	6 (7.5) 7.1	0 (0.0) 0	68 (15.4) (12.2, 19.1) 13.2
Injury, poisoning, and procedural complications	44 (24.2) 22.4	37 (20.7) 24.6	59 (38.6) 29.5	18 (23.7) 43.5	18 (22.5) 26.2	2 (7.7) 16.4	123 (27.9) (23.8, 32.3) 25.8
Fall	14 (7.7) 6.3	12 (6.7) 7.1	29 (19.0) 12.1	10 (13.2) 22.8	5 (6.3) 5.9	0 (0.0) 0	48 (10.9) (8.1, 14.2) 8.6
Musculoskeletal and Connective Tissue Disorders	68 (37.4) 44.2	67 (37.4) 57.5	80 (52.3) 63.1	28 (36.8) 86	36 (45.0) 67	4 (15.4) 33.4	188 (42.6) (38.0, 47.4) 54.3
Back pain	22 (12.1) 10.5	16 (8.9) 9.9	38 (24.8) 16.8	5 (6.6) 11.7	7 (8.8) 8.7	2 (7.7) 15.7	69 (15.6) (12.4, 19.4) 13
Nervous System Disorders	60 (33.0) 35.8	45 (25.1) 32.7	83 (54.2) 58.9	22 (28.9) 62.3	27 (33.8) 41.9	4 (15.4) 33	174 (39.5) (34.9, 44.2) 45.2
Dizziness	23 (12.6) 11.1	16 (8.9) 10.2	36 (23.5) 16.6	4 (5.3) 8.9	5 (6.3) 5.9	1 (3.8) 7.8	65 (14.7) (11.6, 18.4) 12.4

Headache	20 (11.0) 9.4	15 (8.4) 9.3	28 (18.3) 12.1	5 (6.6) 11.6	10 (12.5) 12.7	2 (7.7) 16.1	60 (13.6) (10.5, 17.2) 11.2
Respiratory, Thoracic and Mediastinal Disorders	61 (33.5) 33.4	43 (24.0) 29	77 (50.3) 51.8	28 (36.8) 80	29 (36.3) 55.1	2 (7.7) 16.4	169 (38.3) (33.8, 43.0) 42.7
Dyspnoea	26 (14.3) 12.4	14 (7.8) 8.3	31 (20.3) 13	5 (6.6) 11.3	13 (16.3) 16.4	0 (0.0) 0	70 (15.9) (12.6, 19.6) 12.9
Cough	14 (7.7) 6.3	9 (5.0) 5.3	36 (23.5) 17	10 (13.2) 24.9	9 (11.3) 12.9	0 (0.0) 0	59 (13.4) (10.3, 16.9) 11.4
Vascular disorders	48 (26.4) 25.8	37 (20.7) 24.6	47 (30.7) 21	11 (14.5) 27.3	27 (33.8) 43.8	1 (3.8) 7.8	123 (27.9) (23.8, 32.3) 25.4
Hypertension	27 (14.8) 13.3	16 (8.9) 9.8	20 (13.1) 8	6 (7.9) 14	16 (20.0) 22.2	1 (3.8) 7.8	64 (14.5) (11.4, 18.2) 11.9
Blood and Lymphatic System Disorders	41 (22.5) 20.5	38 (21.2) 25.9	42 (27.5) 19.7	14 (18.4) 35.1	19 (23.8) 26.6	2 (7.7) 15.7	104 (23.6) (19.7, 27.8) 20.9
Anaemia	22 (12.1) 10.2	19 (10.6) 12	19 (12.4) 7.5	6 (7.9) 13.6	7 (8.8) 8.6	0 (0.0) 0	48 (10.9) (8.1, 14.2) 8.5

TEAEs are defined as any new AE or AE that worsened in severity on or after the first dose of IP until 42 days after the last dose of IP, as well as serious AEs made known to the Investigator at any time thereafter that are suspected to be related to the IP.

A subject is counted only once for multiple events within each SOC/PT

EAIR/100 PY = 100 * (the number of subjects with the specific TEAE) / the total exposure time (in years) to the event.

MedDRA Version 25.1 is used for coding.

Source: Appendix 1 Table 14.3.2.1

[a] Includes data collected in Study ACE-536- LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Table 63: TEAEs by SOC and PT Occurring ≥ 2.0% Higher in Luspatercept Arm than Control Arm - ACE-536-MDS-001 (Primary Analysis), ACE-536-MDS-002 (Primary Analysis), Phase 3 TD-MDS Pool, and All TD-MDS Pool - Safety Population

SOC PT (*Adverse Drug Reaction*)	ACE-536-MDS-002 (Primary Analysis) Luspatercept N=182	ACE-536-MDS-001 (Primary Analysis) Luspatercept N=153	Phase 3 MDS Pool Luspatercept N=335	TD-MDS Pool Luspatercept N=441
General disorders and administration site conditions	97 (53.3)	109 (71.2)	206 (61.5)	272 (61.7)
Fatigue	***32 (17.6)***	***41 (26.8)***	***73 (21.8)***	***99 (22.4)***
Asthenia	***25 (13.7)***	***31 (20.3)***	***56 (16.7)***	***71 (16.1)***
Oedema peripheral	***26 (14.3)***	***25 (16.3)***	***51 (15.2)***	***81 (18.4)***
Non-cardiac chest pain	9 (4.9)	7 (4.6)	16 (4.8)	18 (4.1)
Death	4 (2.2)	0	4 (1.2	4 (0.9)
Gait disturbance	2 (1.1)	3 (2.0)	5 (1.5)	6 (1.4)
Injection site erythema	***2 (1.1)***	***3 (2.0)***	***5 (1.5)***	***9 (2.0)***
Injection site pain	***2 (1.1)***	***3 (2.0)***	***5 (1.5)***	***8 (1.8)***
Injection site pruritus	***1 (0.5)***	***3 (2.0)***	***4 (1.19***	***4 (0.9)***
Infections and infestations	96 (52.7)	82 (53.6)	178 (53.1)	251 (56.9)
Bronchitis	***4 (2.2)***	***17 (11.1)***	***21 (6.3)***	***34 (7.7)***
Urinary tract infection	***15 (8.2)***	***17 (11.1)***	***32 (9.6)***	***51 (11.6)***
Upper respiratory tract infection	***8 (4.4)***	***15 (9.8)***	***23 (6.9***	***35 (7.9)***
Viral upper respiratory tract infection	***1 (0.5)***	***12 (7.8)***	***13 (3.9)***	***2 (0.5)***
Influenza	***5 (2.7)***	***10 (6.5)***	***15 (4.5)***	***21 (4.8)***
Nasopharyngitis	8 (4.4)	1 (0.7)	9 (2.7)	44 (10.0)

Sinusitis	2 (1.1)	5 (3.3)	7 (2.1)	12 (2.7)
Cystitis	5 (2.7)	5 (3.3)	10 (3.0)	16 (3.6)
Respiratory tract infection	3 (1.6)	4 (2.6)	7 (2.1)	11 (2.5)
Escherichia urinary tract infection	4 (2.2)	1 (0.7)	5 (1.5)	5 (1.1)
Gastroenteritis	4 (2.2)	3 (2.0)	7 (2.1)	10 (2.3)
Gastrointestinal disorders	83 (45.6)	89 (58.2)	172 (51.3)	225 (51.0)
Diarrhoea	***32 (17.6)***	***34 (22.2)***	***66 (19.7)***	***95 (21.5)***
Nausea	***26 (14.3)***	***31 (20.3)***	***57 (17.0)***	***68 (15.4)***
Vomiting	10 (5.5)	10 (6.5)	20 (6.0)	30 (6.8)
Abdominal pain upper	4 (2.2)	7 (4.6)	11 (3.3)	23 (5.2)
Abdominal discomfort	4 (2.2)	4 (2.6)	8 (2.4)	8 (1.8)
Dyspepsia	4 (2.2)	4 (2.6)	8 (2.4)	11 (2.5)
Abdominal distension	1 (0.5)	3 (2.0)	4 (1.2)	7 (1.6)
Dysphagia	1 (0.5)	3 (2.0)	4 (1.2)	8 (1.8)
Gastrooesophageal reflux disease	2 (1.1)	3 (2.0)	5 (1.5)	12 (2.7)
Nervous system disorders	60 (33.0)	72 (47.1)	132 (39.4)	174 (39.5)
Dizziness	***23 (12.6)***	***30 (19.6)***	***53 (15.8)***	***65 (14.7)***
Headache	***20 (11.0)***	***24 (15.7)***	***44 (13.1)***	***60 (13.6)***
Syncope	***8 (4.4)***	***7 (4.6)***	***15 (4.5)***	***21 (4.8)***
Presyncope	3 (1.6)	3 (2.0)	6 (1.8)	10 (2.3)
Lethargy	2 (1.1)	3 (2.0)	5 (1.5)	5 (1.1)
Sciatica	4 (2.2)	3 (2.0)	7 (2.1)	9 (2.0)
Respiratory, thoracic and mediastinal disorders	61 (33.5)	60 (39.2)	121 (36.1)	169 (38.3)
Cough	***14 (7.7)***	***27 (17.6)***	***41 (12.2)***	***59 (13.4)***
Dyspnoea	***26 (14.3)***	***23 (15.0)***	***49 (14.6)***	***70 (15.9)***
Dyspnoea exertional	9 (4.9)	4 (2.6)	13 (3.9)	20 (4.5)
Epistaxis	***11 (6.0)***	***5 (3.3)***	***16 (4.8)***	***34 (7.7)***
Musculoskeletal and connective tissue disorders	68 (37.4)	66 (43.1)	134 (40.0)	188 (42.6)
Back pain	***22 (12.1)***	***29 (19.0)***	***51 (15.20***	***69 (15.6)***
Muscular weakness	9 (4.9)	7 (4.6)	16 (4.8)	12 (2.7)

Metabolism and nutrition disorders	49 (26.9)	55 (35.9)	104 (31.0)	153 (34.7)
Decreased appetite	10 (5.5)	10 (6.5)	20 (6.0)	26 (5.9)
Hyperglycaemia	9 (4.9)	8 (5.2)	17 (5.1)	26 (5.9)
Hyperkalaemia	7 (3.8)	7 (4.6)	14 (4.2)	20 (4.5)
Hyperuricaemia	12 (6.6)	6 (3.9)	18 (5.4)	27 (6.1)
Dehydration	7 (3.8)	1 (0.7)	8 (2.4)	12 (2.7)
Hypomagnesaemia	1 (0.5)	5 (3.3)	6 (1.8)	9 (2.0)
Vitamin D deficiency	3 (1.6)	3 (2.0)	6 (1.8)	10 (2.3)
Cardiac disorders	31 (17.0)	38 (24.8)	69 (20.6)	102 (23.1)
Angina pectoris	3 (1.6)	7 (4.6)	10 (3.0)	14 (3.2)
Tachycardia	1 (0.5)	7 (4.6)	8 (2.4)	13 (2.9)
Atrial fibrillation	7 (3.8)	5 (3.3)	12 (3.6)	19 (4.3)
Atrioventricular block (complete)	1 (0.5)	3 (2.0)	4 (1.2)	1 (0.2)
Vascular disorders	48 (26.4)	34 (22.2)	82 (24.5)	123 (27.9)
Hypertension	***27 (14.8)***	***13 (8.5)***	***40 (11.9)***	***64 (14.5)***
Orthostatic hypotension	3 (1.6)	6 (3.9)	9 (2.7)	10 (2.3)
Hypotension	9 (4.9)	4 (2.6)	13 (3.9)	22 (5.0)
Skin and subcutaneous tissue disorders	28 (15.4)	33 (21.6)	61 (18.2)	97 (22.0)
Pruritus generalised		4 (2.6)	4 (1.2)	23 (5.2)
Hyperhidrosis	4 (2.2)	3 (2.0)	7 (2.1)	7 (1.6)
Investigations	40 (22.0)	31 (20.3)	71 (21.19	102 (23.1)
Alanine aminotransferase increased	***8 (4.4)***	***9 (5.9)***	***17 (5.1)***	***18 (4.1)***
Blood creatinine increased	***10 (5.5)***	***4 (2.6)***	***14 (4.2)***	***16 (3.6)***
Aspartate aminotransferase increased	***7 (3.8)***	***7 (4.6)***	***14 (4.2)***	***17 (3.9)***
Blood alkaline phosphatase increased	5 (2.7)	1 (0.7)	6 (1.8)	6 (1.4)
Blood bilirubin increased	7 (3.8)	3 (2.0)	10 (3.0)	18 (4.1)
Gamma-glutamyltransferase increased	6 (3.3)	2 (1.3)	8 (2.4)	9 (2.0)
C-reactive protein increased	4 (2.2)	0	4 (1.2)	7 (1.6)
Psychiatric disorders	26 (14.3)	30 (19.6)	56 (16.7)	81 (18.4)
Confusional state	6 (3.3)	7 (4.6)	13 (3.9)	16 (3.6)
Anxiety	***8 (4.4)***	***5 (3.3)***	***13 (3.9)***	***18 (4.1)***
Renal and urinary disorders	29 (15.9)	28 (18.3)	57 (17.0)	81 (18.4)
Renal failure	1 (0.5)	7 (4.6)	8 (2.4)	15 (3.4)
Pollakiuria	2 (1.1)	6 (3.9)	8 (2.4)	8 (1.8)
Acute kidney injury	2 (1.1)	4 (2.6)	6 (1.8)	9 (2.0)
Chronic kidney disease	7 (3.8)	2 (1.3)	9 (2.7)	10 (2.3)
Ear and labyrinth disorders	15 (8.2)	15 (9.8)	30 (9.0)	45 (10.2)
Vertigo/Vertigo positional	***5 (2.7)***	***9 (5.9)***	***14 (4.2)***	***22 (5.0)***
Eye disorders	33 (18.1)	18 (11.8)	51 (15.2)	71 (16.1)
Cataract	7 (3.8)	2 (1.3)	9 (2.7)	12 (2.7)
Reproductive system and breast disorders	6 (3.3)	12 (7.8)	18 (5.4)	22 (5.0)
Benign prostatic hyperplasia	3 (1.6)	6 (3.9)	9 (2.7)	11 (2.5)
Blood and lymphatic system disorders	41 (22.5)	26 (17.0)	67 (20.0)	104 (23.6)
Thrombocytopenia	***12 (6.6)***	***2 (1.3)***	***14 (4.2)***	***23 (5.2)***
Injury, poisoning and procedural complications	44 (24.2)	30 (19.6)	74 (22.1)	123 (27.9)
Pelvic fracture	4 (2.2)	0	4 (1.2)	5 (1.1)
Procedural pain	4 (2.2)	2 (1.3)	6 (1.8)	10 (2.3)

MedDRA version: v20.0 for ACE-536-MDS-001 and v25.1 for ACE-536-MDS-002

Note: Bold italicized events are considered Adverse Drug Reactions by the Sponsor.

Source: ACE-536-MDS-001 primary CSR Table 14.3.1.2.1; Appendix Q42 Table 14.3.2.2.2a; Appendix MO2 Table 14.3.1.2

Serious adverse event/deaths/other significant events

AESIs

Table 64: Summary of AEs of Special Interest by Category - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05 [a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept	Epoetin alfa	Luspatercept	Placebo	Luspatercept TD	Luspatercept	Luspatercept
	N = 182	N = 179	N = 153	N = 76	N = 80	N = 26	N = 441
AESI Category	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%),95%CI EAIR/100 PY
Malignancies	17 (9.3) 7.6	12 (6.7) 7	11 (7.2) 4.1	1 (1.3) 2.2	7 (8.8) 8.5	1 (3.8) 7.7	36 (8.2) (5.8, 11.1) 6.1
Premalignant Disorders	9 (4.9) 3.9	11 (6.1) 6.3	10 (6.5) 3.6	3 (3.9) 6.8	6 (7.5) 6.8	0 (0.0) 0	25 (5.7) (3.7, 8.3) 4.1
Kidney Toxicity	16 (8.8) 7.4	12 (6.7) 7.1	21 (13.7) 8.1	5 (6.6) 11.1	5 (6.3) 6	0 (0.0) 0	42 (9.5) (7.0, 12.7) 7.3
Thromboembolic Events	9 (4.9) 4	5 (2.8) 2.9	7 (4.6) 2.6	3 (3.9) 6.5	7 (8.8) 7.9	0 (0.0) 0	23 (5.2) (3.3, 7.7) 3.8
Immunogenicity Hypersensitivity-type Reactions	7 (3.8) 3.1	3 (1.7) 1.7	9 (5.9) 3.3	2 (2.6) 4.4	4 (5.0) 4.5	2 (7.7) 16.2	22 (5.0) (3.2, 7.5) 3.7
Immunogenicity Injection Local-type Reactions	5 (2.7) 2.2	1 (0.6) 0.6	6 (3.9) 2.2	2 (2.6) 4.4	5 (6.3) 6.2	0 (0.0) 0	16 (3.6) (2.1, 5.8) 2.7
Hypertension	29 (15.9) 14.5	17 (9.5) 10.4	20 (13.1) 8	7 (9.2) 16.9	17 (21.3) 24.3	1 (3.8) 7.8	67 (15.2) (12.0, 18.9) 12.5
Liver Toxicity	3 (1.6) 1.3	5 (2.8) 2.9	4 (2.6) 1.5	1 (1.3) 2.2	3 (3.8) 3.5	1 (3.8) 7.9	11 (2.5) (1.3, 4.4) 1.8
Asthenia	56 (30.8) 30.8	44 (24.6) 31.2	92 (60.1) 62.9	22 (28.9) 61.2	23 (28.8) 28.2	2 (7.7) 16	173 (39.2) (34.6, 44.0) 41

TEAEs are defined as any new AE or AE that worsened in severity on or after the first dose of IP until 42 days after the last dose of IP, as well as serious AEs made known to the Investigator at any time thereafter that are suspected to be related to the IP.

A subject is counted only once for multiple events within each SOC/PT.

EAIR/100 PY = 100 * (the number of subjects with the specific TEAE) / the total exposure time (in years) to the event.

MedDRA Version 25.1 is used for coding.

AESI is selected using either MedDRA Version 25.1SMQ or sub-SMQ or SOC or high-level terms or list of PTs.

Source: Appendix 1 Table 14.3.2.13.1

[a] Includes data collected in the Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Serious Adverse Events

Table 65: Serious TEAEs by SOC and PT in ≥ 1% of Subjects in the TD MDS Pool - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept	Epoetin alfa	Luspatercept	Placebo	Luspatercept TD	Luspatercept	Luspatercept
	N = 182	N = 179	N = 153	N = 76	N = 80	N = 26	N = 441
System Organ Class Preferred Term	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), 95% CI EAIR/100 PY
Subjects with at least 1 specific event	82 (45.1) 45.2	71 (39.7) 50.8	72 (47.1) 39.7	23 (30.3) 55.6	42 (52.5) 86.3	6 (23.1) 48.4	202 (45.8) (41.1, 50.6) 47.7
Infections and infestations	28 (15.4) 13.1	38 (21.2) 23.6	29 (19.0) 12.4	10 (13.2) 23	17 (21.3) 22.8	3 (11.5) 23.4	77 (17.5) (14.0, 21.3) 14.4
Pneumonia	7 (3.8) 3.1	12 (6.7) 7	8 (5.2) 3.1	2 (2.6) 4.4	6 (7.5) 7	0 (0.0) 0	21 (4.8) (3.0, 7.2) 3.6
Sepsis	2 (1.1) 0.9	2 (1.1) 1.1	5 (3.3) 1.8	1 (1.3) 2.2	3 (3.8) 3.3	0 (0.0) 0	10 (2.3) (1.1, 4.1) 1.6
COVID-19	8 (4.4) 3.6	10 (5.6) 5.8	1 (0.7) 0.4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	9 (2.0) (0.9, 3.8) 1.5
Urinary tract infection	3 (1.6) 1.3	2 (1.1) 1.1	4 (2.6) 1.5	1 (1.3) 2.2	1 (1.3) 1.1	0 (0.0) 0	8 (1.8) (0.8, 3.5) 1.3
COVID-19 Pneumonia	3 (1.6) 1.3	6 (3.4) 3.4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (7.7) 15.4	5 (1.1) (0.4, 2.6) 0.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (11.5) 9.3	16 (8.9) 9.3	19 (12.4) 7.1	2 (2.6) 4.3	9 (11.3) 10.9	1 (3.8) 7.7	50 (11.3) (8.5, 14.7) 8.5
Myelodysplastic syndrome	6 (3.3) 2.6	8 (4.5) 4.5	2 (1.3) 0.7	1 (1.3) 2.2	0 (0.0) 0	0 (0.0) 0	8 (1.8) (0.8, 3.5) 1.3
Refractory anaemia with an excess of blasts	0 (0.0) 0	0 (0.0) 0	4 (2.6) 1.4	0 (0.0) 0	2 (2.5) 2.2	0 (0.0) 0	6 (1.4) (0.5, 2.9) 1
Transformation to acute myeloid leukaemia	2 (1.1) 0.9	1 (0.6) 0.6	4 (2.6) 1.4	1 (1.3) 2.2	0 (0.0) 0	0 (0.0) 0	6 (1.4) (0.5, 2.9) 1
Basal cell carcinoma	1 (0.5) 0.4	1 (0.6) 0.6	3 (2.0) 1.1	0 (0.0) 0	1 (1.3) 1.2	0 (0.0) 0	5 (1.1) (0.4, 2.6) 0.8
Injury, poisoning and procedural complications	12 (6.6) 5.4	11 (6.1) 6.3	20 (13.1) 7.7	7 (9.2) 15.6	6 (7.5) 6.8	1 (3.8) 7.8	39 (8.8) (6.4, 11.9) 6.7
Fall	2 (1.1) 0.9	2 (1.1) 1.1	8 (5.2) 2.9	3 (3.9) 6.6	1 (1.3) 1.1	0 (0.0) 0	11 (2.5) (1.3, 4.4) 1.8

Femur fracture	1 (0.5) 0.4	1 (0.6) 0.6	6 (3.9) 2.2	1 (1.3) 2.2	2 (2.5) 2.2	0 (0.0) 0	9 (2.0) (0.9, 3.8) 1.5
Subdural haematoma	2 (1.1) 0.9	1 (0.6) 0.6	1 (0.7) 0.4	0 (0.0) 0	1 (1.3) 1.1	1 (3.8) 7.8	5 (1.1) (0.4, 2.6) 0.8
Cardiac disorders	12 (6.6) 5.4	8 (4.5) 4.6	16 (10.5) 6.2	1 (1.3) 2.2	9 (11.3) 10.8	0 (0.0) 0	37 (8.4) (6.0, 11.4) 6.4
Cardiac failure	2 (1.1) 0.9	0 (0.0) 0	3 (2.0) 1.1	0 (0.0) 0	3 (3.8) 3.6	0 (0.0) 0	8 (1.8) (0.8, 3.5) 1.3
Atrial fibrillation	3 (1.6) 1.3	0 (0.0) 0	2 (1.3) 0.7	0 (0.0) 0	2 (2.5) 2.2	0 (0.0) 0	7 (1.6) (0.6, 3.2) 1.2
Angina pectoris	1 (0.5) 0.4	1 (0.6) 0.6	4 (2.6) 1.5	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	5 (1.1) (0.4, 2.6) 0.8
General disorders and administration site conditions	12 (6.6) 5.3	4 (2.2) 2.3	11 (7.2) 4.1	3 (3.9) 6.6	7 (8.8) 8.1	0 (0.0) 0	30 (6.8) (4.6, 9.6) 5
Pyrexia	3 (1.6) 1.3	3 (1.7) 1.7	5 (3.3) 1.9	2 (2.6) 4.4	1 (1.3) 1.1	0 (0.0) 0	9 (2.0) (0.9, 3.8) 1.5
General physical health deterioration	3 (1.6) 1.3	1 (0.6) 0.6	2 (1.3) 0.7	1 (1.3) 2.2	3 (3.8) 3.3	0 (0.0) 0	8 (1.8) (0.8, 3.5) 1.3
Nervous system disorders	3 (1.6) 1.3	5 (2.8) 2.9	9 (5.9) 3.5	3 (3.9) 6.5	4 (5.0) 4.6	0 (0.0) 0	16 (3.6) (2.1, 5.8) 2.7
Syncope	0 (0.0) 0	0 (0.0) 0	3 (2.0) 1.1	0 (0.0) 0	3 (3.8) 3.5	0 (0.0) 0	6 (1.4) (0.5, 2.9) 1
Respiratory, thoracic and mediastinal disorders	6 (3.3) 2.6	8 (4.5) 4.6	9 (5.9) 3.3	2 (2.6) 4.4	2 (2.5) 2.2	0 (0.0) 0	17 (3.9) (2.3, 6.1) 2.8
Dyspnoea	4 (2.2) 1.7	1 (0.6) 0.6	2 (1.3) 0.7	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	6 (1.4) (0.5, 2.9) 1
Blood and lymphatic system disorders	3 (1.6) 1.3	5 (2.8) 2.9	5 (3.3) 1.9	0 (0.0) 0	3 (3.8) 3.5	0 (0.0) 0	11 (2.5) (1.3, 4.4) 1.9
Anaemia	2 (1.1) 0.9	3 (1.7) 1.7	3 (2.0) 1.1	0 (0.0) 0	3 (3.8) 3.5	0 (0.0) 0	8 (1.8) (0.8, 3.5) 1.3

TEAEs are defined as any new AE or AE that worsened in severity on or after the first dose of IP until 42 days after the last dose of IP, as well as serious AEs made known to the Investigator at any time thereafter that are suspected to be related to the IP.

A subject is counted only once for multiple events within each SOC/PT. A highest grade will be used for a subject who experiences an AE with same PT/SOC more than once.

EAIR/100 PY = 100 * (the number of subjects with the specific TEAE) / the total exposure time (in years) to the event.

MedDRA Version 25.1 is used for coding.

CTCAE version 4.03 is used for A536-03/05, ACE-536-MDS-001 and ACE-536-MDS-002; CTCAE version 5.0 is used for ACE-536-MDS-004 and LTFU-001.

Source: Appendix 1 Table 14.3.2.3

[a] Includes data collected in Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Table 66: Grade 3-4 TEAEs by SOC and PT in ≥ 2% of Subjects in the TD MDS Pool - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05 [a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182	Epoetin alfa N = 179	Luspatercept N = 153	Placebo N = 76	Luspatercept TD N = 80	Luspatercept N = 26	Luspatercept N = 441
System Organ Class Preferred Term	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), 95% CI EAIR/100 PY
Subject with at least one specific event	107 (58.8) 75.4	88 (49.2) 70	88 (57.5) 64	34 (44.7) 102	46 (57.5) 111.7	6 (23.1) 49.6	247 (56.0) (51.2, 60.7) 74.2
Infections and infestations	27 (14.8) 12.5	32 (17.9) 19.3	28 (18.3) 11.8	9 (11.8) 20.6	17 (21.3) 22.2	3 (11.5) 23.4	75 (17.0) (13.6, 20.8) 13.8
Pneumonia	8 (4.4) 3.6	13 (7.3) 7.6	7 (4.6) 2.7	2 (2.6) 4.4	6 (7.5) 6.8	0 (0.0) 0	21 (4.8) (3.0, 7.2) 3.6
Sepsis	2 (1.1) 0.9	2 (1.1) 1.1	4 (2.6) 1.5	1 (1.3) 2.2	3 (3.8) 3.3	0 (0.0) 0	9 (2.0) (0.9, 3.8) 1.5
Blood and lymphatic system disorders	28 (15.4) 13.2	24 (13.4) 15.1	26 (17.0) 10.7	11 (14.5) 26.7	8 (10.0) 9.7	2 (7.7) 15.7	64 (14.5) (11.4, 18.2) 11.6
Anaemia	16 (8.8) 7.3	14 (7.8) 8.5	18 (11.8) 7	5 (6.6) 11.3	5 (6.3) 6	0 (0.0) 0	39 (8.8) (6.4, 11.9) 6.8
Neutropenia	7 (3.8) 3.1	11 (6.1) 6.5	6 (3.9) 2.2	6 (7.9) 13.9	1 (1.3) 1.1	2 (7.7) 15.7	16 (3.6) (2.1, 5.8) 2.7
Thrombocytopenia	8 (4.4) 3.5	2 (1.1) 1.1	0 (0.0) 0	0 (0.0) 0	2 (2.5) 2.2	0 (0.0) 0	10 (2.3) (1.1, 4.1) 1.6
Metabolism and nutrition disorders	12 (6.6) 5.6	14 (7.8) 8.2	33 (21.6) 14	4 (5.3) 8.8	3 (3.8) 3.4	1 (3.8) 7.8	49 (11.1) (8.3, 14.4) 8.9
Hyperuricaemia	1 (0.5) 0.4	1 (0.6) 0.6	9 (5.9) 3.4	1 (1.3) 2.2	0 (0.0) 0	0 (0.0) 0	10 (2.3) (1.1, 4.1) 1.7
Vascular disorders	25 (13.7) 12.2	12 (6.7) 7.2	10 (6.5) 3.8	3 (3.9) 6.8	9 (11.3) 11.4	0 (0.0) 0	44 (10.0) (7.3, 13.2) 7.9
Hypertension	18 (9.9) 8.5	8 (4.5) 4.8	5 (3.3) 1.9	3 (3.9) 6.8	6 (7.5) 7.4	0 (0.0) 0	29 (6.6) (4.4, 9.3) 5
General disorders and administration site conditions	8 (4.4) 3.5	4 (2.2) 2.3	20 (13.1) 8.1	4 (5.3) 8.8	9 (11.3) 10.5	0 (0.0) 0	37 (8.4) (6.0, 11.4) 6.5
Fatigue	1 (0.5) 0.4	1 (0.6) 0.6	7 (4.6) 2.6	2 (2.6) 4.4	1 (1.3) 1.1	0 (0.0) 0	9 (2.0) (0.9, 3.8) 1.5

Injury, poisoning and procedural complications	11 (6.0) 5	10 (5.6) 5.7	19 (12.4) 7.3	6 (7.9) 13.4	7 (8.8) 8	1 (3.8) 7.8	38 (8.6) (6.2, 11.6) 6.6
Fall	4 (2.2) 1.7	1 (0.6) 0.6	11 (7.2) 4.1	2 (2.6) 4.3	1 (1.3) 1.1	0 (0.0) 0	16 (3.6) (2.1, 5.8) 2.7
Nervous system disorders	14 (7.7) 6.4	8 (4.5) 4.6	14 (9.2) 5.5	4 (5.3) 8.9	4 (5.0) 4.6	0 (0.0) 0	32 (7.3) (5.0, 10.1) 5.6
Syncope	7 (3.8) 3.1	2 (1.1) 1.1	6 (3.9) 2.3	1 (1.3) 2.2	3 (3.8) 3.5	0 (0.0) 0	16 (3.6) (2.1, 5.8) 2.7
Respiratory, thoracic and mediastinal disorders	15 (8.2) 6.9	7 (3.9) 4	16 (10.5) 6	3 (3.9) 6.6	3 (3.8) 3.3	0 (0.0) 0	34 (7.7) (5.4, 10.6) 5.8
Dyspnoea	8 (4.4) 3.6	2 (1.1) 1.1	1 (0.7) 0.4	0 (0.0) 0	1 (1.3) 1.1	0 (0.0) 0	10 (2.3) (1.1, 4.1) 1.6

TEAEs are defined as any new AE or AE that worsened in severity on or after the first dose of IP until 42 days after the last dose of IP, as well as serious AEs made known to the Investigator at any time thereafter that are suspected to be related to the IP.

A subject is counted only once for multiple events within each SOC/PT. A highest grade will be used for a subject who experiences an AE with same PT/SOC more than once.

EAIR/100 PY = 100 * (the number of subjects with the specific TEAE) / the total exposure time (in years) to the event.

MedDRA Version 25.1 is used for coding.

CTCAE version 4.03 is used for A536-03/05, ACE-536-MDS-001 and ACE-536-MDS-002; CTCAE version 5.0 is used for ACE-536-MDS-004 and LTFU-001.

Source: Appendix 1 Table 14.3.2.5

[a] Includes data collected in Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Table 67: Grade 3/4 and Serious Adverse Drug Reactions - ACE-536-MDS-002 (Primary Analysis), ACE-536-MDS-001 (Primary Analysis), and Phase 3 TD-MDS Pool

	ACE-536-MDS-002 (Primary Analysis) Luspatercept N=182		ACE-536-MDS-001 (Primary Analysis) Luspatercept N=153		Phase 3 TD-MDS Pool Luspatercept N=335	
ADR, n (%)	Grade 3/4	Serious	Grade 3/4	Serious	Grade 3/4	Serious
Hypertension	18 (9.9)	0	5 (3.3)	0	23 (6.9)	0
Thrombocytopenia	8 (4.4)	0	0	0	8 (2.4)	0
Dyspnoea	8 (4.4)	4 (2.2)	1 (0.7)	1 (0.7)	9 (2.7)	5 (1.5)
Syncope	7 (3.8)	0	5 (3.3)	3 (2.0)	12 (3.6)	3 (0.9)
Urinary Tract Infection	3 (1.6)	3 (1.6)	2 (1.3)	3 (2.0)	5 (1.5)	6 (1.8)
Back Pain	2 (1.1)	1 (0.5)	3 (2.0)	3 (2.0)	5 (1.5)	4 (1.2)
Fatigue	1 (0.5)	0	7 (4.6)	0	8 (2.4)	0
Asthenia	0	0	4 (2.6)	0	4 (1.2)	0

Source: Appendix MO2 Table 14.3.1.6 (MDS-002 Grade 3/4) and Table 14.3.1.4.1 (MDS-002 SAEs); ACE-536-MDS-001 primary CSR Table 14.3.1.5.1 (Grade 3/4) and Table 14.3.1.4.1 (SAEs)

Deaths

Overall, the causes of death in the TD MDS Pool were generally consistent with the natural course of MDS in a predominantly older population, and the rate of death was consistent with that expected in this population. In studies ACE-536-MDS-001 and ACE-536-MDS-002, the frequency of deaths was similar across arms. There was a total of 108 deaths (24.5% of subjects) in the TD MDS Pool. Twenty-five subjects (6.8%) died while on-treatment (within 42 days after last dose of study drug) and 78 (17.7%) died while off-treatment (at least 42 days after of last dose of study drug). The most common SOCs for Grade 5 TEAEs in the TD MDS Pool were General Disorders and Administration Site Conditions (8 subjects; 1.8%) and Infections and Investigations (7 subjects;1.6%). PTs that occurred in more than

single subjects included events coded as "death" (4 subjects), sepsis (4 subjects), multiple organ dysfunction syndrome (2 subjects) and cardiac failure (2 subjects). In ACE-536-MDS-002, 1 Grade 5 TEAE was considered by the Investigator to be related to study drug: a subject receiving 1 mg/kg of luspatercept had a Grade 5 TEAE of acute myeloid leukemia. The subject received the last dose of luspatercept on study Day 43, was diagnosed with AML on study Day 81, and died on study Day 83.

Table 68: Summary of Deaths - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182	Epoetin alfa N = 179	Luspatercept N = 153	Placebo N = 76	Luspatercept TD N = 80	Luspatercept N = 26	Luspatercept N = 441
Total number of deaths	39 (21.4)	38 (21.2)	58 (37.9)	27 (35.5)	11 (13.8)	0 (0.0)	108 (24.5)
On Treatment Deaths (Within 42 Days After Last Dose of Study Drug)	15 (8.2)	14 (7.8)	10 (6.5)	4 (5.3)	5 (6.3)	0 (0.0)	30 (6.8)
< 4 months	3 (1.6)	4 (2.2)	3 (2.0)	1 (1.3)	0 (0.0)	0 (0.0)	6 (1.4)
4 - ≤ 12 months	5 (2.7)	7 (3.9)	2 (1.3)	2 (2.6)	1 (1.3)	0 (0.0)	8 (1.8)
12 - ≤ 24 months	4 (2.2)	3 (1.7)	3 (2.0)	1 (1.3)	0 (0.0)	0 (0.0)	7 (1.6)
≥ 24 months	3 (1.6)	0 (0.0)	2 (1.3)	0 (0.0)	4 (5.0)	0 (0.0)	9 (2.0)
Off Treatment Deaths (After 42 Days of Last Dose of Study Drug)	24 (13.2)	24 (13.4)	48 (31.4)	23 (30.3)	6 (7.5)	0 (0.0)	78 (17.7)
< 4 months	1 (0.5)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
4 - ≤ 12 months	3 (1.6)	5 (2.8)	4 (2.6)	1 (1.3)	1 (1.3)	0 (0.0)	8 (1.8)
12 - ≤ 24 months	15 (8.2)	10 (5.6)	10 (6.5)	11 (14.5)	2 (2.5)	0 (0.0)	27 (6.1)
≥ 24 months	5 (2.7)	9 (5.0)	33 (21.6)	11 (14.5)	3 (3.8)	0 (0.0)	41 (9.3)

On/Off treatment death is relative to the date of last dose of study drug.

The category by month is relative to date of first dose of study drug.

Source: Appendix 1 Table 14.3.3

[a] Includes data collected in the Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Table 69: Grade 5 TEAEs by SOC - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182	Epoetin alfa N = 179	Luspatercept N = 153	Placebo N = 76	Luspatercept TD N = 80	Luspatercept N = 26	Luspatercept N = 441
System Organ Class	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), 95% CI EAIR/100 PY
Subjects with at least 1 specific event	11 (6.2), 6.1	12 (6.8), 8.4	9 (5.9), 3.3	4 (5.3), 8.7	5 (6.3), 5.6	0 (0.0), 0	25 (5.9) (3.9, 8.6), 4.5
Infections and infestations	2 (1.1) 0.9	6 (3.4) 3.4	3 (2.0) 1.1	1 (1.3) 2.2	2 (2.5) 2.2	0 (0.0) 0	7 (1.6) (0.6, 3.2) 1.1
General disorders and administration site conditions	6 (3.3) 2.6	1 (0.6) 0.6	2 (1.3) 0.7	2 (2.6) 4.3	0 (0.0) 0	0 (0.0) 0	8 (1.8) (0.8, 3.5) 1.3
Cardiac disorders	3 (1.6) 1.3	5 (2.8) 2.8	0 (0.0) 0	0 (0.0) 0	1 (1.3) 1.1	0 (0.0) 0	4 (0.9) (0.2, 2.3) 0.7
Nervous system disorders	2 (1.1) 0.9	0 (0.0) 0	1 (0.7) 0.4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	3 (0.7) (0.1, 2.0) 0.5
Injury, poisoning and procedural complications	0 (0.0) 0	0 (0.0) 0	1 (0.7) 0.4	0 (0.0) 0	1 (1.3) 1.1	0 (0.0) 0	2 (0.5) (0.1, 1.6) 0.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5) 0.4	0 (0.0) 0	1 (0.7) 0.4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (0.5) (0.1, 1.6) 0.3
Vascular disorders	0 (0.0) 0	0 (0.0) 0	1 (0.7) 0.4	0 (0.0) 0	1 (1.3) 1.1	0 (0.0) 0	2 (0.5) (0.1, 1.6) 0.3
Gastrointestinal disorders	1 (0.5) 0.4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.2) (0.0, 1.3) 0.2
Renal and urinary disorders	0 (0.0) 0	0 (0.0) 0	1 (0.7) 0.4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.2) (0.0, 1.3) 0.2
Metabolism and nutrition disorders	0 (0.0), 0	1 (0.6), 0.6	0 (0.0), 0	0 (0.0), 0	0 (0.0), 0	0 (0.0), 0	0 (0.0) (0.0, 0.8), 0
Respiratory, thoracic and mediastinal disorders	0 (0.0) 0	1 (0.6) 0.6	0 (0.0) 0	1 (1.3) 2.2	0 (0.0) 0	0 (0.0) 0	0 (0.0) (0.0, 0.8) 0

TEAEs are defined as any new AE or AE that worsened in severity on or after the first dose of IP until 42 days after the last dose of IP, as well as serious AEs made known to the Investigator at any time thereafter that are suspected to be related to the IP.

A subject is counted only once for multiple events within each SOC/PT. A highest grade will be used for a subject who experiences an AE with same PT/SOC more than once.

EAIR/100 PY = 100 * (the number of subjects with the specific TEAE) / the total exposure time (in years) to the event.

MedDRA Version 25.1 is used for coding.

CTCAE version 4.03 is used for A536-03/05, ACE-536-MDS-001 and ACE-536-MDS-002; CTCAE version 5.0 is used for ACE-536-MDS-004 and LTFU-001.

Source: Appendix 1 Table 14.3.2.6

[a] Includes data collected in Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Immunogenicity

The number of ADA-positive subjects was small (36 subjects in the TD MDS Pool). Since the original BLA, there was only 1 newly identified subject who tested positive to TEADA in Study A536-05. No AEs of systemic hypersensitivity were reported; only a transient Grade 1 injection-site reaction (erythema) that lasted 1 day was reported for this subject.

Table 70: Summary of Subjects with Anti-drug Antibodies in study ACE-536-MDS-001 (ITT Population)

Anti-drug Antibodies	Luspatercept (N = 153) n (%)			Placebo (N = 76) n (%)		
	Pre-existing	Treatment-emergent	Positive	Pre-existing	Treatment-emergent	Positive
ADA Against Luspatercept[a]	7 (4.6)	11 (7.2)	18 (11.8)	2 (2.6)	3 (3.9)	5 (6.6)
Specificity for ACE-mECD[b]	1 (0.7)	5 (3.3)	6 (3.9)	0	1 (1.3)	1 (1.3)
Specificity for ActRIIB ECD	1 (0.7)	3 (2.0)	4 (2.6)	0	1 (1.3)	1 (1.3)
Neutralizing Luspatercept[c]	2 (1.3)	5 (3.3)	7 (4.6)	0	2 (2.6)	2 (2.6)
Neutralizing ActRIIB-ECD-Fc[d]	0	0	0	0	0	0

ACE-mECD = modified ECD of human ActRIIB on luspatercept; ActRIIB = activin receptor type IIB; ActRIIB ECD = natural ECD of human ActRIIB; ActRIIB-ECD-Fc = a fusion protein joining the natural ECD of human ActRIIB to Fc portion of human immunoglobulin G; ADA = anti-drug antibody; ECD = extracellular domain; ITT = intent-to-treat; N = total number of subjects providing evaluable ADA sample; n = number of subjects in each ADA-positive category; Nab = neutralizing antibody.

[a] ADA against luspatercept is ANTI-ACE-536 in the source table.

[b] ACE-mECD is ANTI-536-HIS in the source table.

[c] Neutralizing luspatercept is Nab ACE-536 in the source table.

[d] Neutralizing ActRIIB-ECD-Fc is Nab ACE-031 in the source dataset (Data on File).

Note: A subject was counted as "treatment emergent" if there was a positive postbaseline sample while the baseline sample was ADA negative, or there was a positive postbaseline sample with a titer ≥ 4-fold of the baseline titer while the baseline sample was ADA positive. A subject was counted as "preexisting" if the baseline sample was ADA positive and all postbaseline samples were negative, or both baseline and postbaseline samples were positive but all positive postbaseline samples had a titer < 4-fold of the baseline titer.

Source: Table 14.2.15.2.d and Data on File.

Table 71: Anti-Drug Antibody Measurement for Luspatercept by Parameter and Positive Category in study ACE-536-MDS-002: Safety Population (data extraction date Nov-2023)

ADA Test	Luspatercept (N=175) n % — Preexisting	Treatment-emergent	Total
Anti-luspatercept [a]	4 (2.3)	13 (7.4)	17 (9.7)
Specificity for ACE-mECD [b]	0 (0.0)	7 (4.0)	7 (4.0)
Specificity for ActRIIB-ECD [b]	0 (0.0)	4 (2.3)	4 (2.3)
Neutralizing Luspatercept [b]	1 (0.6)	12 (6.9)	13 (7.4)
Neutralizing ActRIIB-ECD-Fc [b]	0 (0.0)	1 (0.6)	1 (0.6)

Include both scheduled and unscheduled visits. Percentages are based on all Luspatecept treated subjects with baseline and at least one post-baseline immunogenicity assessment result.

Luspatercept=ACE-536 in the source data; ACE-mECD=modified extracellular domain of human ActRIIB on luspatercept, ADA against ACE-mECD is named as ANTI-536-HIS in the source data; ActRIIB-ECD=natural extracellular domain of human ActRIIB; Neutralizing luspatercept=Nab ACE-536 in the source data; ActRIIB-ECD-Fc = a fusion protein joining the natural extracellular domain of human Act RIIB to Fc portion of human IgG, neutralizing ADA against ActRIIB-ECD-Fc is named as Anti-ACE-031 in the source data.

[a] Number of subjects under each ADA positive category. A subject is counted as >Treatment-Emergent> if there is a positive post-baseline sample while the baseline sample is ADA negative, or there is a positive post-baseline sample with a titer >= 4-fold of the baseline titer while the baseline sample is ADA positive. A subject is counted as >Preexisting> if the baseline sample is ADA positive and the subject is not qualified for >Treatment-Emergent>.

[b] Number of subjects with at least one positive result for each test.

Program path: /u02/projects/ace_536/ace_536_mds_002/deliverables/d021_48weeks_dbl_nov2023/programs/tables/final/31mar2023cut/t_14_2_15_2_d.sas

Data Extraction Date: 09NOV2023

Laboratory findings

Baseline abnormalities in hematological and renal chemistry were consistent with those expected from this patient population. Changes in hematological parameters were similar between arms in ACE-536-MDS-002. Changes in the TD MDS pool were comparable to luspatercept-treated subjects in ACE-536-MDS-002 and supportive studies. There was no evidence of liver or renal toxicity associated with luspatercept treatment.

Hematology

Leukocytes: In the TD MDS Pool 5.6% of subjects had leukocyte values of Grade 3 or 4 at baseline. Shifts in leukocytes from Grades 0 or 1 to Grades 3 or 4 occurred at similar frequencies between arms in ACE-536-MDS-002 and at a similar frequency to ACE-536-MDS-002 in the TD MDS Pool.

Absolute neutrophil count: In the TD MDS Pool 12.3% of subjects had ANC values of Grade 3 or 4 at baseline. Shifts in ANC from Grades 0 or 1 to Grades 3 or 4 occurred at similar frequencies between arms in ACE-536-MDS-002 and at a similar frequency to ACE-536- MDS-002 in the TD MDS Pool.

Platelets: Most subjects had platelet values of Grade 0 or 1 at baseline. Shifts from Grades 0 or 1 to Grades 3 or 4 were reported for a small and similar proportion of subjects in the luspatercept and epoetin alfa arms in study ACE-536-MDS-002 and at a similar frequency to ACE-536-MDS-002 in the TD MDS Pool.

Table 72: Shifts in Hematology Parameters to Grade 3 or 4 - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept	Epoetin Alfa	Luspatercept	Placebo	Luspatercept TD	Luspatercept	Luspatercept
	N = 182	N = 179	N = 153	N = 76	N = 80	N = 26	N = 441
Laboratory Test	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Leukocytes (10^9/L)							
	*m=180	*m=169	*m=146	*m=74	*m=78	*m=25	*m=429
Shift from Gr 0 to Gr 3	2 (1.1)	4 (2.4)	2 (1.4)	0 (0.0)	2 (2.6)	0 (0.0)	6 (1.4)
Shift from Gr 0 to Gr 4	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (1.3)	0 (0.0)	2 (0.5)
Shift from Gr 1 to Gr 3	3 (1.7)	8 (4.7)	2 (1.4)	1 (1.4)	1 (1.3)	0 (0.0)	6 (1.4)
Shift from Gr 1 to Gr 4	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	2 (0.5)
Absolute neutrophil counts (10^9/L)							
	*m=179	*m=171	*m=148	*m=72	*m=77	*m=25	*m=429
Shift from Gr 0 to Gr 3	8 (4.5)	6 (3.5)	3 (2.0)	0 (0.0)	4 (5.2)	0 (0.0)	15 (3.5)
Shift from Gr 0 to Gr 4	1 (0.6)	1 (0.6)	1 (0.7)	1 (1.4)	3 (3.9)	0 (0.0)	5 (1.2)
Shift from Gr 1 to Gr 3	4 (2.2)	2 (1.2)	3 (2.0)	4 (5.6)	1 (1.3)	2 (8.0)	10 (2.3)
Shift from Gr 1 to Gr 4	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Platelets (10^9/L)							
	*m=157	*m=152	*m=129	*m=66	*m=70	*m=21	*m=377
Shift from Gr 0 to Gr 3	2 (1.3)	2 (1.3)	1 (0.8)	0 (0.0)	1 (1.4)	0 (0.0)	4 (1.1)
Shift from Gr 0 to Gr 4	0 (0.0)	1 (0.7)	2 (1.6)	0 (0.0)	1 (1.4)	0 (0.0)	3 (0.8)
Shift from Gr 1 to Gr 3	2 (1.3)	6 (3.9)	3 (2.3)	0 (0.0)	3 (4.3)	1 (4.8)	9 (2.4)
Shift from Gr 1 to Gr 4	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	2 (0.5)

[a] Includes data collected in the Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.
CTCAE version 4.03 is used.
Absolute Neutrophils Count is derived using segmented and band neutrophils for MDS-001, MDS-002 and MDS-004 and using neutrophils only for A536-03/05 and LTFU.
*m = number of subjects with baseline value and at least one post-baseline value. Percentages are based on m.
Baseline is the last value measured before the first IP dose.

Clinical Chemistry - Liver Laboratory Results

There was only 1 subject in the TD MDS Pool who met laboratory criteria for Hy's Law.

- ACE-536-MDS-001: One subject in the luspatercept arm experienced an increase in ALT and AST ≥ 3 × ULN and direct bilirubin ≥ 2 × ULN. However, these liver laboratory abnormalities were temporally associated with concurrent acute SAEs, and not the result of drug-induced liver injury. The subject was a 77-year-old male with a medical history of congestive cardiac failure, diabetes mellitus and was diagnosed with chronic kidney disease on Study Day 1. He experienced cholelithiasis, lactic acidosis related to metformin, acute kidney injury, pancreatitis and subsequently acute pulmonary failure; and died due to multiple organ dysfunction syndrome on Study Day 135.

There was 1 subject in the ACE-536-MDS-002 study who met laboratory criteria for Hy's Law.

- ACE-536-MDS-002: One subject in the epoetin alpha arm experienced an increase in ALT and AST ≥ 3 × ULN and direct bilirubin ≥ 2 × ULN: This was a 70-year-old subject with SAE of worsening of chronic cholelithiasis that was resolved in 9 days with appropriate treatment. Chronic cholelithiasis was reported in Medical History.

Most subjects in the TD MDS Pool had ALT, AST, ALP, and total bilirubin of Grade 0 or 1 at baseline and remained at Grade 0 or 1 throughout the study. Shifts to Grade 3 were observed infrequently and there were no shifts to Grade 4.

Table 73: Incidence of Subjects with ALT, AST, or Bilirubin Exceeding Predefined Thresholds - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182 n (%), EAIR/100 PY	Epoetin Alfa N = 179 n (%), EAIR/100 PY	Luspatercept N = 153 n (%), EAIR/100 PY	Placebo N = 76 n (%), EAIR/100 PY	Luspatercept TD N = 80 n (%), EAIR/100 PY	Luspatercept N = 26 n (%), EAIR/100 PY	Luspatercept N = 441 n (%), EAIR/100 PY
Hepatic Function							
ALT ≥ 3*ULN	9 (4.9) 4.1	13 (7.3) 7.4	25 (16.3) 10.4	6 (7.9) 13.9	6 (7.5) 6.8	0 (0.0)	40 (9.1) 7.1
AST ≥ 3*ULN	4 (2.2) 1.7	7 (3.9) 4	12 (7.8) 4.7	0 (0.0)	3 (3.8) 3.3	0 (0.0)	19 (4.3) 3.2
Direct Bilirubin ≥ 2*ULN	6 (3.3) 2.6	4 (2.2) 2.3	9 (5.9) 3.5	0 (0.0)	26 (32.5) 38.7	0 (0.0)	41 (9.3) 7.2
(ALT ≥ 3*ULN or AST ≥ 3*ULN) and Total Bilirubin ≥ 2*ULN	0 (0.0)	1 (0.6) 0.6	1 (0.7) 0.4	1 (1.3) 2.2	0 (0.0)	0 (0.0)	1 (0.2) 0.2
(ALT ≥ 3*ULN or AST ≥ 3*ULN) and Direct Bilirubin ≥ 2*ULN	1 (0.5) 0.4	1 (0.6) 0.6	1 (0.7) 0.4	0 (0.0)	2 (2.5) 2.2	0 (0.0)	4 (0.9) 0.7

[a] Includes data collected in the Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.
A subject is counted if any post-baseline value meets the specified threshold(s).
Baseline is the last value measured before the first IP dose.
EAIR/100 PY: Exposure adjusted incidence rate (EAIR) per 100 person-year is 100 times the number of subjects with the specified threshold divided by the total exposure time (in years) to the abnormality event.
Exposure time is the overall treatment exposure for subjects without the event and the time up to the first event start date for subjects with the event.

Clinical Chemistry - Renal Laboratory Results

As expected for this elderly study population, a significant proportion of subjects in the TD MDS Pool had Grade 1 or 2 eGFR values at baseline, and GFR post-baseline increases were mostly shifts of 1 grade. Creatinine clearance less than 0.5 times baseline occurred in a higher proportion of subjects in the luspatercept arm compared with the epoetin alfa arm in ACE-536-MDS-002. The proportion of subjects with creatinine clearance less than 0.5 times baseline was observed in 5% of subjects (3.7/100 PY) in the TD MDS Pool, which was generally consistent with luspatercept-treated subjects in ACE-536-MDS-002 and other supporting studies. Serum creatinine greater than 2 times baseline occurred in a similar proportion of subjects in the luspatercept arm compared with the epoetin alfa arm in ACE-536-MDS-002. The proportion of subjects with serum creatinine greater than 2 times baseline was observed in 2.7 % of subjects (2/100 PY) in the TD MDS Pool, which was generally consistent with luspatercept-treated subjects in ACE-536-MDS-002 and other supporting studies.

Proteinuria was assessed and reported as the laboratory value of spot urinary albumin to creatinine ratios (ACR). ACRs have been categorised in the literature as normal (0 - 30 mg/g), microalbuminuria (30 - 300 mg/g), and macroalbuminuria or overt nephropathy (> 300 mg/g). ACR values > 3500 mg/g represent nephrotic range proteinuria. In ACE-535-MDS-002, shifts from Grade 0 (< 30 mg/g) to Grade 1 (30-<1000 mg/g) were observed in 38.7% of subjects in the luspatercept arm and 25.2% of subjects in the epoetin alfa arm. Grade 2 ACRs (1000 - < 3500 mg/g) were observed in 6 subjects (3.0%) in the luspatercept arm and 6 subjects (3.9%) in the epoetin alfa arm. One shift from Grade 2 to Grade 3 ACR (>3500 mg/g) was observed in the luspatercept arm. Shifts in ACR from Grade 0 to Grade 1 occurred in a similar proportion of subjects in the TD MDS Pool (38.7%) as the luspatercept arm of ACE-536-MDS-002. Shifts from Grade 0 to Grade 2 occurred in 2 subjects (0.5%).

Table 74: Incidence of Subjects with Creatine Clearance or Serum Creatinine Exceeding Predefined Thresholds - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies[a] A536-03/05	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept N = 182	Epoetin Alfa N = 179	Luspatercept N = 153	Placebo N = 76	Luspatercept TD N = 80	Luspatercept N = 26	Luspatercept N = 441
	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY
Renal Function							
Creatinine clearance < 0.5×baseline	11 (6.0) 4.9	2 (1.1) 1.1	6 (3.9) 2.2	1 (1.3) 2.2	5 (6.3) 5.9	0 (0.0)	22 (5.0) 3.7
Serum creatinine > 2×baseline	4 (2.2) 1.7	3 (1.7) 1.7	4 (2.6) 1.4	1 (1.3) 2.2	4 (5.0) 4.5	0 (0.0)	12 (2.7) 2

[a] Includes data collected in the Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

A subject is counted if any post-baseline value meets the specified threshold(s).
Baseline is the last value measured before the first IP dose.
EAIR/100 PY: Exposure adjusted incidence rate (EAIR) per 100 person-year is 100 times the number of subjects with the specified threshold divided by the total exposure time (in years) to the abnormality event.
Exposure time is the overall treatment exposure for subjects without the event and the time up to the first event start date for subjects with the event.

Vital Signs - Blood Pressure

Transient increases of ≥ 20 mm Hg in SBP and ≥ 10 mmHg in DBP were observed in most subjects in the TD MDS Pool. Most subjects with ≥ 20 mm Hg increase in SBP or DBP did not have concurrent elevated absolute SBP or DBP. At the time of the last assessment, these increases had resolved to baseline levels or <10 mm Hg above baseline for most subjects. In ACE-536-MDS-002, the observed maximum

increases in SBP and DBP were similar between the luspatercept and epoetin alfa treatment arms. Luspatercept treatment led to no mean increase in SBP from baseline and a ≤ 3 mm Hg increase from baseline DBP.

Table 75: Summary of Blood Pressure - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept	Epoetin Alfa	Luspatercept	Placebo	Luspatercept TD	Luspatercept	Luspatercept
System Organ Class	N = 182	N = 179	N = 153	N = 76	N = 80	N = 26	N = 441
Preferred Term	n (%),	n (%),	n (%),	n (%),	n (%),	n (%),	n (%)
Systolic Blood Pressure (maximum post-baseline)							
No Increase	10 (5.5)	13 (7.3)	14 (9.2)	7 (9.2)	4 (5.0)	3 (11.5)	31 (7.0)
Increased < 10 mmHg	37 (20.3)	36 (20.1)	19 (12.4)	12 (15.8)	8 (10.0)	6 (23.1)	70 (15.9)
Increased ≥ 10 mmHg and < 20 mmHg	51 (28.0)	61 (34.1)	40 (26.1)	32 (42.1)	23 (28.8)	11 (42.3)	125 (28.3)
Increased ≥ 20 mmHg	83 (45.6)	69 (38.5)	80 (52.3)	24 (31.6)	45 (56.3)	5 (19.2)	213 (48.3)
SBP ≥ 160 mmHg	35 (19.2)	24 (13.4)	29 (19.0)	7 (9.2)	23 (28.8)	0 (0.0)	87 (19.7)
SBP < 160 mmHg	48 (26.4)	45 (25.1)	51 (33.3)	17 (22.4)	22 (27.5)	5 (19.2)	126 (28.6)
Diastolic Blood Pressure (maximum post-baseline)							
No Increase	10 (5.5)	16 (8.9)	4 (2.6)	8 (10.5)	4 (5.0)	0 (0.0)	18 (4.1)
Increased < 10 mmHg	42 (23.1)	51 (28.5)	27 (17.6)	36 (47.4)	16 (20.0)	11 (42.3)	96 (21.8)
Increased ≥ 10 mmHg and < 20 mmHg	73 (40.1)	65 (36.3)	75 (49.0)	21 (27.6)	28 (35.0)	11 (42.3)	187 (42.4)
Increased ≥ 20 mmHg	56 (30.8)	47 (26.3)	47 (30.7)	10 (13.2)	32 (40.0)	3 (11.5)	138 (31.3)
DBP ≥ 100 mmHg	8 (4.4)	2 (1.1)	5 (3.3)	0 (0.0)	12 (15.0)	0 (0.0)	25 (5.7)
DBP < 100 mmHg	48 (26.4)	45 (25.1)	42 (27.5)	10 (13.2)	20 (25.0)	3 (11.5)	113 (25.6)
Systolic Blood Pressure (last available assessment)							
No Increase	99 (54.4)	96 (53.6)	88 (57.5)	42 (55.3)	43 (53.8)	12 (46.2)	242 (54.9)
Increased < 10 mmHg	39 (21.4)	37 (20.7)	30 (19.6)	18 (23.7)	12 (15.0)	6 (23.1)	87 (19.7)
Increased ≥ 10 mmHg and < 20 mmHg	22 (12.1)	28 (15.6)	20 (13.1)	8 (10.5)	15 (18.8)	5 (19.2)	62 (14.1)
Increased ≥ 20 mmHg	21 (11.5)	18 (10.1)	15 (9.8)	7 (9.2)	10 (12.5)	2 (7.7)	48 (10.9)
SBP ≥160 mmHg	8 (4.4)	2 (1.1)	2 (1.3)	0 (0.0)	2 (2.5)	0 (0.0)	12 (2.7)
SBP < 160 mmHg	13 (7.1)	16 (8.9)	13 (8.5)	7 (9.2)	8 (10.0)	2 (7.7)	36 (8.2)
Diastolic Blood Pressure (last available assessment)							
No Increase	77 (42.3)	95 (53.1)	66 (43.1)	41 (53.9)	48 (60.0)	8 (30.8)	199 (45.1)
Increased < 10 mmHg	63 (34.6)	53 (29.6)	52 (34.0)	26 (34.2)	17 (21.3)	10 (38.5)	142 (32.2)
Increased ≥ 10 mmHg and < 20 mmHg	32 (17.6)	23 (12.8)	30 (19.6)	7 (9.2)	11 (13.8)	5 (19.2)	78 (17.7)
Increased ≥ 20 mmHg	9 (4.9)	8 (4.5)	5 (3.3)	1 (1.3)	4 (5.0)	2 (7.7)	20 (4.5)
DBP ≥ 100 mmHg	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	3 (0.7)
DBP < 100 mmHg	8 (4.4)	8 (4.5)	5 (3.3)	1 (1.3)	2 (2.5)	2 (7.7)	17 (3.9)

[a] Includes data collected in the Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Vital Signs - Weight

Weight decreases of at least 10% were observed in similar proportions of subjects in the luspatercept and epoetin alfa arms in ACE-536-MDS-002 (12.9% and 10.2%, respectively) and in a similar proportion (15.8%) in the TD MDS Pool.

Safety in special populations

Intrinsic and Extrinsic Factors

Effects of age, sex, baseline transfusion burden, ring sideroblast status, and baseline eGFR on AE profiles were observed as summarized below.

Age: In the TD MDS Pool, no major differences in the frequency or EAIR of all-grade TEAEs were observed between subjects aged ≤64 years, 65-74 years, and >75 years. Serious TEAEs, Grade 3/4 TEAEs, Grade 5 TEAEs, and TEAEs leading to discontinuation increased in both frequency and EAIR with increasing age. No major differences by age were noted in TEAEs leading to dose interruption or dose reduction.

Sex: In the TD MDS Pool, the frequency of all-grade TEAEs was similar between males and females but the EAIR was higher in females. Both frequency and EAIR for events in the SOCs of General Disorders and Administration Site Conditions and Infections and Infestations were higher in females than males. No major differences between males and females were observed in frequencies of serious TEAEs, Grade 3/4 TEAEs, Grade 5 TEAEs, TEAEs leading to discontinuation, dose interruption, or dose reduction.

Race: The difference between the number of White (n=329) and non-White (n=36) subjects limits the interpretability of potential differences in safety by race.

Baseline Transfusion Burden: In the TD MDS Pool, the frequency of all-grade TEAEs was similar between subjects with a baseline transfusion burden of < 4 units and those with a baseline transfusion burden of ≥ 4 units but the EAIR was higher in those with burden ≥ 4 units. Subjects with a baseline transfusion burden ≥ 4 units had a higher frequency and EAIR in the SOC of General Disorders and Administration Site Conditions, with higher rates of the PTs of fatigue, peripheral edema, and asthenia. No major differences were observed in frequencies of serious TEAEs, Grade 3/4 TEAEs, Grade 5 TEAEs, TEAEs leading to discontinuation, dose interruption, or dose reduction.

Ring Sideroblasts status: In ACE-536-MDS-002, there were no notable differences between luspatercept-treated RS+ and RS- subjects in the frequencies of all-grade TEAEs, Grade 3/4 TEAEs, or SAEs. Frequencies of TEAEs leading to dose reduction, dose interruption and discontinuation were higher in luspatercept-treated RS- than in luspatercept-treated RS+ subjects but similar to epoetin alfa RS - treated subjects. Except for events of asthenia, there were no notable differences with respect to AESI categories between luspatercept-treated RS + and RS- subjects or between luspatercept- and epoetin alfa-treated RS- subjects.

Table 76: Summary of Exposure and Safety in LR-MDS Subjects -Safety Population and RS Subgroup – Full Primary Analysis

	RS+		RS-		Safety Population	
Parameter, n (%) EAIR/100 PY	Luspatercept (N=133)	Epoetin Alfa (N=128)	Luspatercept (N=49)	Epoetin Alfa (N=50)	Luspatercept (N=182)	Epoetin Alfa (N=179)
Any TEAE	130 (97.7) 569.2	118 (92.2) 370.7	48 (98.0) 745.7	46 (92.0) 573.2	178 (97.8) 608	165 (92.2) 413.5
Gr. 3/4 TEAE	77 (57.9)	58 (45.3)	30 (61.2)	29 (58.0)	107 (58.8) 75.4	88 (49.2) 70
SAEs	56 (42.1) 38.6	44 (34.4) 44	26 (53.1) 71.4	26 (52.0) 65.5	82 (45.1) 45.2	71 (39.7) 50.8
Grade 5 TEAE	8 (6.0) 4.4	8 (6.3) 6.6	7 (14.3) 14.5	6 (12.0) 10.8	15 (8.2) 6.5	14 (7.8) 7.9
AEs leading to drug withdrawal	14 (10.5) 7.7	7 (5.5) 5.7	7 (14.3) 14.6	6 (12.0) 10.8	21 (11.5) 9.1	13 (7.3) 7.3
AEs leading to dose reduction	4 (3.0) 2.2	3 (2.3) 2.5	3 (6.1) 6.8	3 (6.0) 5.7	7 (3.8) 3.1	6 (3.4) 3.5
AEs leading to dose interruption	45 (33.8) 30.7	31 (24.2) 32.2	16 (32.7) 39.9	19 (38.0) 44.6	61 (33.5) 32.7	51 (28.5) 36.7
AESI Category						
Asthenia	38 (28.6)	28 (21.9)	18 (36.7)	15 (30.0)	56 (30.8) 30.9	44 (24.6) 31.2
Hypertension	22 (16.5)	12 (9.4)	7 (14.3)	5 (10.0)	29 (15.9) 14.5	17 (9.5) 10.4
TEE	5 (3.8)	3 (2.3)	4 (8.2)	2 (4.0)	9 (4.9) 4	5 (2.8) 2.9
Malignancies	13 (9.8)	6 (4.7)	4 (8.2)	6 (12.0)	17 (9.3) 7.6	12 (6.7) 7

Note: EAIRs were not calculated for Grade 3/4 events in the RS subgroups.
Source: Appendix MO-2.1 Table 14.3.1.6.5 (Grade 3/4, RS), Table 14.3.1.4.6 (SAE, RS), Table 14.3.1.2.7 (all TEAEs, RS), Table 14.3.1.17.1.1 (Asthenia, RS), Table 14.3.1.17.8.1 (Malignancies, RS), Table 14.3.1.17.7.1 (TEEs, RS), Table 14.3.1.17.2.1 (Hypertension, RS), Table 14.3.1.1.1 (TEAE summary, Safety Population), Table 14.3.1.18.1 (AESIs, Safety Population)
Appendix Q52 Table 14.3.1.12a (Exposure RS+), Table 14.3.1.13a (Exposure RS-), Table 14.3.2.7.12a (withdrawal RS+), Table 14.3.2.7.13a (withdrawal RS-), Table 14.3.2.8.12a (Dose Reduction RS+), Table 14.3.2.8.13a (Dose Reduction RS+), Table 14.3.2.9.12a (Dose Interruption RS+), Table 14.3.2.9.13a (Dose Interruption RS-), Table 14.3.2.6.12a (Grade 5 RS+), Table 14.3.3.2.6.13a (Grade 5 RS-)

Baseline Serum EPO: In the TD MDS Pool, no major differences in the frequency or EAIR of all-grade TEAEs were observed between subjects with baseline serum EPO ≤ 200 U/L and those with baseline serum EPO > 200 U/L. Frequency and EAIR of Grade 5 TEAEs were higher in subjects with baseline serum EPO > 200 U/L but the number of events in each category was small.

Baseline eGFR: In the TD MDS Pool, no major differences in the frequency or EAIR of all-grade TEAEs were observed between subjects with eGFR <60, eGFR ≥60 to <90, or eGFR >90. The frequencies and EAIR of serious TEAEs and Grade 3/4 TEAEs decreased with higher eGFR. No major differences were observed in frequencies of, Grade 5 TEAEs, TEAEs leading to discontinuation, dose interruption, or dose reduction.

Baseline SF3B1 Mutational Status: In the TD MDS Pool, no major differences in the frequency or EAIR of all-grade TEAEs were observed between subjects with or without SF3B1 mutations. Frequencies of serious, Grade 3/4 TEAEs, and TEAEs leading to discontinuation were similar between subjects with and without SF3B1 mutations, but EAIRs for these events were higher in non-mutated subjects.

Region: The difference between the number of non-US (n=391) and US (n=33) subjects limits the interpretability of potential differences in safety by region.

Table 77: Exposure and Treatment Emergent AEs and SAEs by Subgroups in Study ACE-536-MDS-002 (primary analysis, data cutoff: 31-Mar-2023): Safety Population

	Luspatercept					Epoetin Alfa				
	N	Median Treatment Duration (wks)	Median Doses Received	SAEs N (%) EAIR/ 100 PY	All TEAEs N (%) EAIR/ 100 PY	N	Median Treatment Duration (wks)	Median Doses Received	SAEs N (%) EAIR/ 100 PY	All TEAEs N (%) EAIR/ 100 PY
Total	**182**	**51.3**	**16.5**	**82 (45.1) 45.2**	**178 (97.8) 608.0**	**176**	**37.0**	**33.0**	**71 (39.7) 50.8**	**165 (92.2) 413.5**
By Baseline TB										
< 4 pRBC units	118	57.1	18.5	54 (45.8) 44.0	117 (99.2) 567.1	109	45.4	39.0	45 (41.3) 48.2	100 (91.7) 371.8
≥ 4 pRBC units	64	41.0	13.0	28 (43.8) 47.8	61 (95.3) 705.5	70	27.8	27.0	26 (37.1) 56.0	65 (92.9) 499.7
By RS Status										
RS+	133	57.1	19.0	56 (42.1) 38.6	130 (97.7) 569.2	128	37.0	36.0	44 (34.4) 44.0	118 (92.2) 370.7
RS-	49	33.0	10.0	26 (53.1) 71.4	48 (98.0) 745.7	50	46.4	28.5	26 (52.0) 65.5	46 (92.0) 573.2
By Baseline sEPO (U/L)										
≤ 200	145	57.0	18.0	66 (45.5) 43.8	142 (97.9) 600.6	143	46.0	39.0	62 (43.4) 51.7	134 (93.7) 394.6
> 200 to < 500	37	41.3	12.0	16 (43.2) 52.0	36 (97.3) 638.9	36	25.0	24.5	9 (25.0) 45.4	31 (86.1) 520.8
SF3B1 Mutation										
Yes	114	66.2	20.0	48 (42.1) 37.4	112 (98.2) 624.8	100	43.5	42.0	34 (34.0) 41.3	90 (90.0) 320.2
No	65	38.3	11.0	32 (49.2) 63.5	63 (96.9) 590.3	71	31.3	25.0	35 (49.3) 66.2	67 (94.4) 674.9

Treatment-emergent AEs: any AE occurring or worsening on or after the first dose of the study drug and within 42 days after the last dose of study drug.

Safety with PROCRIT and EPREX Epoetin Alfa

ACE-536-MDS-002 was a global, multi-regional study, enrolling subjects from 26 countries. In the US, subjects received epoetin alfa licensed as PROCRIT and, outside of the US, subjects received epoetin alfa licensed as EPREX or ERYPO. Given that different forms of epoetin alfa were used in this study depending on geographic location, an ad-hoc analysis was performed to examine the safety profile of subjects treated with EPREX/ERYPO, compared with that of the total study population, who may have received either EU-licensed EPREX/ERYPO or US-licensed PROCRIT. The safety profile of EPREX-treated subjects, the majority of subjects in ACE-536-MDS-002, did not differ appreciably from that of the total Safety Population.

Safety related to drug-drug interactions and other interactions

Given that drug-drug interactions generally do not occur with biologic agents, drug-drug interaction studies with luspatercept were not performed.

Discontinuation due to adverse events

The overall frequency and EAIR of TEAEs leading to study drug discontinuation (all-causality) was higher in the luspatercept arm compared with the epoetin alfa arm in ACE-536-MDS-002 (11.5%, 9.1/100 PY compared with 7.3%: 7.3/100 PY). When adjusted for exposure, there were no TEAEs of any causality

that led to treatment discontinuation with an exposure-adjusted incidence rate ≥ 2 events per 100 person-years higher in the luspatercept arm than in the epoetin alfa arm.

At the Week 24 safety assessment, the frequency of TEAEs leading to study drug discontinuation was similar between arms (3.8% in the luspatercept arm versus 5.0% in the epoetin arm).

TEAEs leading to discontinuation of study drug occurred in 14.3% (10.3/100 PY) of the TD MDS Pool (Table below). The most frequently observed PTs leading to study drug discontinuation were MDS (1.8%; 1.3/100 PY) and Sepsis (1.6%; 1.1/100 PY).

Table 78: TEAEs leading to Study Drug Discontinuation by SOC and PT in ≥ 2 Subjects in the TD MDS Pool - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05[a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept	Epoetin alfa	Luspatercept	Placebo	Luspatercept TD	Luspatercept	Luspatercept
	N = 182	N = 179	N = 153	N = 76	N = 80	N = 26	N = 441
System Organ Class	n (%),	n (%),	n (%),	n (%),	n (%),	n (%),	n (%), 95% CI
Preferred Term	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY	EAIR/100 PY
Subject with at least one specific event	21 (11.5) 9.1	13 (7.3) 7.3	24 (15.7) 8.6	6 (7.9) 13	16 (20.0) 17.8	2 (7.7) 15.8	63 (14.3) (11.2, 17.9) 10.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (5.5) 4.3	5 (2.8) 2.8	10 (6.5) 3.6	2 (2.6) 4.3	6 (7.5) 6.6	1 (3.8) 7.7	27 (6.1) (4.1, 8.8) 4.4
Myelodysplastic syndrome	6 (3.3) 2.6	3 (1.7) 1.7	2 (1.3) 0.7	1 (1.3) 2.2	0 (0.0) 0	0 (0.0) 0	8 (1.8) (0.8, 3.5) 1.3
Refractory anaemia with an excess of blasts	0 (0.0) 0	0 (0.0) 0	3 (2.0) 1.1	0 (0.0) 0	4 (5.0) 4.4	0 (0.0) 0	7 (1.6) (0.6, 3.2) 1.1
Transformation to acute myeloid leukaemia	2 (1.1) 0.9	1 (0.6) 0.6	3 (2.0) 1.1	1 (1.3) 2.2	0 (0.0) 0	0 (0.0) 0	5 (1.1) (0.4, 2.6) 0.8
Infections and infestations	3 (1.6) 1.3	4 (2.2) 2.2	3 (2.0) 1.1	0 (0.0) 0	2 (2.5) 2.2	0 (0.0) 0	8 (1.8) (0.8, 3.5) 1.3
Sepsis	1 (0.5) 0.4	2 (1.1) 1.1	3 (2.0) 1.1	0 (0.0) 0	1 (1.3) 1.1	0 (0.0) 0	5 (1.1) (0.4, 2.6) 0.8

General disorders and administration site conditions	1 (0.5) 0.4	0 (0.0) 0	3 (2.0) 1.1	1 (1.3) 2.2	2 (2.5) 2.2	0 (0.0) 0	6 (1.4) (0.5, 2.9) 1
General physical health deterioration	1 (0.5) 0.4	0 (0.0) 0	0 (0.0) 0	1 (1.3) 2.2	2 (2.5) 2.2	0 (0.0) 0	3 (0.7) (0.1, 2.0) 0.5
Fatigue	0 (0.0) 0	0 (0.0) 0	2 (1.3) 0.7	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (0.5) (0.1, 1.6) 0.3
Vascular disorders	1 (0.5) 0.4	1 (0.6) 0.6	1 (0.7) 0.4	0 (0.0) 0	1 (1.3) 1.1	0 (0.0) 0	3 (0.7) (0.1, 2.0) 0.5
Aortic stenosis	1 (0.5) 0.4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (1.3) 1.1	0 (0.0) 0	2 (0.5) (0.1, 1.6) 0.3

TEAEs are defined as any new AE or AE that worsened in severity on or after the first dose of IP until 42 days after the last dose of IP, as well as serious AEs made known to the Investigator at any time thereafter that are suspected to be related to the IP.

A subject is counted only once for multiple events within each SOC/PT. A highest grade will be used for a subject who experiences an AE with same PT/SOC more than once.

EAIR/100 PY = 100 * (the number of subjects with the specific TEAE) / the total exposure time (in years) to the event.

MedDRA Version 25.1 is used for coding.

CTCAE version 4.03 is used for A536-03/05, ACE-536-MDS-001 and ACE-536-MDS-002; CTCAE version 5.0 is used for ACE-536-MDS-004 and LTFU-001.

[a] Includes data collected in Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Treatment-emergent Adverse Events Leading to Dose Modification

In ACE-536-MDS-002, TEAEs leading to dose reduction were infrequent and occurred at similar frequencies across arms (3.8%; 3.1/100 PY in the luspatercept arm versus 3.4%; 3.5/100 PY in the epoetin alfa arm). At the Week 24 safety assessment, the frequency of TEAEs leading to dose reduction was similar between arms; 7 subjects (3.8%) in the luspatercept arm compared with 6 subjects (3.4%) in the epoetin alfa arm. TEAEs leading to dose reduction occurred in 4.1% (EAIR 3.1/100 PY) of the TD MDS Pool. The only TEAEs leading to dose reduction that occurred in more than 1 subject in the TD MDS Pool were: headache, 3 subjects (0.7%; EAIR 0.5/100 PY), diarrhea, 2 subjects (0.5%; EAIR 0.3/100 PY), ALT increased, 2 subjects (0.5%; EAIR 0.3/100 PY) and hypertension, 2 subjects (0.5%; EAIR 0.3/100 PY).

In ACE-536-MDS-002 TEAEs leading to dose interruption occurred at similar frequencies across arms (33.5%; 32.7/100 PY in the luspatercept arm versus 28.5%; 36.7/100 PY in the epoetin alfa arm).When adjusted for exposure, the only TEAE of any causality in ACE-536-MDS-002 that led to treatment interruption with an exposure-adjusted incidence rate ≥ 2 events per 100 person-years higher in the luspatercept arm versus the epoetin alfa arm was diarrhea (2.2/100 PY vs 0). At the Week 24 safety assessment, the frequency of TEAEs leading to dose interruption was similar between arms; 33.5% in the luspatercept arm compared with 28.5% in the epoetin alfa arm. AEs leading to study drug interruption occurred in 28.3% of the TD MDS Pool (Table below). The most frequently observed PTs leading to study drug interruption included COVID-19 (4.3%; 3.2/100 PY) and Pneumonia (2.3%; 1.7/100 PY). Dose interruption due to anemia was observed in 3 subjects (0.7%; 0.5/100 PY) in the TD-MDS Pool.

Table 79: TEAEs leading to Study Drug Interruption by SOC and PT in ≥ 1% of Subjects in the TD MDS Pool - TD MDS Safety Population

	Pivotal Study ACE-536-MDS-002		Supportive Study ACE-536-MDS-001[a]		Supportive Studies A536-03/05 [a]	Supportive Study ACE-536-MDS-004	TD MDS Pooled
	Luspatercept	Epoetin Alfa	Luspatercept	Placebo	Luspatercept TD	Luspatercept	Luspatercept
	N = 182	N = 179	N = 153	N = 76	N = 80	N = 26	N = 441
System Organ Class Preferred Term	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), EAIR/100 PY	n (%), 95% CI EAIR/100 PY
Subject with at least 1 specific event	61 (33.5) 32.7	51 (28.5) 36.7	42 (27.5) 20.5	4 (5.3) 9.1	17 (21.3) 23.2	5 (19.2) 39.9	125 (28.3) (24.2, 32.8) 26.1
Infections and infestations	25 (13.7) 11.7	27 (15.1) 16.8	17 (11.1) 6.9	1 (1.3) 2.2	6 (7.5) 7	5 (19.2) 39.9	53 (12.0) (9.1, 15.4) 9.5
COVID-19	11 (6.0) 5	11 (6.1) 6.4	2 (1.3) 0.7	0 (0.0) 0	1 (1.3) 1.1	5 (19.2) 39.9	19 (4.3) (2.6, 6.6) 3.2
Pneumonia	4 (2.2) 1.7	9 (5.0) 5.2	4 (2.6) 1.5	0 (0.0) 0	2 (2.5) 2.3	0 (0.0) 0	10 (2.3) (1.1, 4.1) 1.7
Injury, poisoning and procedural complications	7 (3.8) 3.1	10 (5.6) 5.9	11 (7.2) 4.2	0 (0.0) 0	3 (3.8) 3.4	0 (0.0) 0	21 (4.8) (3.0, 7.2) 3.6
Femur fracture	0 (0.0) 0	0 (0.0) 0	4 (2.6) 1.5	0 (0.0) 0	1 (1.3) 1.1	0 (0.0) 0	5 (1.1) (0.4, 2.6) 0.8
Gastrointestinal disorders	11 (6.0) 4.9	2 (1.1) 1.1	4 (2.6) 1.5	0 (0.0) 0	3 (3.8) 3.4	0 (0.0) 0	18 (4.1) (2.4, 6.4) 3
Diarrhoea	5 (2.7) 2.2	0 (0.0) 0	2 (1.3) 0.7	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	7 (1.6) (0.6, 3.2) 1.2
Blood and lymphatic system disorders	7 (3.8) 3.1	5 (2.8) 2.9	7 (4.6) 2.7	1 (1.3) 2.2	2 (2.5) 2.2	0 (0.0) 0	16 (3.6) (2.1, 5.8) 2.7
Neutropenia	3 (1.6) 1.3	1 (0.6) 0.6	3 (2.0) 1.1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	6 (1.4) (0.5, 2.9) 1
Thrombocytopenia	4 (2.2) 1.7	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (1.3) 1.1	0 (0.0) 0	5 (1.1) (0.4, 2.6) 0.8
Respiratory, thoracic and mediastinal disorders	10 (5.5) 4.5	2 (1.1) 1.1	3 (2.0) 1.1	1 (1.3) 2.2	1 (1.3) 1.1	0 (0.0) 0	14 (3.2) (1.7, 5.3) 2.3
Dyspnoea	4 (2.2) 1.7	0 (0.0) 0	1 (0.7) 0.4	1 (1.3) 2.2	1 (1.3) 1.1	0 (0.0) 0	6 (1.4) (0.5, 2.9) 1

TEAEs are defined as any new AE or AE that worsened in severity on or after the first dose of IP until 42 days after the last dose of IP, as well as serious AEs made known to the Investigator at any time thereafter that are suspected to be related to the IP.

A subject is counted only once for multiple events within each SOC/PT. A highest grade will be used for a subject who experiences an AE with same PT/SOC more than once.

EAIR/100 PY = 100 * (the number of subjects with the specific TEAE) / the total exposure time (in years) to the event.

MedDRA Version 25.1 is used for coding.

CTCAE version 4.03 is used for A536-03/05, ACE-536-MDS-001 and ACE-536-MDS-002; CTCAE version 5.0 is used for ACE-536-MDS-004 and LTFU-001.

Source: Appendix 1 Table 14.3.2.9

[a] Includes data collected in Study ACE-536-LTFU-001 for TD subjects who rolled over from Studies ACE-536-MDS-001 and A536-05.

Post marketing experience

Luspatercept Marketing Experience

Luspatercept is marketed worldwide using the trade name "REBLOZYL." Luspatercept is approved in the US, EU, and other countries for the treatment of adult patients with transfusion-dependent anemia due to very low-, low- and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy and for adult patients with transfusion-dependent anemia associated with beta-thalassemia. A list of approvals and indications by country can be found in the luspatercept Investigator's Brochure.

Reporting of Results From Post-Authorisation Safety Studies

Study ACE-536-LTFU-001 is considered as PASS Category 3 in the EU-RMP. The currently available safety and efficacy data from this ongoing clinical trial has been reviewed through 24- Jun-2023 and a new significant safety finding of extramedullary hematopoietic masses with complications in patients with transfusion dependent and non-transfusion dependent β-thalassemia was identified as having potential impact on the safety profile of luspatercept and has been summarised in the SmPC and PI for β-thalassemia approved indications.

No ongoing interventional or non-interventional PASS studies were discontinued due to safety concerns through 24-Jun-2023.

An annual assessment of cases of secondary primary malignancies and progression to AML is conducted in Sponsor-initiated and Investigator-initiated clinical trials across the luspatercept clinical development program for 5 years post approval (PMR 3709-4) of BLA 761136 which required that the Sponsor conduct an assessment of cases of secondary primary malignancies (and malignancies for β-thalassemia), to include hematological malignancies (AML, de-novo AML, transformation to AML), and solid tumors identified in sponsor-initiated and investigator-initiated clinical trials across the entire luspatercept development program for 5 years post approval. In addition, a post-marketing safety commitment (PMR 3784-1) was made to the US FDA for REBLOZYL BLA 761136 dated 03-Apr-2020 to characterise the long-term safety of luspatercept in patients with MDS-RS or MDS/MPN-RS-T for study ACE-536-MDS-001 with at least 5 years of follow-up for enrolled subjects, which was completed May 2022; the final report is dated 22-Mar-2023.

2.5.1. Discussion on clinical safety

Luspatercept is a recombinant fusion protein that binds transforming growth factor-beta (TGF-β) superfamily ligands and inhibits Smad2/3 signalling. In subjects suffering from MDS and β-thalassemia, Smad2/3 inhibition is expected to reduce the abnormal high Smad2/3 activity that hampers effective erythropoiesis. However, TGF-ß signalling is involved in cellular development and differentiation of various tissues and cell types besides erythropoiesis. Possible consequences of the inhibition of TGF-ß superfamily ligands are not well studied at clinical level. (Long-term) treatment with substances that regulate such pleiotropic pathways, especially pathways involved in cell growth, harbour an intrinsic potential of abnormal cell growth, among others.
Luspatercept (REBLOZYL; BMS-986346, ACE-536) is currently licensed for the treatment of "*adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy"* as well as *"anaemia associated with transfusion-dependent and non-transfusion-dependent beta-thalassaemia"*. With the current submission, the MAH intends to extend the MDS-related indication to "adults for the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS)."

Safety data in this submission include 1 pivotal phase 3 study, 4 supporting clinical studies and one long-term follow-up study (Pivotal study: ACE-536-MDS-002, Supportive studies: A536-03, A536-05, ACE-536-MDS-001, ACE-536-MDS-004, Long-term follow-up study: ACE-536-LTFU-001). All were open-label studies in transfusion-dependent subjects with anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS). Furthermore, available narratives for malignancy events are provided from a study in Japanese patients (ACE-536-MDS-003).
Studies ACE-536-MDS-002 (MDS-002; n=182 subjects treated with luspatercept) and ACE-536-MDS-001 (MDS-001; n=153 subjects treated with luspatercept) had a study control arm with either active comparator (epoetin alfa; n=179) or placebo (n=76), respectively. Studies A536-03 and its follow-up study A536-05 followed different dosing strategies for luspatercept. The long-term follow-up study ACE-536-LTFU-001 currently enrolled subjects from study A536-05 (n=5) and ACE-536-MDS -001 (n=73). Importantly, study ACE-536-MDS-001 was conducted in subjects refractory/ineligible for ESA therapy and exclusively in patients with ring sideroblasts. This study is completed and was already submitted and assessed for the existing marketing authorisation application in MDS patients (see EPAR for Reblozyl). Study ACE-536-MDS-002 is completed and intended to support the approval of ESA-naïve patients and patients without ring sideroblasts (see discussion on the baseline characteristics of included patients below). Thus, this pivotal study is the main source of evidence for this type II variation and therefore will be the focus of assessment.

Safety data from luspatercept treated transfusion-dependent subjects from the above mentioned clinical studies, except for study ACE-536-MDS-003, are also reported as TD MDS safety pool. Study ACE-536-MDS-003 followed subjects that do not require RBC transfusions. The study narratives provide information on malignancies which are considered highly relevant to assess the safety profile of luspatercept in patients with MDS.

Study population and exposure
In total 441 transfusion-dependent patients with MDS are included in the provided TD MDS safety pool (ACE-536-MDS-002, ACE-536-MDS-001, A536-03, A536-05, ACE-536-MDS-004; data from study ACE-536-LTFU-001 are included in the respective original study subjects participated before enrolling to the long-term follow-up study).
The overall treatment discontinuation of subjects was higher in respective control arms compared to luspatercept in studies MDS-002 and MDS-001 (70.4% vs. 57.1% in MDS-002 and 100% vs. 92.8% in MDS-001, respectively). Lack of efficacy was the main reasons of treatment discontinuation and the proportion of subjects that discontinued treatment with epoetin alfa due to lack of efficacy was substantially higher compared to luspatercept (38% vs. 22.5%, respectively). Also, a mildly higher proportion of subjects discontinued the study MDS-002 (41.9% vs. 36.8% for epoetin alfa and luspatercept, respectively). Discontinuations due to death were very similar for both treatment arms. Thus, based on reported discontinuations the treatment with luspatercept appears favourable, at least in the study setup of MDS-002. As per fewer discontinuations, patients were treated longer with luspatercept (median/mean treatment duration of 51.64/66.17 weeks vs. 37/51.93 weeks for lupatercept and epoetin alfa in study MDS-002, respectively), but with fewer doses required (median/mean number of doses received was 16.5/20.6 vs. 33/46.6 weeks for lupatercept and epoetin alfa in study MDS-002, respectively) as per the intended/established posology of either product. Data from studies MDS-001 as well as A536-03/05 also include subjects currently enrolled in the long-term follow up study ACE-536-LTFU-001. Thus, data include subjects following a longer treatment on luspatercept as compared to already assessed data for TD MDS subjects in the published EPAR and as compared to subjects that were randomized to placebo treatment in study MDS-001 (median/mean treatment duration of 50.9/95.3 weeks vs. 24/31.7 weeks for lupatercept and placebo in study MDS-001, respectively). The TD MDS pool currently includes subjects with median/mean exposure of 46.4/72.6 weeks. This appears principally acceptable and comparable to the extent of exposure submitted for the licensed MDS indication with

median/mean exposure of 49/45.6 weeks in the MDS pool (see EPAR).

Subject demographics and baseline (disease) characteristics appear mostly balanced across treatment arms within studies MDS-001 and MDS-002. The median baseline transfusion burden was the same for both treatment arms within each study, but substantially higher in study MDS-001 compared to MDS-002 (3 units in study MDS-002 and 6 units within study MDS-001).
Within each study a mildly lower proportion of subjects treated with luspatercept were categorised as transfusion burden category ≥4 units compared to epoetin alfa (MDS-002; 35.2% and 39.1% in luspatercept and epoetin alfa, respectively) or placebo (MDS-001; 81.7% and 85.5% in luspatercept and placebo, respectively). Also, in study MDS-002 more intermediate (18.7% and 16.2% in luspatercept and epoetin alfa, respectively) and less low risk MDS patients (71.4% and 73.2% in luspatercept and epoetin alfa, respectively) were included in the luspatercept arm. This mild imbalance is also reflected in the total TD MDS pool compared to control arms in studies MDS-001 and MDS-002. Furthermore, the majority of subjects had the SF3B1 mutation (70.7% of the TD MDS pool) and a higher proportion of subjects with mutation was included in luspatercept arms of controlled studies (e.g. 62.6% and 55.9% in luspatercept and epoetin alfa in study MDS-002, respectively). However, imbalances in TD burden, MDS risk and mutation status across treatment arms within studies appear too small to crucially affect the overall evaluation of the safety profile for transfusion-dependent patients with MDS. For a discussion on safety results for subgroups please see below. It is critically noted that subjects without ring sideroblasts were limited in study MDS-002 with 27-28% of all subjects (n=49 and n=50 for the luspatercept and epoetin alfa arms, respectively) and the TD MDS safety pool with 17.9% of all TD MDS subjects treated with luspatercept (n=79). It is noted that subjects without ring sideroblasts were more likely to reduce, interrupt or discontinue dosing due to TEAEs, which is in line with shorter median treatment duration and number of doses, compared to subjects with ring sideroblasts. Furthermore, subjects without ring sideroblasts also had a substantially worse treatment effect for the treatment with luspatercept compared to patients without ring sideroblasts. Upon request the MAH provided a thorough depiction of the safety profile for RS- and RS+ patients separated by treatment groups for study MDS-002. In many aspects RS- patients show higher incidences of safety events compared to RS+ subjects (especially SAEs, grade 5 TEAEs, AEs leading to drug withdrawal or dose reduction as well as AESIs asthenia and thromboembolic events), but incidences between treatment groups of study MDS-002 within the RS- subgroup are largely comparable (i.e. epoetin and luspatercept). In conclusion, it appears that patients without ring sideroblasts are indeed more vulnerable to unwanted effects of treatment against MDS or the background disease drives more comorbidities compared to patients with ring sideroblasts. A more heterogenous disease background in this subgroup might be one possible contributing factor. In any case, it is evident that a worse safety profile is to be expected for the treatment of the RS- subgroup with luspatercept (but also epoetin alfa) compared to RS+ subjects.

Also the higher proportion of subjects with ECOG Performance of 2 in respective control arms of studies MDS-001 and MDS-002 is critically noted. Reported post-baseline ECOG of 3 (3.5% and 3% for luspatercept and epostin alfa, respectively) and 4 (0.6% and 0.6% for luspatercept and epostin alfa, respectively) were comparable across treatment arms in study MDS-002. However, as baseline measures were imbalanced, the worsening of ECOG status might not be reflected in the depiction of subjects with status of 3 or 4. During study MDS-001 in total 38.5% of subjects worsened by 1 or more points and 15% worsened by 2 or more points during luspatercept treatment, whereas 15.7% of subjects worsened by 1 or more points and 2.6% by 2 or more points during placebo treatment. Similarly, during study MDS-002 in total 27% of subjects worsened by 1 or more points and 11.7% worsened by 2 or more points while on luspatercept treatment, but only 17.5% of subjects worsened by 1 or more points and 6.2% by 2 or more points while on epoetin alfa treatment. Thus, the risk of worsening in ECOG Performance appears to be higher while on luspatercept treatment compared to placerbo (MDS-001) or epoetin alfa (MDS-002) treatment. However, in both studies subjects were followed longer in the

luspatercept arm compared to the respective comparator arms. Time is indeed a relevant factor for the assessment of ECOG performance as the underlying disease, but also other comorbidities and age-related health decline might contribute to a worsening of performance status. Thus, no clear relation to luspatercept treatment can be established for the worsening of ECOG performance compared to placebo or epoetin alfa.

Baseline laboratory values were well balanced across treatment arms within studies MDS-001 and MDS-002. The patient population included in clinical studies was rather old (>80% was ≥65 years in the TD MDS pool) and a variety of disease comorbidities were reported that are, however, to be expected for the selected patient population. A total of 98.4% of subjects in the TD MDS pool had at least one medical history event and a similar proportion is reported for control arms of studies MDS-001 and MDS-002. It is noted, that the SOC Blood and lymphatic system disorders affected more subjects in the active control group of study MDS-002 compared to the group treated with luspatercept (7.7% and 13.4% of subjects treated with luspatercept and epoetin alfa, respectively). Despite the described imbalances in historical laboratory findings on the SOC Blood and lymphatic system disorders, no safety relevant differences between treatment groups of study MDS-002 are apparent from the laboratory data during the study. The aged patient population with several comorbidities is also reflected in the reported use of prior and concomitant medications. In total, 97.5% of subjects in the TD MDS pool had at least one prior medication used and 98.6% of subjects used at least one concomitant medication. No major imbalances were identified across study groups within MDS-001 and MDS-002 that are expected to crucially impact the interpretation of study results.

During the procedure the MAH noted that several sites inadvertently collected additional blood samples (beyond the pre-specified time points in the protocol) from subjects in Study ACE-536-MDS-002, which was reported as a Potential Serious Breach of GCP. Upon request, the MAH presented a root cause analysis together with corresponding corrective and preventive actions (CAPA). According to the MAH the excess sampling was mainly caused by providing only one sort of sampling kit referring to a sampling schedule of "every 3 weeks" and including material for all sampling procedures that would be required for this sampling schedule. In total 4057 samples from 271 subjects (out of 363) and at 119 study sites (out of 144) were taken in excess and oversampling was roughly balanced between both treatment groups of study MDS-002. For ADA analysis in total 756 samples (407 in the luspatercept and 349 in the epoetin alfa treatment arm) from 92 subjects were taken in excess. This GCP breach is critically noted. However, the presented explanation can be followed and the proposed corrective measures to prevent such protocol violations in future studies seem reasonable. Furthermore, the additional sampling is not expected to negatively impact the interpretation of results as only 3 samples were positive for ADAs from patients that were also concluded as ADA positive from regular samples taken for ADA analysis. It is concluded that no concerns regarding ADA status derive from the excess samples taken.

Adverse Events

As mentioned above, the assessment will focus on controlled studies (i.e. pivotal study MDS-002 for this application and study MDS-001) and the TD MDS safety pool. Safety data form study MDS-001 were also assessed in the scope of a previous authorisation application. Limitations that come along comparisons across studies (e.g. differences in study populations) should be kept in mind when following cross references.

With respect to reported TEAEs it is noted that several categories were documented with higher proportion of subjects that were treated with luspatercept in comparison to the active comparator epoetin alfa (within study MDS-002). Subjects with at least one TEAE as well as *suspected related* TEAE occurred more often for luspatercept (97.8% and 92.2% of subjects with TEAEs as well as 33.5% and 20.1% of subjects with *suspected related* TEAEs for luspatercept and epoetin alfa, respectively) in study MDS-002, which is also reflected in exposure adjusted incidence rates.

SOCs with a difference ≥2% in *suspected related* TEAEs between study groups in study MDS-002 were General disorders and administration site conditions (especially PT fatigue with 4.4% vs. 0%), Gastrointestinal disorders (especially PT nausea with 4.9% vs. 1.1%), Nervous System disorders (especially PTs headache with 3.3% vs. 1.7% and dizziness with 2.2% vs. 0.6%), Respiratory thoracic and mediastinal disorders (especially PT dyspnoea with 3.3% vs. 0%) and Blood and lymphatic system disorders (especially PTs neutropenia with 2.2% vs. 0% and thrombocytopenia with 1.6% vs. 0%) with higher frequencies for subjects treated with luspatercept. Only the SOC Musculoskeletal and connectivity disorders was reported more frequently (i.e. ≥2%) in subjects treated with epoetin alfa. The most common TEAEs by SOCs in the TD MDS Pool were General disorders and Administration site conditions (61.7%), Infections and infestations (56.9%), Gastrointestinal disorders (51%) and Musculoskeletal and Connective tissue disorders (42.6%), the most common PTs in the TD MDS Pool were fatigue (22.4%), diarrhoea (21.5%), peripheral oedema (18.4%), asthenia (16.1%), dyspnoea (15.9%), back pain (15.6%) nausea (15.4%), dizziness (14.7%) and hypertension (14.5%). Notably, the causality of study treatment and traumatic fractures was not excluded from clinical data in beta thalassemia patients (see section 4.4 and 4.8 of the SmPC). With respect to all reported PTs of TEAEs referring to fracture (tooth fracture excluded) in the most recent ISS (Data Extraction Date: 17MAY2023), the incidence rate is comparable between luspatercept and epoetin alfa in study MDS-002 (11.5% and 11.7%, respectively) and does appear to reasonably reflect the longer treatment duration of subjects treated with luspatercept in study MDS-001 (including data from the long term-follow-up ACE-536-LTFU-001) compared to subjects treated with placebo (17.6% of subjects compared to 13.1% with fracture and a mean treatment duration of 76.7 and 31.7 weeks, respectively). Thus, a general increased risk of fractures in MDS patients upon treatment with luspatercept is currently not established, which is also in line with conclusions during the initial marketing authorisation application for MDS patients. Still, the risk of fractures could be increased after longer treatment duration and cannot be fully excluded at the present. Notably, the causality of study treatment and traumatic fractures was not excluded from clinical data in beta thalassemia patients (see 4.4 and 4.8 of the SmPC). Thus, the risk of fractures (traumatic and pathological) has been added as Event Of Interest in the ongoing LTFU study (ACE-536-LTFU-001) with a respective protocol amendment and bone fractures have been added as important potential risk to the RMP. The potential risk will be discussed in future reports. Based on the ISS (Data Extraction Date: 17MAY2023) the PTs atrial fibrillation as well as cardiac failure both were observed as TEAE, as grade 3/4 TEAEs and as serious TEAE with higher frequencies compared to the respective control treatment in either phase 3 study (TEAEs PT atrial fibrillation: 3.8%, 1.1%, 5.9%, 1.3%; TEAEs PT cardiac failure: 2.2%, 1.7%, 2.6%, 0%; serious TEAE PT atrial fibrillation: 1.6%, 0%, 1.3%, 0%; serious TEAE PT cardiac failure: 1.1%, 0%, 2%, 0%; all for luspatercept MDS-002, epoetin alfa MDS-002, luspatercept MDS-001 and placebo MDS-001, respectively). Notably, both PTs could also be a further consequence of hypertension as an identified very common unwanted effect of luspatercept. Thus, it is concluded that a possible causal relation to study treatment is at least reasonable and both PTs should be included as ADR in section 4.8 of the SmPC. A possible relation of study drug treatment to possible mineral imbalances (e.g. PTs hyperkalaemia, hyperglycaemia and hypomagnesaemia) could principally also be related to the identified ADR of dehydration as well as kidney injury or abnormal heart rhythm (especially related to imbalances in potassium). Furthermore, it is noted that cases of hyperkalaemia were considered related to study treatment by the investigator and some of the laboratory imbalances did not resolve while luspatercept treatment was ongoing. Thus, the MAH should group PTs that indicate electrolyte imbalances (especially calcium, chloride, magnesium, phosphate, potassium and sodium) and report duration and severity of events as well as the conclusion by the investigator regarding possible relation to study treatment (OC). The detailed list of TEAEs and *suspected related* TEAEs (i.e. SOCs and PTs) appears to roughly reflect events as documented from previous marketing authorisation application of TD MDS patients with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy, as reported from study MDS-001. However, applied criteria to concluded adverse drug reactions are currently not supported. The currently applied reasoning of causality based on difference in EAIRs >2 or a

crude incidence difference of > 2.0% compared to placebo in study MDS-001 is based on a minimum incidence rate for the conclusion as ADR. Causality could also be concluded independent from incidence rates and even a single event could be concluded with possible causal relation to the study treatment. It is principally acknowledged that the elderly population might have a higher prevalence of possible background diseases and physiological dysfunctions, however, the population is also more vulnerable for possible unwanted effects and any exacerbation of a possible medical background is also to be considered an unwanted drug effect.
It is further noted that TEAEs (SOCs and PTs) in study MDS-002 appear with an incidence rate that is approximately a factor 2 of the incidence rate reported for study MDS-001. It could be speculated whether longer study duration and higher number of doses received might increase the chance of an event to occur. However, this difference is also reflected in exposure adjusted incidence rates, even though somewhat less pronounced. In fact subjects in study MDS-001 had a longer treatment duration, a more advanced disease status (i.e. higher baseline transfusion burden and unsatisfactory response to previous therapy), a higher rate of comorbidities and a mildly higher rate in subjects with ECOG performance status 2 compared to subjects included in study MDS-002. In sum these factors might explain higher rates in study MDS-001 compared to study MDS-002.
Grade 3 or 4 events occurred in a higher proportion in patients treated with luspatercept during study MDS-002 compared to subjects treated with epoetin alfa (58.8% and 49.2% of subjects had at least one TEAE of category 3 or 4, and 7.7% and 2.2% of subjects had at least one *suspected related* TEAE of category 3 or 4 for luspatercept and epoetin alfa, respectively). The most frequent PT of grade 3 or 4 in subjects treated with luspatercept in study MDS-002 was hypertension with 9.9% of subjects experiencing at least one event, but only 4.5% of subjects treated with epoetin alfa experiencing at least one event. Also, the most frequent PT in *suspected related* TEAS of grade 3 or 4 was hypertension (2.2% and 0.6% of subjects treated with luspatercept and placebo, respectively). Thus, it is concluded that hypertension is a risk that is to be expected for the treatment with luspatercept. Other TEAEs of grade 3 or 4 with a difference ≥2% were pneumonia (4.4% vs. 7.3%) and neutropenia (3.8% vs. 6.1% with higher rates for epoetin alfa as well as thrombocytopenia (4.4% vs. 1.1%), syncope (3.8% vs. 1.1%) as well as dyspnoea (4.4% vs. 1.1%) with higher rates for luspatercept.
The long-term Follow-up Period of study MDS-002 consists of 3 years post last dose or 5 years post first dose, whichever is longer, unless the subject withdraws consent from the study, dies, or is lost to follow-up. The assessment of critical safety parameters is covered in this long-term follow-up period. Furthermore, study treatment can be followed by participating subjects as long as they are receiving benefit and consent to remain on treatment. This plan is acknowledged.
In summary it can be concluded that treatment-related adverse events, including grade 3 or 4 events, occurred more frequently for patients treated with luspatercept compared to epoetin alfa during study MDS-002. Upon request the MAH clarified that the imbalance in safety profiles reflects the known safety profiles and adverse drug reactions of both luspatercept and epoetin alfa. Also, the longer reporting period for AEs (as per median treatment duration) in the luspatercept arm compared with the epoetin alfa arm might further support a higher rate of reported AEs. The general pattern of events reported in the TD-MDS pool appears principally comparable to data reported in the previous application for MDS patients (study MDS-001, see EPAR for Reblozyl).

Serious AEs and Deaths

Slightly more subjects with serious TEAEs (45.1% vs. 39.7% of subjects treated with lupatercept vs. epoetin alfa, respectively), but apparently a bit less subjects with serious TEAEs considered as *suspected related* (0.5% vs. 1.7% of subjects treated with lupatercept vs. epoetin alfa, respectively) were reported during study MDS-002. The rate of serious adverse events appears generally rather high, but is certainly driven to a big proportion by the aged population with a multitude of disease comorbidities as is also supported by rates seen in comparator arms in studies MDS-001 and MDS-002. As discussed for TEAEs above, in some cases serious events occurred with evidently higher frequency in study MDS-001, but the

pattern is not as clear.

PTs of serious fractures appear to have occurred in more subjects treated with luspatercept compared to epoetin alfa during interim analysis (11 vs. 4 events, respectively), but this discrepancy was not evident after final analysis (13 vs. 10 events in 10 vs. 9 subjects, respectively). History of osteopenia (5 vs. 3 subjects), osteoporosis (18 vs. 17 subjects) or osteoarthritis (20 vs. 19 subjects) was reported for both treatment groups (with mildly more cases in the group treated with luspatercept). The difference in SOC General disorders and administration site conditions in study MDS-002 (6.6% vs. 2.2% in luspatercept vs. epoetin alfa, respectively) appears to be driven mostly by the higher rate in PT death rated as serious TEAE in subjects treated with luspatercept (4 events in luspatercept vs. no event for epoetin alfa) without further specification of reasons for the event. However, the total number of deaths was comparable for both treatment arms within study MDS-002 (n=39 and n=38 subjects treated with luspatercept and epoetin alfa, respectively). Also, the time of death since on/off treatment does not indicate any specific pattern of concern. The cause of death (as reported as grade 5 TEAE in 11 and 12 subjects treated with luspatercept and epoetin alfa, respectively) also does not reveal any further imbalance that would indicate higher risk for the treatment with luspatercept. Causes of deaths appear overall as expected for the natural course of the disease in the rather aged patient population. A higher rate in deaths is evident for study MDS-001 (37.9% of subjects treated with luspatercept) compared to study MDS-002 (21.4% of subjects treated with luspatercept), without apparent difference across study groups within each study (35.5% of subjects treated with placebo in MDS-002 and 21.2% of subjects treated with epoetin alfa in MDS-001). Differences across studies are most likely based on the longer study duration of study MDS-001 in a vulnerable study population.

Adverse events of special interest

The selection of AESI as presented by the MAH can be followed based on MoA, underlying disease, signals from preclinical studies and signals from previous clinical studies (see also SmPC). However, it is noted that musculoskeletal disorders (including e.g. bone pain) are not included in the list of AESIs for study MDS-002 despite respective events of interest in the previous data submission for initial MAA (see EPAR). TEAEs in the SOC Musculoskeletal and connective tissue disorders were reported by 37.4% of subjects during study MDS-002, for both treatments. The most common PTs were back pain (12.1% vs. 8.9%), arthralgia (8.8% and 11.2%), myalgia (4.9% and 2.8%), osteoarthritis (4.9% vs. 3.9%) and pain in extremity (3.8% vs. 4.5%). As per study MDS-001 it appears that treatment might cause a higher rate of events in the SOC, as a higher proportion of subjects reported TEAEs when treated with luspatercept compared to placebo (52.3% and 36.8% of subjects, respectively), but the trend was not evident when considering EAIR (63.1 and 86, respectively). Also, TEAEs of grade 3 or 4 in the SOC were a bit more frequent in subjects treated with luspatercept in studies MDS-001 (6.5%) and MDS-002 (4.4%) compared to placebo (3.9%) or active comparator (2.2%), respectively, but the trend in EAIR was not as evident (MDS-002: 3.6 vs. 2.3) or even reversed (MDS-001) when considering EAIR. Also, based on final data analysis fractures rated as serious TEAE appeared to occur in comparable frequency in subjects treated with luspatercept or epoetin alfa (see discussion on serious TEAEs above).

AESI: Malignancies and premalignant disorders

The reporting of malignancies and premalignant disorders is considered highly relevant for the evaluation of the risk profile of luspatercept treatment due to the interference with TGF-ß signalling. However, currently available data do not cover a sufficiently long period to provide robust insight in potential malignancies caused by the treatment with luspatercept. Importantly, a long-term follow-up period of 5 years from the date of the first dose of study drug, or 3 years from the last dose, is planned for all subjects that participated in TD MDS studies (unless the subject withdrew consent from the study, died or was lost to follow-up) to record malignancies/pre-malignancies and progression to AML. This is acknowledged. Available data from the final analysis of study MDS-002 indicate a mild imbalance in the

rate of subjects with at least one malignancy event also (9.3% and 6.7% of subjects treated with luspatercept and epoetin alfa, respectively), which is also apparent for the respective list of AESIs (8.8% and 5.6% of subjects with malignancies treated with luspatercept and epoetin alfa, respectively). The imbalance in events is also confirmed when compared to placebo during study MDS-001, with 7.2% and 1.3% of subjects treated with lupatercept and placebo (including data from the long-term extension study ACE-536-LTFU-001). The total number of subjects with malignancies is small, the study population is aged and the study duration currently appears too short for robust conclusions. From study ACE-536-MDS-003 currently narratives for 4 subjects with events rated as pre-malignancy were reported. However, context for these events is unclear as no further information for this study is provided. In conclusion, as per mechanism of action and reported incidences, an increased risk of malignancies cannot be excluded.

The risk for a progression to acute myeloid leukaemia currently does not appear to be higher for the treatment with luspatercept when compared to epoetin alfa or placebo in exposure adjusted incidence rates. The same applies for premalignant disorders, with rather higher EAIR for comparator arms across studies MDS-001 and MDS-002. For a more meaningful interpretation regarding a potential malignancy risk (including progression to AML and premalignant disorders) upon treatment with luspatercept, a longer observation period of treatment will be required. The outlined long-term follow-up strategy for study MDS-002 is acknowledged in this aspect.

AESI: Progression to higher risk MDS

The progression to higher risk MDS is a natural risk of the disease progression and currently appears comparable for the treatment with luspatercept when compared to epoetin alfa in study MDS-002. However, data from study MDS-001, including the now available data from the long-term study ACE-536-LTFU-001, indicate a higher rate in subjects treated with luspatercept compared to placebo (n=4 and n=0, respectively). This was not evident from data available during the licensure for MDS patients with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy (n=1 and n=0, respectively, see EPAR). However, only a few subjects on placebo treatment were followed during the long-term follow-up study ACE-536-LTFU-001 for disease progression and three of four events of MDS disease progression in the luspatercept treatment arm were reported during this long-term study. Thus, the higher rate of MDS disease progression in subjects treated with luspatercept during study MDS-001 (with long-term data included) compared to subjects treated with placebo is distorted by the longer observation (and treatment) period of this group. Furthermore, the observed rate of progressing disease during MDS-001 is below the reported historical data and the rate of MDS disease progression within study MDS-002 was comparable between the luspatercept and epoetin alfa treatment groups (3.3% and 4.5%, respectively).

AESI: Thromboembolic events

During the evaluation of the initial MAA an imbalance in thromboembolic events was observed in subjects treated with luspatercept in studies following subjects with beta-thalassaemia but was not evident in the MDS population (see EPAR). Available data for study MDS-002 indicate that thromboembolic events appear in mildly more subjects treated with luspatercept compared to epoetin alfa (4.9% and 2.8% and with EAIRs of 4 and 2.9 per 100 PY, respectively). Most events were reported in single subjects per treatment arm only. However, it is noted that 4 cerebral events (2 cerebral ischemia and 2 cerebrovascular accident) occurred in luspatercept treated subjects until the available interim analysis of study MDS-002. As per available narratives 3 of the 4 subjects with cerebral event had multiple other comorbidities, 2 of the events were fatal and none of the events recovered. In one case study drug was interrupted and none was suspected to be related to study drug as per investigator judgement. No subject treated with epoetin alfa had a cerebral thrombotic event, despite comparable age and comorbidities. A relation of treatment on the observed cerebral events and thromboembolic events in

general currently cannot be ruled out. Available data indicate an incidence rate of thromboembolic events in around 5.2% of subjects and of cerebral thromboembolic events in around 1% of subjects treated with luspatercept as per total TD MDS Safety Pool.

AESI: Hypertension

Hypertension is a described adverse drug reaction with common (as per currently licensed MDS indication) to very common (as per currently licensed beta-thalassaemia) incidence during treatment with luspatercept. This risk of hypertension during treatment with luspatercept is supported by data available for study MDS-002 (15.9% of subjects), MDS-001 (13.1% of subjects) and by pooled data for TD MDS patients (15.2%). The risk is higher compared to epoetin alfa (9.5%) and placebo (9.2%) in the respective studies. Half of the events in the TD MDS pool was considered grade 3 or 4 and 2 luspatercept-treated subjects had serious events (as per TD MDS pool, none in study MDS-002). In fact, the most frequent PT of grade 3 or 4 in subjects treated with luspatercept in study MDS-002 was hypertension with 9.9% of subjects experiencing at least one event, but only 4.5% of subjects treated with epoetin alfa experiencing at least one event.

Until week 73, the mean systolic blood pressure during study MDS-002 was rather stable on a mildly elevated level (mean between 125 and 130 mmHg), without clear change from baseline and comparable between treatment groups (despite during weeks 49 to 55 and at week 70 with higher values for subjects treated with epoetin alfa). On the contrary, the mean diastolic blood pressure was stable and without increase from baseline for subjects treated with epoetin alfa (approximately 65-69 mmHg), but was consistently higher for subjects treated with luspatercept (around 70-72 mmHg for available data until week 73) with an immediate change from baseline (66-68 mmHg) after exposure start. Thus, the risk for hypertension is considered a confirmed adverse reaction for the treatment with luspatercept and available data for the TD MDS pool suggest a very common incidence for this patient population. It is further noted that during the evaluation of the MAA of Reblozyl an increased risk of hypertension over time on luspatercept treatment was concluded (see currently available EPAR).

AESI: Kidney injury

An increased rate of kidney injury for subjects treated with luspatercept was already concluded after the previous assessment of TD MDS patients treated with luspatercept as per available data from studies MDS-001 and A536-03/05 (see EPAR). This conclusion is further supported by data available for MDS-002 and further ongoing data from the other TD MDS studies (including ACE-536-LTFU-001 as the long-term extension of MDS-001 and A536-03/05). A total of 9.5% of subjects treated with luspatercept had reported kidney injury (PTs used to evaluate this EOI category were based on the MedDRA broad scope of SMQ acute renal failure, PTs with at least one event in study MDS-002 were: blood creatinine increased, renal impairment, acute kidney injury, glomerular filtration rate decreased, creatinine renal clearance decreased, renal failure, azotemia, proteinuria, tubulointerstitial nephritis) in the TD MDS pool and rates were higher than control treatments in both controlled studies (8.8% vs. 6.7% in MDS-002 and 13.7% vs. 6.6% in MDS-001). Increased blood creatinine was the most frequent PT related to kidney injury in study MDS-002 that also had the biggest difference between treatment groups (5.5% and 2.2% of subjects treated with luspatercept and epoetin alfa, respectively). In contrast, renal failure was the most frequent PT related to kidney injury in study MDS-001 (6.5% and 2.6% of subjects treated with luspatercept and placebo, respectively) with 3 additional subjects compared to data reported for the study in the available EPAR. The increased level of creatinine is in line with laboratory results that show a higher proportion of subjects with reduced creatinine clearance (i.e. <0.5 x baseline) for subjects treated with luspatercept (5% in the TD MDS pool as well as 6% in MDS-002 and 3.9% in MDS-001) compared to epoetin alfa (1.1% in MDS-002) or placebo (1.3% in MDS-001). No subject had post baseline eGFR of grade 4 and only 2 subjects of the TD MDS safety pool hat grade 3 (1 in study MDS-002 for each treatment arm). Post-baseline urinary albumin/creatinine ratios stayed in the normal range (grade 0: 0 - 30 mg/g) or microalbuminuria (grade 1: 30 - 300 mg/g) for the vast majority of subjects (i.e. 999% in

the TD MDS pool).
However, it is also noted that PT renal failure was not reported to the same extent in study MDS-002 as was in study MDS-001 (0.5% and 6.5% of subjects treated with luspatercept). The reasons for this discrepancy across studies are currently not entirely clear, but potentially renal failure might occur only after longer treatment duration (as long-term study treatment observation is ongoing in MDS-001 in the scope of study ACE-536-LTFU-001). This is supported by conclusions during the initial Marketing authorisation application for Reblozyl suggesting late-onset kidney injuries (see the available EPAR).

AESI: Liver toxicity
Data from study MDS-002 do not indicate a higher risk of liver toxicity from the treatment with luspatercept compared to epoetin alfa. This is also in line with relevant laboratory measures (i.e. AST, ALT and bilirubin) in this study. Regarding laboratory liver markers no subject had a post-baseline grade 4 value during treatment with luspatercept and only very few had post baseline values of grade 3 (TD MDS safety pool: 0.7% AST – change for 0.5% from grade 0 and 0.2% from grade 1, 2.5% ALT – change for 1.4% from grade 0 and 1.2% from grade 1, 3.2% bilirubin – change for 0.2% from grade 0, 0.7% from grade 1 and 2.3% from grade 2). No critical difference is evident for luspatercept treatment compared to epoetin alfa in study MDS-002. However, the difference to placebo in study MDS-001 appears more evident. ALT and AST equal or above 3 times upper limit of normal (ULN) as well as direct bilirubin equal or above twice ULN were substantially higher for subjects on luspatercept treatment (ALT: 16.3% vs. 7.9%, AST: 7.8% vs. 0%, bilirubin 5.9% vs. 0%). One patient treated with luspatercept had all of these values increased. Post-baseline grading of laboratory data indicates a similar trend (MDS-001: ALT: 4.6% of subjects with grade 3 level vs. 0 subjects and to a lower degree for AST: 1.5% of subjects with grade 3 level vs. 0 subjects treated with luspatercept and placebo, respectively). In total 2.5% of TD MDS subjects treated with luspatercept were recorded with PTs that would indicate liver toxicity. One event was serious and none of the events led to study discontinuation. However, considering data from study MDS-001, laboratory data on hepatic function were more often critically elevated for subjects treated with luspatercept compared to placebo. Liver toxicity also occurred more frequently in luspatercept-treated subjects in this study (2.6% and 1.3% of subjects treated with luspatercept and placebo).

AESI: Asthenia
The AESI category asthenia was frequently reported for subjects treated with luspatercept (39.2% of subjects in the TD MDS pool) and is especially driven by PTs fatigue (22.4% of subjects in the TD MDS pool) and asthenia (16.1% of subjects in the TD MDS pool). Fatigue and asthenia had higher rates in study MDS-001 compared to placebo (around double), but only fatigue had higher rates than epoetin alfa in study MDS-002 (17.6% vs. 7.3%). Asthenia/fatigue appears to be a confirmed risk for the treatment of TD MDS patients with luspatercept.

AESI: Extramedullary Hematopoiesis Mass
No event of Extramedullary Hematopoiesis Mass (EHM) was identified in clinical studies following TD MDS patients.

AESI: immunogenicity-type reactions
Immunogenicity type reactions occurred in all clinical TD MDS studies and treatment groups. Within study MDS-002 hypersensitivity type reactions and local type reactions were more frequent in subjects treated with luspatercept compared to epoetin alfa (3.8% vs. 1.7% and 2.7% vs. 0.6% of subjects, respectively). In the TD MDS pool only injection site erythema was reported in ≥2% of subjects. Luspatercept also appears more reactogenic than placebo as evaluated in study MDS-001. However, it appears that not all TEAEs that could be related to hypersensitivity reactions were included in the respective AESI categories (i.e. Immunogenicity Hypersensitivity Type Reactions and Immunogenicity Injection Local Type

Reactions). Of those not included, the PTs injection site pain, injection site reaction, injection site bruising, injection site haematoma, injection site mass, injection site oedema and localised oedema were all reported in <2% of subjects of the TD MDS pool. However, peripheral oedema was reported by 18.4% in the TD MDS pool and with substantially higher rates for subjects exposed to luspatercept compared to subjects exposed to epoetin alfa in study MDS-002 (14.3% vs. 7.8%, respectively) or placebo (26.1% vs. 17.1%). It is concluded that even though less injections are required for luspatercept vs. epoetin alfa in the same study duration, more adverse events are associated with the administration of luspatercept.

Immunogenicity

During study MDS-002 7.4% of subjects exposed to luspatercept developed ADAs (n=13) and almost all of the subjects with treatment emergent ADAs had neutralising antibodies against luspatercept (i.e. n=12 subjects exposed to luspatercept; as per database lock Nov-2023). It is critically noted that the MAH did not include the information on Immunogenicity Results in the final CSR of study MDS-002, but instead refers to the interim CSR. However, the MAH committed to include the latest immunogenicity data and a respective discussion in the upcoming addendum to the ACE-536-MDS-002 CSR (with data extraction Nov-2023). During study MDS-001 7.2% of subjects exposed to luspatercept developed ADAs and 3.3% had treatment emergent neutralising antibodies against luspatercept.

The rate of subjects with neutralising antibodies after exposure appears rather high, considering that neutralising activity could hamper efficacious drug action and that longer exposure might further increase the number of subjects with neutralizing antibodies. However, of in total 9 subjects with neutralising antibodies (as per interim analysis, note that n=12 as per database lock Nov-2023) against luspatercept 6 achieved RBC-TI for $\geqslant$ 12 weeks (66.7%), which is a comparable measure of efficacy as identified for the general population (also 66.7%). Thus, a negative effect of neutralising antibodies on the primary efficacy analysis does not appear apparent. Interestingly, also subjects exposed to placebo developed ADAs (3.9%) and neutralising antibodies against luspatercept (2.6%). It is critically noted that no data exist for subjects treated with epoetin alfa on ADA status as per protocol blood samples to assess ADAs against luspatercept in serum were analysed only in subjects treated with luspatercept (samples from subjects treated with epoetin alfa were collected, however, were out of the scope of the study protocol and thus part of a GCP Breach). Pre-existing neutralising antibodies were also reported in both studies (2.3% of subjects exposed to luspatercept in study MDS-002 as per database lock Nov-2023, 1.3% of subjects exposed to luspatercept in study MDS-001 and none for subjects treated with placebo). In both studies also antibodies directed against the extracellular domain of human ActRIIB were detected (5.3% and 2.3% of subjects had treatment-emergent antibodies in MDS-001 and MDS-002). Across all studies in the TD MDS pool 14.7% of subjects with treatment-emergent ADAs had Immunogenicity Injection Local Type Reactions (AESI category), whereas only 2.8% of subjects without ADAs reported events in this AESI category (as per summary of clinical safety dated Dec-2023 based on data base lock Mar-2023 for study MDS-002).

From provided data from the final analysis of study MDS-002 (with 13 subjects being identified with anti-drug antibodies against luspatercept) it is evident that subjects with treatment emergent ADAs were more likely to report a serious TEAE (69.4%% and 45.7% for ADA positive and negative subjects, respectively) or a TEAEs of grade 3 or 4 (77.8% and 56.8% for ADA positive and negative subjects, respectively) compared to subjects without ADAs in the TD MDS pool (based on data extraction date Nov-2023 for study MDS-002). It is agreed that incidence rates in specific PTs can be difficult to interpret based on the low total number of ADA positive subjects (n=11 in study MDS-001 and n=13 in study MDS-002). It is also reassuring that no immediate anaphylactic reaction was observed in close temporal association to luspatercept administration. Still, a negative effect of treatment-emergent ADAs cannot be excluded. The respective information regarding observed higher rates in serious TEAEs and TEAEs of grade 3 or 4 in subjects positive for ADAs is included in section 4.8 of the SmPC.

Discontinuations due to AEs

Within study MDS-002 a higher rate of subjects had TEAEs that lead to permanent study drug discontinuation when treated with luspatercept (11.5%) compared to epoetin alfa (7.3%). The most frequent reason for discontinuation due to AE was PT myelodysplastic syndrome (3.3.% and 1.7% of subjects treated with luspatercept and epoetin alfa, respectively). The PT myelodysplastic syndrome is also the most frequent reason for discontinuation in the TD MDS pool (1.8% of subjects).

Adverse events related to disease progression also were the most common reasons for discontinuation of luspatercept treatment in study MDS-001 (PTs myelodysplastic syndrome in 1.3% of subjects, transformation to acute myeloid leukaemia and refractory anaemia with excess of blasts in 2% of subjects each), whereas no AEs leading to study discontinuation appears to be clearly related to the mode of action of luspatercept.

Dose reduction and interruption

Dose reduction due to TEAE was followed by 4.1% of subjects in the TD MDS pool and reasons that occurred in ≥2 subjects were diarrhoea, headache, ALT increase and hypertension with 2 subjects for each TEAE and with potential relation to the MoA of luspatercept. All other TEAEs leading to dose reduction occurred in single subjects only. Also data from study MDS-002 do not indicate any reason of concern regarding the treatment with luspatercept compared to epoetin alfa (3.8% and 3.4% of subjects with at least one TEAE leading to dose reduction, respectively).

Dose interruption due to TEAE was followed by about one quarter of all subjects treated with luspatercept during the clinical study program in TD MDS patients (28.3% in the TD MDS pool; PTs Covid-19 and pneumonia being the most frequent causes and the only reasons in ≥2%). Also, more subjects treated with luspatercept interrupted the study dosing compared to epoetin alfa (33.5% and 28.5% of subjects, respectively) and placebo (27.5% and 5.3% of subjects, respectively) within respective studies. PTs driving this difference between treatment arms within study MDS-002 were diarrhoea (2.7% vs. 0%), thrombocytopenia (2.2% vs. 0%) and dyspnoea (2.2% vs. 0%) reported as reason for study interruption with ≥2% difference more by subjects treated with luspatercept. However, EAIRs suggest a higher rate for subjects treated with epoetin alfa (32.7 and 36.7 per 100 patient years). The difference to placebo in study MDS-001 is evident as also EAIRs suggest higher rates on luspatecept treatment (20.5 and 9.1 per 100 patient years).

Laboratory Evaluations

As per protocol abnormal laboratory value severity was graded using version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Reported worsening of haematology measures (leukocytes, neutrophils and platelets) ≥2 grades from baseline indicates potential shifts during treatment but does not indicate an increased risk during treatment with luspatercept compared to the active control. A shift ≥2 grades from baseline grade was reported in 3.3% of subjects for leukocyte values (12.6% with grade 3, 2.6% with grade 4 post baseline), in 7.2% of subjects for absolute neutrophil counts (17.9% with grade 3 and 8.6% with 4 post baseline) and in 4.8% of subjects for platelet values (6.9% with grade 3 and 2.7% with grade 4 post baseline) in the TD MDS pool. However, critical differences to subjects treated with epoetin alfa are not evident from study MDS-002 and differences to placebo in study MS-002 do also not indicate a higher risk for subjects treated with luspatercept. Even though it should be mentioned that only one subject had grade 3 platelet values during placebo treatment, but 3.1% had grade 3 and 2.3% had grade 4 values while treated with luspatercept during study MDS-001.

For a discussion regarding laboratory markers of liver and kidney function please refer to the respective AESI sections above (i.e. kidney injury and liver toxicity).

Blood pressure changes during clinical studies in TD MDS patients are discussed in the scope of the AESI hypertension above. In short, especially diastolic blood pressure appears to be increased by luspatercept treatment. The risk of hypertension during treatment with luspatercept is also evident from reported

TEAEs and from data presented in the EPAR.
Weight decreases of ≥10% were observed in 17.5% of subjects in the TD MDS pool, which could be related to the underlying disease, advanced age of the study population as well as the multiple disease comorbidities and concomitant medications.

Subgroups
Especially subjects with higher treatment burden (i.e. ⩾4 units), higher baseline EPO (i.e. >200 U/L), without ring sideroblasts and without SF3B1 mutation are to be considered at specific risk with a higher chance of experiencing an unfavourable disease course. Thus, it can be followed that subjects of these subgroups had a lower treatment duration with lower total amount of luspatercept doses and a higher rate in treatment-emergent AEs (for subgroups serum EPO > 200 U/L, RS- status, transfusion burden ⩾ 4 pRBC units, and non-mutated SF3B1) and SAEs (for subgroups RS- and SF3B1 not mutated).
Differences in safety results were identified for intrinsic factors age, sex, baseline transfusion burden, ring sideroblast status, baseline serum EPO, baseline eGFR and baseline SF3B1 mutational status in the TD MDS pool. Serious and grade 3 or higher TEAEs leading to discontinuation were higher with increasing age. Females had higher rates in the SOCs of General Disorders and Administration Site Conditions and Infections and Infestations. The incidence of General Disorders and Administration Site Conditions (SOC) was higher for subjects with ≥4 units transfusion burden. Grade 5 TEAEs were higher for subjects with baseline serum EPO > 200 U/L. Serious and grade 3 or 4 TEAEs were more likely in subjects with lower eGFR.
Notably, subjects without ring sideroblasts and subjects with mutation status SF3B1 non-mutated appear to have a consistently increased risk profile compared to subjects with ring sideroblasts and with mutational status SF3B1 mutated. Subjects without ring sideroblasts are more likely to experience serious AEs, grade 5 TEAEs, AEs leading to drug withdrawal or dose reduction compared to subjects with ring sideroblasts. Subjects with mutational status SF3B1 non-mutated are more likely to experience grade 3/4 TEAEs, serious AEs, grade 5 TEAEs, AEs leading to drug discontinuation, dose reduction as well as dose interruption compared to subjects with mutational status SF3B1 mutated. Importantly, the higher risk of an unfavourable disease course is specific for the subgroups (as included in study MDS-002), but did not appear consistently increased by the treatment with luspatercept compared to epoetin alfa.

Reported safety data separated by PROCRIT (US product) and EPREX/ERYPO (EU product) epoetin alfa do not indicate relevant differences between the products.

2.5.2. Conclusions on clinical safety

During data assessment the MAH informed on a Potential Serious GCP Breach regarding the collection/use of unconsented blood samples for PK and immunogenicity analysis. No impact on data integrity or data interpretation is concluded from blood samples collected in excess.

The provided safety database is considered principally sufficient to support an extension of indication in transfusion dependent adult patients with anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts. Data on TEAEs, treatment-related TEAE and respective EAIRs as well as grade 3 or 4 events and serious TEAEs suggest that subjects treated with luspatercept are more likely to experience an event compared to the active comparator epoetin alfa in study MDS-002.

Still, reported adverse events as per TD MDS safety pool (including ESA naïve subjects from study MDS-002) appear to roughly reflect events as documented from previous licensure of TD MDS patients with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy, as reported previously from study MDS-001. Frequencies of TEAEs across controlled studies (ACE-536-MDS-001 and ACE-536-MDS-002 with distinct patient populations) show substantial differences in SOCs and PTs (also deaths), which is also reflected to a lesser extent in exposure adjusted incidence

rates. However, subjects in study MDS-001 had a longer treatment duration, a more advanced disease status (i.e. higher baseline transfusion burden and unsatisfactory response to previous therapy), a higher rate of comorbidities and a mildly higher rate in subjects with ECOG performance status 2 compared to subjects included in study MDS-002. In sum these factors might explain the higher rates in study MDS-001 compared to study MDS-002.

As per mechanism of action and reported incidences in controlled studies, an increased risk of malignancies cannot be excluded for the treatment with luspatercept. However, currently available data do not cover a sufficiently long period to provide robust insight in potential malignancies caused by the treatment with luspatercept. Renal injury and Hypertension appear as adverse drug reactions that are also supported by respective laboratory data (i.e. creatinine clearance and blood pressure). Conclusions during previous licensure suggested that the chance for renal injury and hypertension appears to be related to time on treatment. The planned long-term follow-up period of 5 years from the date of the first dose of study drug, or 3 years from the last dose, is acknowledged in this regard. Even though less injections are required for luspatercept vs. epoetin alfa in the same study duration during MDS-002, it appears that more adverse events are associated with the administration of luspatercept.

It is concluded that the safety profile of the TD MDS pool roughly reflects the expected safety profile in line with the evaluation of the MAA of luspatercept. However, additional safety updates of section 4.4 (relating to cerebral ischemia, cerebrovascular accident and traumatic fractures) and 4.8 of the SmPC (update of ADRs) were agreed as part of this application.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.3 with the following content:

Safety concerns

Table 80: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• TEEs (only in the TD and NTD β-thalassaemia population with splenectomy) • EMH masses (in the TD and NTD β-thalassaemia population)
Important potential risks	• Haematologic malignancies (including AML) • Off-label use in paediatric patients (developmental toxicity of luspatercept) • Use during pregnancy and lactation • Bone fractures

Summary of safety concerns	
Missing information	• Long-term safety

Pharmacovigilance plan

Table 81: Additional pharmacovigilance activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
ACE-536-LTFU-001/ Ongoing	To evaluate the long-term safety (including progression to AML and/or other malignancies/pre-malignancies) of luspatercept in subjects who have participated in other luspatercept clinical trials.	TEEs (only in the TD and NTD β-thalassaemia population with splenectomy) EMH masses (In the TD and NTD β-thalassaemia population), Haematologic malignancies (including AML). Bone fractures Long-term safety.	Final report Interim safety updates	Q2 2029 Annually for the first 5 years.

Risk minimisation measures

Table 82: Patient card (for women of childbearing potential only)

Objectives:

Provision of information to WCBP for the risk of use during pregnancy and lactation.

Patient Card (for Women of Childbearing Potential Only)
Rationale for the Additional Risk Minimisation Activity:
Women of childbearing potential to understand the occurrence of reproductive and embryo-foetal toxicity and the appropriate management of this risk.
Target Audience and Planned Distribution Path:
The target audience is WCBP who are prescribed luspatercept and the planned distribution path is the provision of the Patient Card by the HCP and as agreed upon by the National Competent Authority (NCA).
Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:
Routine PV activities will provide information on any pregnancies occurrences. Pregnancy reports will be reviewed on an ongoing basis and reported in future regulatory safety reports (eg, PBRERs/PSURs). Modifications and corrective actions will be taken accordingly.

Table 83: Healthcare professional checklist

Healthcare Professional Checklist
Objectives:
Luspatercept HCP Checklist to be provided to raise awareness to HCPs who intend to prescribe and administer luspatercept for the risk of use during pregnancy and lactation.
Rationale for the Additional Risk Minimisation Activity:
Healthcare professionals to understand the occurrence of the risk specified above and the appropriate management of this risk.
Target Audience and Planned Distribution Path:
The target audience is HCPs who intend to prescribe and administer luspatercept.
Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:
Routine PV activities will provide information on any pregnancies occurrences. Pregnancy reports and utilization of the HCP Checklist will be reviewed on an ongoing basis and reported in future regulatory safety reports (eg, PBRERs/PSURs). Modifications and corrective actions will be taken accordingly.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The readability of the PL of Reblozyl (luspatercept), in English, was assessed during the assessment of the initial Marketing Authorisation Application (MAA) according to the methods outlined in the European Commission's guideline titled: A guideline on the readability of the label and package leaflet of medicinal products for human use, Revision 1, 12 January 2009. The final report was then submitted to the EMA in December 2019 (Response to the List of Questions, original Marketing Authorisation Application (MAA)) as per EMA operational procedure guidance (EMEA/277378/2005). Reblozyl (luspatercept) was approved on 25 June 2020.
- The new indication applied for, which includes the use of Reblozyl (luspatercept) for first line treatment of adult patients with transfusion dependent anemia due to very low- to intermediate-risk MDS, concerns the same route of administration and has a similar safety profile as the previously approved indications (i.e., key safety messages for the existing and newly proposed indications are essentially the same).
- Administration of Reblozyl (luspatercept) is done by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal are currently reflected in the approved PL.
- The general design and layout of the proposed PL have not changed compared to the tested one.
- Overall, the proposed PL already contains large text sections identical to the approved one. The modifications relevant to the new indication that are now proposed do not represent major changes.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH has applied for an extension of indication to include treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS).

3.1.2. Available therapies and unmet medical need

The diagnosis and management of MDS are similar across different regions, including the US and Europe. The standard of care for lower-risk MDS remains supportive treatment with ESAs (ie, recombinant epoetin alfa or darbepoetin alfa), RBC and/or platelet transfusions, infection prophylaxis and/or treatment, and use of hematopoietic growth factors such as G-CSF and nutritional supplements when needed. In the EU, epoetin alfa has been approved since 2017 for the treatment of symptomatic anaemia (Hb concentration $\leq$ 10 g/dL) in adults with low- or intermediate-1-risk primary MDS who have low sEPO (< 200 mU/mL), however, ESAs are not approved in the US for the treatment of anemia due to MDS.

Anemia is a major contributor to morbidity associated with MDS. While ESAs are the SOC for lower risk MDS with endogenous sEPO level < 500 U/L, approximately 50% of patients do not respond or have limited response to ESAs, and ultimately become increasingly transfusion dependent. Sub-optimal HI-E response to ESAs is observed in TD MDS patients with high transfusion burden, higher baseline sEPO level, lower hemoglobin, and high ferritin. Additionally, for patients with sEPO > 200 U/L, HI-E response rates are between 0 and 5% and, for those patients who achieve a HI-E response, the duration of HI-E response is limited.

In the EPOANE3021 Phase 3 study, 2/45 (4.4%) subjects in the placebo group achieved the primary endpoint of IWG 2006 erythroid response vs 27/85 (31.8%) in the epoetin alfa group ($p < 0.001$). Of those, only 7/31 (22.6%) subjects with prior transfusions achieved an erythroid response. All responders in this study had serum erythropoietin level less than 200 mU/mL. The median duration of erythroid response in the epoetin alfa group was 197 days. While transfusions are effective in temporarily correcting the anemia and its associated symptoms, they are associated with both short-term and long-term complications, as well as patient, caregiver, and healthcare system burdens.

Altogether, this evidence indicates there remains an unmet need for more effective therapeutic options that have a greater likelihood of a higher and/or more durable TI response or reduce transfusion burden while maintaining QoL in patients with lower-risk MDS.

Reblozyl is currently approved for the treatment of adult patients with transfusion-dependent (TD) anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy. With the current variation procedure, the intended extension of indication is to use luspatercept as first-line therapy, without having considered prior erythropoietin-based therapy and to include patients without ring sideroblasts (RS).

3.1.3. Main clinical studies

ACE-536-MDS-002 is an ongoing active-controlled, open-label, randomized Phase 3 study comparing the efficacy and safety of luspatercept vs. epoetin alfa in adult subjects with anemia due to IPSS-R very low,

low or intermediate risk MDS, who are ESA naïve and require RBC transfusions. Subjects were randomized 1:1 to receive either luspatercept (1.0 mg/kg SQ Q3W up to a maximum of 1.75 mg/kg SQ Q3W) or epoetin alfa (450 IU/kg SC QW up to a maximum of 1,050 IU/kg). Randomization was stratified based on baseline RBC transfusion burden (< 4 vs ≥ 4 pRBC units/8 weeks), baseline RS status (RS+ vs RS-), and baseline endogenous sEPO level (≤ 200 vs > 200 to < 500 U/L).

The study population of the pivotal study ACE-536-MDS-002 (COMMANDS) included adult patients with confirmed MDS according to WHO 2016 classification meeting IPSS-R classification of very low, low, or intermediate risk disease with a transfusion requirement of 2 to 6 pRBCs units/8 weeks. Patients were required to be erythropoietin treatment-naïve, with or without the presence of ring sideroblasts.

The main treatment period was 24 weeks for all subjects. Subjects who experienced clinical benefit and absence of disease progression per IWG-MDS criteria per protocol at the Week 24 Visit MDS Disease Assessment continued treatment until they met any discontinuation criteria as per protocol.

The primary objective was to evaluate the efficacy of luspatercept on RBC-TI for 12 weeks (84 days) with a concurrent mean Hb increase ≥ 1.5 g/dL compared with epoetin alfa within 24 weeks of treatment.

Approximately 350 randomized subjects were planned to be included in the trial. The pre-specified interim analysis of the primary endpoint was planned when approximately 300 subjects (85%) completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment (31-Aug-2022 clinical data cutoff). The analysis population for the primary analysis of the primary endpoint (31-Mar-2023 clinical data cutoff) included 182 subjects in the luspatercept arm and 181 subjects in the epoetin alfa arm. The median treatment duration was 51.3 weeks in the luspatercept arm and 37.0 weeks in the epoetin alfa arm.

3.2. Favourable effects

The median duration of treatment was longer in the luspatercept arm compared to epoetin (51.3 vs 37.0 weeks), and a higher proportion of subjects completed 48 weeks of treatment (55.5% vs 42.5%).

The primary efficacy endpoint showed a significantly higher proportion of subjects with RBC-TI for 12 weeks with a concurrent mean Hb increase ≥ 1.5 g/dL (Week 1 to 24) in the luspatercept treatment arm compared with epoetin alfa: 60.4% (95% CI: 52.9, 67.6) vs 34.8% (95% CI: 27.9, 42.2); common risk difference on response rate: 25.4% (95% CI: 15.8, 35.0); 1-sided stratified CMH test p-value < 0.0001.

Hierarchically tested secondary efficacy endpoints showed a significantly higher response rate in luspatercept compared to epoetin alfa (Week 1 to 24):

- 74.2% (95% CI: 67.2, 80.4) vs 53.0% (95% CI: 45.5, 60.5); common risk difference on response rate: 21.5% (95% CI: 12.2, 30.7) [p < 0.0001] achieved HI-E per IWG over any consecutive 56-day period
- 47.8% (95% CI: 40.4, 55.3) vs 30.9% (95% CI: 24.3, 38.2); common risk difference on response rate: 16.3% (95% CI: 7.1, 25.4) [p = 0.0003] achieved RBC-TI for 24 weeks
- 68.1% (95% CI: 60.8, 74.8) vs 48.6% (95% CI: 41.1, 56.1): common risk difference on response rate: 18.8% (95% CI: 9.5, 28.0) [p < 0.0001] achieved RBC-TI for ≥12 weeks

RBC-TI for 24 weeks from Week 1-48 indicate a higher response rate in the luspatercept group: 60.7% (95% CI: 52.8, 68.3) vs 48.6% (95% CI: 41.1, 56.1) epoetin alfa [p<0.0001].

In primary endpoint responders, the median duration (of the longest single RBC TI period) during Week 1 to EOT (ad hoc analysis), was numerically longer in the luspatercept arm vs the epoetin alfa arm: 71.9 (95% CI: 39.9, 83.9) vs 55.6 (95% CI: 39.9, 77.9) weeks.

The median duration of the longest single RBC TI period for subjects who achieved RBC TI ≥ 12 weeks (84 days) from Week 1 to EOT (3rd hierarchically tested secondary endpoint) was longer in the luspatercept arm vs the epoetin alfa arm: 128.1 (95% CI: 108.3, Not estimable) vs 89.7 (95% CI: 55.9, 157.3) weeks.

Median RBC transfusion burden (Week 1 to 24) was lower in the luspatercept group compared to epoetin alfa (1.0 vs 3.0 RBC units).

The median time to first pRBC transfusion (Week 1 to EOT) was longer in the luspatercept arm vs the epoetin alfa arm: 155.0 vs 42.0 days.

The mean Hb increase from baseline during Week 1 to 24 for luspatercept-treated subjects was greater compared with epoetin alfa-treated subjects: 2.0 vs 1.5 g/dL.

The median time to HI-E (Week 1 to 24) was shorter in the luspatercept group compared to epoetin alfa: 1.0 vs 6.0 days.

Most subgroup analyses showed similar results to the overall study population [except the subgroup of subjects without ring sideroblasts (RS-)].

3.3. Uncertainties and limitations about favourable effects

Several sites inadvertently collected additional PK and ADA samples (beyond the pre-specified time points in the protocol) from patients in Study ACE-536-MDS-002, which was reported as a Potential Serious Breach of GCP. Although the submitted information do not raise doubts regarding the overall integrity of the study, corrective measures were implemented as proposed by the MAH. Although no impact on the overall conclusions of the PK analysis is expected, the exact impact is not clear. Thus, two recommendations were agreed to be submitted by the MAH to address the remaining uncertainties by June and September 2024. No concerns regarding conclusions on immunogenicity derive from the excess samples taken.

The open-label study design may affect the outcome of subjective endpoints.

Onset of treatment effect is delayed in the epoetin alfa arm due to its mode of action, potentially favouring luspatercept for responder endpoints from Week 1-24.

The 3rd hierarchically tested secondary endpoint (RBC-TI for ≥12 weeks) adds no relevant information to the primary efficacy endpoint (RBC-TI for 12 weeks and mean Hb increase ≥ 1.5 g/dL) and 2nd hierarchically tested secondary endpoint (RBC-TI for 24 weeks).

Incomplete data are available for the assessment of maintenance of treatment effect (e.g. RBC-TI for 24-week period from Week 1-48; n=163/182 for luspatercept and n=167/181 for epoetin alfa).

The duration of longest single RBC-TI responses is based on subjects who became responder during the first 24 weeks.

In supportive studies A536-03/05 a considerably shorter median duration of RBC-TI ≥12 weeks was observed (73.0 weeks vs 128.1 weeks in the luspatercept arm of the pivotal study).

Prohibiting G-CSF and GM-CSF use may lead to lower efficacy of the ESA treatment arm compared to the routine clinical setting.

The overall effect of luspatercept appears mainly driven by the overrepresented RS+ subgroup (72.5% instead of a maximum of 60% planned): in the RS+ subgroup, for the primary endpoint 65.4% were considered responder in luspatercept vs 29.2% in epoetin alfa; in contrast, in the RS- subgroup, 46.9% were considered responder in the luspatercept arm vs 50.0% in the epoetin alfa arm.

Similarly, in patients with MDS-MLD, 46.0% were considered responder in the luspatercept arm vs 44.7% in the epoetin alfa arm.

There is little support from PRO data to demonstrate superior efficacy of luspatercept as results were similar between groups for most EORTC QLQ-C30 and FACT-An scores. For the assessment of PRO (EORTC QLQ-C30, FACT-An and QUALMS-P) better baseline health scores in the luspatercept arm suggest limited room for improvement. The completion rate for QUALMS-P was low (38.6% at baseline).

3.4. Unfavourable effects

The most common SOCs in the TD MDS Pool (with data integrated from all studies in TD MDS patients) were General disorders and Administration site conditions 61.7%), Infections and infestations (56.9%%), Gastrointestinal disorders (51%) and Musculoskeletal and Connective tissue disorders (42.6%), the most common PTs in the TD MDS Pool were fatigue (22.4%), diarrhoea (21.5%), peripheral oedema (18.4%), asthenia (16.1%) and dyspnoea (15.9%). Reported adverse events as per TD MDS safety pool (including ESA naïve subjects from study MDS-002) appear to roughly reflect events as documented from previous licensure of TD MDS patients with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy, as reported previously from study MDS-001.

SOCs with a difference ≥2% in *suspected related* TEAEs between study groups in study MDS-002 were General disorders and administration site conditions (especially PTs fatigue with 4.4% vs. 0%), Gastrointestinal disorders (especially PT nausea with 4.9% vs. 1.1%), Nervous System disorders (especially PTs headache with 3.3% vs. 1.7% and dizziness with 2.2% vs. 0.6%), Respiratory thoracic and mediastinal disorders (especially PT dyspnoea with 3.3% vs. 0%) and Blood and lymphatic system disorders (especially PTs neutropenia with 2.2% vs. 0% and thrombocytopenia with 1.6% vs. 0%) with higher frequencies for subjects treated with luspatercept. Only the SOC Musculoskeletal and connectivity disorders was reported more frequently (i.e. ≥2%) in subjects treated with epoetin alfa.

Dose delays were more frequent in luspatercept treated subjects compared with epoetin alfa treated subjects (60.4% vs 43.0%). Dose delay due to predose Hb ≥12.0 g/dL was almost 2 times more frequent in the luspatercept arm compared to epoetin alfa (44/182, 24.2% vs 22/179, 12.3%).

More subjects had at least one TEAE as well as *suspected related* TEAE when treated with luspatercept compared to the active comparator epoetin alfa during study MDS-002 (97.8% and 92.2% of subjects with TEAEs as well as 33.5% and 20.1% of subjects with treatment-emergent TEAEs for luspatercept and epoetin alfa, respectively), which is also reflected in exposure adjusted incidence rates.

Grade 3 or 4 events occurred in a higher proportion in patients treated with luspatercept during study MDS-002 compared to subjects treated with epoetin alfa (58.8% and 49.2% of subjects had at least one TEAE of category 3 or 4, and 7.7% and 2.2% of subjects had at least one *suspected related* TEAE of category 3 or 4 for luspatercept and epoetin alfa, respectively).

Serious TEAEs and deaths

Slightly more subjects with serious TEAEs (45.1% vs. 39.7% of subjects treated with luspatercept vs. epoetin alfa, respectively), but less subjects with serious TEAEs considered as *suspected related* (0.5% vs. 1.7% of subjects treated with luspatercept vs. epoetin alfa, respectively) were reported by subjects treated with luspatercept during study MDS-002.

The number of deaths was high, but comparable across treatment arms within studies MDS-001 and MDS-002 (35-38% and around 21% of study participants, respectively).

AESIs

Currently available data on malignancies indicate a slightly higher chance for malignant disorders in patients treated with luspatercept – 8.8% and 5.6% of subjects were diagnosed with malignancy while on treatment with luspatercept and epoetin alfa as per CSR of MDS-002. The imbalance in events is also confirmed when compared to placebo during study MDS-001, with 7.2% and 1.3% of subjects treated with luspatercept and placebo (including data from the long-term extension study ACE-536-LTFU-001).

Available data for study MDS-002 indicate that thromboembolic events appear in slightly more subjects treated with luspatercept compared to epoetin alfa (4.9% and 2.8% and with EAIRs of 4 and 2.9 per 100 PY, respectively). Most events were reported in single subjects per treatment arm only, but 4 cerebral events (2 cerebral ischemia and 2 cerebrovascular accident) occurred in luspatercept treated subjects until the available interim analysis of study MDS-002, whereas no event occurred in the active control arm.

The suspected risk of hypertension during treatment with luspatercept is supported by data available for study MDS-002 (15.9% of subjects), MDS-001 (13.1% of subjects) and by pooled data for TD MDS patients (15.2%). The risk is higher compared to epoetin alfa (9.5%) and placebo (9.2%) in the respective studies. Half of the events in the TD MDS pool was considered grade 3 or 4 and 2 luspatercept-treated subjects had serious events. In fact, the most frequent PT of grade 3 or 4 in subjects treated with luspatercept in study MDS-002 was hypertension with 9.9% of subjects experiencing at least one event, but only 4.5% of subjects treated with epoetin alfa experiencing at least one event.

The mean systolic blood pressure during study MDS-002 was rather stable on a mildly elevated level (mean between 125 and 130 mmHg) for both treatment groups, but in contrast to subjects treated with epoetin alfa, the mean diastolic blood pressure was consistently higher for subjects treated with luspatercept (around 70-72 mmHg for available data until week 73) with an immediate change from baseline (66-68 mmHg) after exposure start.

Based on the ISS (Data Extraction Date: 17MAY2023) the PTs atrial fibrillation as well as cardiac failure both were observed as TEAE, as grade 3/4 TEAEs and as serious TEAE with higher frequencies compared to the respective control treatment in either phase 3 study (TEAEs PT atrial fibrillation: 3.8%, 1.1%, 5.9%, 1.3%; TEAEs PT cardiac failure: 2.2%, 1.7%, 2.6%, 0%; serious TEAE PT atrial fibrillation: 1.6%, 0%, 1.3%, 0%; serious TEAE PT cardiac failure: 1.1%, 0%, 2%, 0%; all for luspatercept MDS-002, epoetin alfa MDS-002, luspatercept MDS-001 and placebo MDS-001, respectively). Notably, both PTs could also be a further consequence of hypertension as an identified very common unwanted effect of luspatercept.

A total of 9.5% of subjects treated with luspatercept had reported kidney injury in the TD MDS pool and rates were higher than control treatments in both controlled studies (8.8% vs. 6.7% in MDS-002 and 13.7% vs. 6.6% in MDS-001). This is also reflected in blood creatinine levels and measured the higher proportion of subjects with reduced creatinine clearance (i.e. <0.5 x baseline) for subjects treated with luspatercept compared to control groups in studies MDS-001 and MDS-002.

In total 2.5% of TD MDS subjects treated with luspatercept were recorded with PTs that would indicate liver toxicity.

Local type reactions were more frequent in subjects treated with luspatercept compared to epoetin alfa (2.7% and 0.6% of subjects, respectively). Peripheral oedema was reported by 18.4% in the TD MDS pool and with higher rates for subjects exposed to luspatercept compared to subjects exposed to epoetin alfa in study MDS-002 (14.3% vs. 7.8%, respectively) or placebo (26.1% vs. 17.1%).

The rate of subjects with neutralising antibodies after exposure appears rather high (MDS-002: 6.9%, MDS-001: 3.3%). In both studies also antibodies directed against the extracellular domain of human

ActRIIB were detected (2.3% and 3.9% of subjects had treatment-emergent antibodies in MDS-001 and MDS-002). A negative effect of treatment-emergent ADAs currently cannot be excluded. Subjects with treatment emergent ADAs were more likely to report a serious TEAE compared to subjects without ADAs in the TD MDS pool (69.4% and 45.7% of subjects, respectively) or a TEAEs of grade 3 or 4 (77.8% and 56.8% for ADA positive and negative subjects, respectively; as per database lock Nov-2023 for study MDS-002). Furthermore, across all studies in the TD MDS 14.7% of subjects with treatment-emergent ADAs had Immunogenicity Injection Local Type Reactions (AESI category), whereas only 2.8% of subjects without ADAs reported events in this AESI category (as per summary of clinical safety dated Dec-2023 based on data base lock Mar-2023 for study MDS-002).

Within study MDS-002 a higher rate of subjects had a TEAE that lead to permanent study drug discontinuation when treated with luspatercept (11.5%) compared to epoetin alfa (7.3%). Dose reduction due to TEAE was followed by 4.1% of subjects in the TD MDS pool, dose interruption due to TEAE was followed by about one quarter of all subjects treated with luspatercept.

Weight decreases of ≥10% were observed in 17.5% of subjects in the TD MDS pool.

Median treatment duration and median number of luspatercept doses were lower within subgroups for subjects with baseline transfusion burden ≥4 units, ring sideroblast-negative subjects, subjects with baseline serum EPO >200 U/L and SF3B1 nonmutated subjects. Differences in safety results were identified for intrinsic factors age, sex, baseline transfusion burden, ring sideroblast status, baseline serum EPO, baseline eGFR and baseline SF3B1 mutational status in the TD MDS pool. Patients without ring sideroblasts and subjects with mutation status SF3B1 non-mutated appear to have a consistently increased risk profile compared to subjects with ring sideroblasts and with mutational status SF3B1 mutated.

3.5. Uncertainties and limitations about unfavourable effects

Patients in the clinical program for TD MDS patients were rather old (median age of 72 years in the TD MDS pool) and with multiple reported disease comorbidities and respective concomitant medication. These baseline characteristics might contribute to reported safety events and causalities might not always be clear. Study MDS-002 with active control arm was open-label, which might influence the reporting of safety relevant information.

Currently available data do not cover a sufficiently long period to provide robust insight in potential malignancies caused by the treatment with luspatercept. Long-term data from the planned 5-year follow-up period to follow malignancies/pre-malignancies and progression to AML in study MDS-002 are needed for a more informative time period regarding a potential malignancy (including progression to AML and premalignant disorders) risk. Also, fractures will be monitored in the LTFU study, please refer to the RMP.

The PT renal failure was not reported to the same extent in study MDS-002 as was in study MDS-001 (0.5% and 6.5% of subjects treated with luspatercept). The reasons for this discrepancy across studies are currently unknown, but potentially renal failure might occur only after longer treatment duration (as study MDS-001 is completed and data collections is ongoing for long-term treatment in study ACE-536-LTFU-001, please refer to the RMP).

3.6. Effects Table

Table 84: Effects Table for Reblozyl as first-line therapy in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) (data cut-off: 31-Mar-2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
RBC-TI and mean Hb increase ⩾ 1.5 g/dL	Proportion of subjects with RBC-TI for any 12 weeks with a concurrent mean Hb increase ⩾ 1.5 g/dL (Week 1 to 24)	n/N (%)	110/182 (60.4%) [95% CI 52.9, 67.6]	63/181 (34.8%) [95% CI 27.9, 42.2]	Open-label design; onset of treatment effect may be delayed in the active control arm, potentially favouring luspatercept; effect mainly driven by RS+ subgroup	Pivotal Study ACE536-MDS-002
mHI-E per IWG	Proportion of subjects who achieved HI-E over any consecutive 56-day period (Week 1 to 24)	n/N (%)	135/182 (74.2%) [95% CI: 67.2, 80.4]	96/181 (53.0%) [95% CI: 45.5, 60.5]	Partial overlap with primary efficacy endpoint	Pivotal Study ACE536-MDS-002
Duration of RBC-TI	Median duration of the longest single RBC-TI for subjects who achieved RBC-TI ⩾12 weeks (Week 1 to EOT)	Weeks	128.1 [95% CI: 108.3, NE]	89.7 [95% CI: 55.9, 157.3]	Based on (early) RBC-TI responder (Week 1 to 24)	Pivotal Study ACE536-MDS-002
RBC-TI for 24 Weeks	Proportion of subjects with RBC-TI for any 24 weeks (Week 1 to 48)	n/N (%)	99/163 (60.7%) [95% CI: 52.8, 68.3]	81/167 (48.5%) [95% CI: 41.1, 56.1]	91% of subjects are included in this analysis	Pivotal Study ACE536-MDS-002
Unfavourable Effects						
TEAE	Subjects with at least one event	%	97.8	92.2	Frequencies in SOCs and PTs across controlled studies (MDS-001 and MDS-002 with distinct patient populations) show substantial differences	ACE-536-MDS-002 (ESA-naïve patients)
Suspected related TEAE	Subjects with at least one event	%	33.5	20.1		ACE-536-MDS-002 (ESA naïve patients)
Grade 3 or 4 TEAEs	Subjects with at least one event	%	58.8	49.2		ACE-536-MDS-002 (ESA naïve patients)
Serious TEAEs	Subjects with at least one	%	45.1	39.7		ACE-536-MDS-002

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	event					(ESA naïve patients
Deaths	Total number of deaths	n	39 (21.4%)	38 (21.2%)	Frequencies across controlled studies (MDS-001 and MDS-002 with distinct patient populations) show substantial differences	ACE-536-MDS-002 (ESA naïve patients

Abbreviations: AESI: Adverse event of special interest, mHI-E: modified hematologic improvement – erythroid response, PT: Preferred term, RBC-TI: red blood cell transfusion independence, SOC: System organ class, TEAE: treatment emergent adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In transfusion dependent MDS patients classified as lower risk based on the IPSS criteria, progression to AML occurs later and survival is longer compared with patients with higher risk MDS. Therefore, treatment is mainly focussed on controlling anaemia (and other cytopenias) and improving quality of life.

Transfusion independence and reduction of transfusion requirement are important objectives of treatment, and this was evaluated in the pivotal phase 3 trial. In the primary analysis for the primary and hierarchically tested secondary efficacy endpoints, statistically significant results in favour of luspatercept compared to epoetin alfa were achieved, indicating higher responder rates in terms of transfusion independence and erythroid response. These effects are also considered clinically relevant. However, since the effect of luspatercept on haemoglobin is expected to be faster compared to the comparator epoetin alfa due to its mode of action, a response from Week 1-24 week may overestimate the effect of luspatercept, and early discontinuation in the epoetin arm may underestimate the true responder rate in this treatment arm to some extent. Yet, the HI-E (IWG 2006) response rate was higher in the epoetin alfa treatment arm in study ACE-536-MDS-002 compared to what would be expected from the registrational study of epoetin alfa, alleviating the concern of reduced efficacy in the epoetin alfa arm. Furthermore, the benefit of luspatercept has also been demonstrated over a period of 48 Weeks, also suggesting sustainability of the effect. Nevertheless, the uncertainty of an open-label study design, which may impact subjective assessments or the decision to discontinue treatment, remains.

Despite lower response rates in patients without ring sideroblasts treated with luspatercept, a broad MDS indication is considered justified. Primary and hierarchically tested secondary efficacy endpoints indicate that efficacy appears similar compared to epoetin alfa in this subgroup. Furthermore, even if the benefit is comparable to epoetin alfa for the responder endpoints, a clinically relevant response after luspatercept treatment is evident also for the RS- subgroup, and other benefits of luspatercept over epoetin alfa were observed, such as increased durability of response and continued benefit with longer follow-up. Consistent and sustained increases among pharmacodynamic markers (erythroid precursors, reticulocytes) in the luspatercept arm suggest that luspatercept treatment leads to gradual improvements in erythropoiesis in both subgroups, which may partially explain a delayed onset of treatment effect with luspatercept in RS- patients, in particular when compared to epoetin alfa. In fact, a higher clinical response rate was observed in RS- patients compared to RS+ patients treated with epoetin alfa. While epoetin alfa acts on early bone marrow erythroid precursors, luspatercept acts at various stages of erythroid maturation, independent of RS status. Although the evidence of a beneficial effect in RS-

patients in the previously approved second line setting is very limited, as no RS- patients were included in the pivotal MEDALIST (ACE-536-MDS-001) study, long-term efficacy results from Phase 2 study (A536-03/05) indeed indicate a treatment benefit also in RS- patients, albeit again lower compared to RS+ patients. Taken together, these observations enable extrapolation also to the previously approved second line setting and a broad MDS indication. Accordingly, information on missing or limited efficacy data in section 5.1 of the SmPC has been included. In addition to the generally rather unfavourable safety profile of luspatercept, a subgroup analysis for safety aspects identified that patients without ring sideroblasts and patients with mutation status SF3B1 non-mutated appear to have a consistently increased risk profile compared to subjects with ring sideroblasts and with mutational status SF3B1 mutated.

The focus of treatment with luspatercept is improvement of MDS associated anaemia, without any claims regarding delaying progression to higher MDS risk groups or AML and prolonging overall survival. Nonetheless, any detrimental effect in terms of progression of disease or shortened OS compared to patients treated with best standard of care would not be acceptable. The primary data analysis from study ACE-536-MDS-002 do not indicate higher chance of high risk MDS compared to the active control epoetin alfa. Considering data from both controlled studies no increased risk appears evident for disease progression to AML. The same applies for the number of deaths across treatment arms within studies ACE-536-MDS-001 and ACE-536-MDS-002.

Even though the treatment of TD MDS patients with luspatercept appears beneficial compared to epoetin alfa from efficacy perspective for most patients included in clinical studies, several risks appear to be increased on luspatercept treatment compared to the alternative epoetin alfa. Especially the potential of malignancies appears increased as per mechanism of action and as indicated by available data, although the observation period is currently limited. Long-term follow-up data for up to 5 years after treatment will allow for a more robust evaluation of this risk (please see RMP). Besides others, the risk for hypertension, kidney injury, thromboembolic events, asthenia and local immunogenicity-type reactions appears increased on treatment with luspatercept and subjects rather discontinue the treatment with luspatercept due to adverse events. Accordingly, adequate information has been provided in section 4.4 and 4.8 of the SmPC. Also, the general rate of subjects with at least one TEAE (including TEAEs of grade 3 or 4 and serious TEAEs) is higher for subjects on luspatercept. A high proportion of subjects also develops neutralising antibodies and antibodies directed against the extracellular domain of human ActRIIB were also detected. A negative effect of treatment-emergent ADAs on safety can also be concluded.

Frequencies of TEAEs across controlled studies (ACE-536-MDS-001 and ACE-536-MDS-002 with distinct patient populations) show substantial differences in SOCs and PTs (also deaths), which is also reflected to a lesser extent in exposure adjusted incidence rates. However, subjects in study MDS-001 had a longer treatment duration, a more advanced disease status (i.e. higher baseline transfusion burden and unsatisfactory response to previous therapy), a higher rate of comorbidities and a mildly higher rate in subjects with ECOG performance status 2 compared to subjects included in study MDS-002. In sum these factors are indeed considered relevant for the occurrence of safety incidences and might explain rates in study MDS-001 compared to study MDS-002.

3.7.2. Balance of benefits and risks

In the pivotal trial, luspatercept showed superiority over epoetin alfa for the primary data set in all primary and hierarchically tested secondary analyses, assessing responder rates of subjects becoming transfusion independent and/or having a mean haemoglobin increase above 1.5 g/dL up to week 24. Secondary analyses of duration of transfusion independence, change in transfusion rates and RBC units as well as in mean haemoglobin increase are in support of the primary/ hierarchically tested secondary analyses.

For the elderly population of MDS patients (with a mean age above 70 years), chronic anaemia represents a significant burden associated with multiple complications, but frequent RBC transfusions are also burdensome. In transfusion-dependent MDS patients, for whom regular transfusions are a substantial burden due to adverse events or cumbersome scheduling of clinical appointments and affect their quality of life, the achieved reduction in transfusion frequency is considered beneficial. However, little support is provided from patient reported outcomes, aiming to assess the quality of life of patients.

No signal for an increase in progression to/ time to progression to high risk MDS or AML was identified compared to epoetin alfa in study ACE-536-MDS-002. However, due to the still limited duration of exposure, uncertainty remains with regard to long-term safety, which has to be addressed by continuing surveillance, e.g. the long-term follow-up period of study MDS-002 and the long-term follow-up study ACE-536-LTFU-001. However, it is noted that available data from ACE-536-MDS-001 including the long-term study ACE-536-LTFU-001 are one-sided as mostly subjects on luspatercept treatment were enrolled in the long-term study.

Still, several risks appear to be increased on luspatercept treatment compared to the alternative epoetin alfa in patients with MDS (e.g. hypertension, kidney injury, thromboembolic events, asthenia and local immunogenicity-type reactions) and also the general rate of subjects with at least one TEAE (including TEAEs of grade 3 or 4 and serious TEAEs) is higher for subjects on luspatercept. Furthermore, also the frequency of TEAEs leading to discontinuations was higher in luspatercept-treated patients, compared to epoetin alfa-treated subjects. Also, subjects with treatment emergent ADAs were more likely to report a serious TEAE or a TEAEs of grade 3 or 4 compared to subjects without ADAs in the TD MDS pool.

Clinical benefit has been consistently shown for MDS patients treated with luspatercept. Although the response rates are lower in patients without ring sideroblasts, clinical benefit is also evident in this subgroup and comparable to patients without ring sideroblast treated with epoetin alfa. The remaining uncertainties associated with efficacy evaluation along with the non-negligible safety profile of luspatercept are appropriately reflected in the SmPC to inform treatment decisions. Therefore, the B/R balance can be considered positive for luspatercept to be used as first-line therapy in transfusion dependent MDS patients classified as lower risk based on the IPSS criteria.

3.7.3. Additional considerations on the benefit-risk balance

Since the final dataset was not yet available and additional updates are required due to the GCP violation regarding excess PK and ADA sampling the MAH committed to submit the following RECs:

REC 1 by Q2 2024: The updated descriptive analysis, including plotting of trough PK concentrations and tabular summaries of ADA data in relation to efficacy and safety, based on the final clean dataset excluding the excess samples, will be included in Addendum 01 to the ACE-536-MDS-002 Primary CSR.

REC 2 by Q3 2024: The popPK and E-R models will be updated with the final clean PK dataset of study ACE-536-MDS-002 to remove excess samples for any future application of the models. A comparison to the models including the excess samples (as currently submitted) should be included.

3.8. Conclusions

The overall B/R of Reblozyl as first-line therapy in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), based on results from study ACE-536-MDS-002 (COMMANDS), an active-controlled, open-label, randomized Phase 3 study comparing the efficacy and safety of luspatercept vs epoetin alfa in adult subjects with anemia due to IPSS-R very low, low or intermediate risk MDS, who are ESA naïve and require RBC transfusions, and studies ACE-536-MDS-001(MEDALIST), ACE-536-MDS-004 , A536-03, A536-05 and ACE-536-LTFU-001; As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Extension of indication to include treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS), based on results from study ACE-536-MDS-002 (COMMANDS).

Please refer to Scientific Discussion ‘Product Name-H-C-4444-II-21.