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RESEARCH AND DEVELOPMENT

LUSPATERCEPT

RISK MANAGEMENT PLAN

Version Number: 3.3

Data-lock Point for this RMP: 24-Jun-2023

Date of final sign off: 08-Feb-2024

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LIST OF ABBREVIATIONS

Term	Definition
ACR	albumin-to-creatinine ratio
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	Adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCL	B-cell lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum concentration
CMML	chronic myelomonocytic leukemia
CrCl	creatinine clearance
DBP	diastolic blood pressure
DVT	deep vein thrombosis
EAIR	exposure-adjusted incidence rate
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMH	extramedullary haematopoiesis
EPAR	European Public Access Report
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
EU	European Union
EU PAS	European Union electronic Register of Post-Authorisation Studies
F1	first filial generation
HCP	healthcare professional
HIV	human immunodeficiency virus
HR	hazard ratio
IPSS	International Prognostic Scoring System
IPSS-R	International Prognostic Scoring System-Revised
MAH	Marketing Authorisation Holder
MDS	myelodysplastic syndromes

Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
NOAEL	no observed adverse effect level
NTD	non-transfusion-dependent
OS	overall survival
PDCO	paediatric committee of the European Medicines Agency
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PL	package leaflet
PSUR	periodic safety update report
PT	preferred term
QPPV	qualified person for pharmacovigilance
RBC	red blood cell
RMP	risk management plan
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SEER	Surveillance, Epidemiology and End Results
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
TAO	Thalassemia-associated osteoporosis
TD	transfusion-dependent
TEAE	treatment-emergent adverse event
TEE	thromboembolic event
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WCBP	women of childbearing potential

EU RISK MANAGEMENT PLAN (RMP) FOR LUSPATERCEPT

RMP version to be assessed as part of this application:

Version Number: 3.3

Data-lock Point for this RMP: 24-Jun-2023

Date of Final Sign-off: 08-Feb-2024

Rationale for submitting an updated RMP:

- Proposed indication (in adults for the treatment of TD anaemia due to very low, low and intermediate-risk MDS).
- Important Potential Risk "Bone Fractures (in the NTD B-thalassemia population)" updated to remove the reference to NTD B-thalassemia population so as to apply to all approved indications.
- Update of post-authorization exposure information.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part I	Updated to current indication	V3.3 / pending
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	Update to current indication	V 3.3/ pending
SII Non-clinical part of the safety specification	Updated to include information from Study ACE-536-MDS-002	V3.3 / pending
SIII Clinical trial exposure	Updated to include clinical trial exposure from Study ACE-536-MDS-002	V3.3 / pending
SIV Populations not studied in clinical trials	Updated to include information from Study ACE-536-MDS-002	V3.3 / pending
SV Post-authorization experience	Update of post-authorization exposure	V3.3 / pending
SVI Additional EU requirements for the safety specification	Not applicable	V1.5 / 27-Feb-2023
SVII Identified and potential risks	Updated to include safety data from Study ACE-536-MDS-002. Important Potential Risk "Bone Fractures (in the NTD B-thalassemia population)" updated to remove the reference to NTD B-thalassemia population.	V3.3 / pending
SVIII Summary of the safety concerns	Important Potential Risk "Bone Fractures (in the NTD B-thalassemia population)" to	V 3.3/ pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
	remove the reference to NTD B-thalassemia population.	
Part III Pharmacovigilance Plan	Not applicable	V3.2 / 11-Jan-2024
Part IV Plan for post-authorization efficacy studies	Not applicable	V1.0 / 30-Apr-2020
Part V Risk Minimisation Measures	Administrative update of Table 5.1.3	V3.3 / pending
Part VI Summary of the Risk Management Plan	Updated with changes in the RMP	V3.3 / pending
Part VII Annexes		
ANNEX 1 EudraVigilance interface	NA	V1.5 / 27-Feb-2023
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Not applicable	V3.2 / 11-Jan-2024
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	Not applicable	V1.5 / 27-Feb-2023
ANNEX 4 Specific adverse drug reaction follow-up forms	Not applicable	V3.2 / 11-Jan-2024
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	Not applicable	V1.5 / 27-Feb-2023
ANNEX 6 Details of proposed additional risk minimisation activities	Not applicable	V3.2 / 11-Jan-2024
ANNEX 7 Other supporting data	Not applicable	V1.5 / 27-Feb-2023
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include current RMP.	V3.3 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

- Version number: 3.2
- Approved with procedure: EMEA/H/C/004444/II/0023
- Date of approval: 11-Jan-2024

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler, EU QPPV

Qualified Person for Pharmacovigilance (QPPV) oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Overview

Active substance(s) (International Nonproprietary Name or common name)	Luspatercept
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical Code)	Anti-anaemic preparations, other anti-anaemic preparations (B03XA06)
Marketing Authorisation Holder or Applicant	Bristol Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Reblozyl
Marketing authorization procedure	Centralised - European Medicines Agency
Brief description of product including chemical class, summary of mode of action, important information about its composition (eg, origin of active substance of biologicals, relevant adjuvants or residual vaccines)	Luspatercept (BMS-986346, ACE-536), an erythroid maturation agent, is a recombinant fusion protein that binds selected transforming growth factor-β superfamily ligands and is produced in Chinese Hamster Ovary cells. By binding to specific endogenous ligands (eg, growth differentiation factor 11, activin B) luspatercept inhibits Smad2/3 signalling, resulting in erythroid maturation through expansion and differentiation of late-stage erythroid precursors (normoblasts) in the bone marrow, thereby restoring effective erythropoiesis. Smad2/3 signalling is abnormally high in disease models characterised by ineffective erythropoiesis (ie, MDS and β-thalassaemia) and in the bone marrow of MDS patients.
Hyperlink to the Product Information	Refer to summary of product characteristics (SmPC) for luspatercept

Table 1-1: Product Overview

Indication(s) in the EEA	**Current:** In adults for the treatment of TD anaemia due to very low, low and intermediate-risk MDS In adults for the treatment of anaemia associated with TD and NTD β-thalassaemia. **Proposed:** None
Dosage in the EEA	**Current:** Recommended starting dose of 1.0 mg/kg once every 3 weeks by subcutaneous (SC) injection. MDS: patients may have the dose level increased to a maximum of 1.75 mg/kg every 3 weeks. TD and NTD β-thalassaemia: patients may have the dose level increased to a maximum of 1.25 mg/kg every 3 weeks. **Proposed:** None
Pharmaceutical form (s) and strength(s)	**Current:** Luspatercept 25 mg and 75 mg powder for solution for injection. After reconstitution, each mL of solution contains 50 mg luspatercept. **Proposed:** None.
Is the product subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Indication

The current indications are:

- In adults for the treatment of TD anaemia due to very low, low and intermediate-risk MDS.
- In adults for the treatment of anaemia associated with TD and NTD β-thalassaemia.

2.1.2 Epidemiology of the Disease

2.1.2.1 Incidence, Prevalence, Mortality and Demographic Profile of the Population of Patients with Myelodysplastic Syndromes and β-thalassaemia

The incidence, prevalence, mortality, and demographics of the population of patients with MDS and β-thalassaemia are summarised in Table 2.1.2.1-1 and Table 2.1.2.1-2, respectively.

Table 2.1.2.1-1: Epidemiology of Patients with Myelodysplastic Syndromes

Indication/target population	Current: In adults for the treatment of TD anaemia due to very low, low and intermediate-risk MDS.
Incidence of target indication	An analysis of 64 cancer registries from European countries indicates that the incidence of MDS was 1.5 per 100,000 individuals per year from 1995 to 2002.[1] Data from the Düsseldorf registry in Germany suggest that the overall crude incidence rate was 3.78 per 100,000 person-years for MDS as defined by World Health Organization (WHO) subtypes and 4.88 per 100,000 person-years using French American British classification).[2] In the United States (US), estimates of age-adjusted incidence per 100,000 individuals from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) were reported as 3.3 per year during 2001 to 2003 and 4.9 per year during 2007 to 2011.[3] 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.[4]
Prevalence of target indication	An analysis of 22 European cancer registries indicated that the prevalence of MDS was approximately 25,000 cases in 2008.[1] The accuracy of the estimates for the number of people living with MDS is difficult to gauge. MDS prevalence is rarely reported to registries and underestimation is suspected.[3] Between 60,000 and 170,000 individuals in the US are estimated to have MDS and this number is projected to grow as the life expectancy of patients with MDS increases.[3] The global prevalence of MDS was reported within a range of 0.022 to 1.32 per 10,000 for all age categories, genders, and ethnicities.[5] Approximately 30% of all MDS patients have > 15% of bone marrow erythroid precursors consisting of ring sideroblasts.[6]
Natural history, including mortality and morbidity	In the 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. TD patients had a median survival of 44 months compared to 97 months for transfusion-independent patients.[7] Among MDS patients reported to the SEER (17 regions) during 2001 to 2008, the 3-year observed survival has been reported to be 42% and the 5-year survival rate is 29%.[8] Previous studies have shown that age, sex, transfusion dependence, MDS subtype, bone marrow blast percentage, number of cytopenias, and cytogenetics are prognostic factors.[8,9,10] Younger patients have demonstrated better survival, and men with MDS are 25% more likely to die than women.[11] Progression to AML occurs at a variable rate depending on the presence of adverse prognostic risk factors. In the Multicentre Registry study, the cumulative AML progression risk was 4.7% after 2 years of diagnosis and 14.7% after 5 years. In the first 2 years following diagnosis, the probability of developing AML was 11% for patients presenting with transfusion dependency compared with 2% among patients without transfusion dependency.[7]
Risk factors for the disease	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

Table 2.1.2.1-1: Epidemiology of Patients with Myelodysplastic Syndromes

	exposure to environmental irritants.[12,13,14] Advancing age is the single greatest risk factor.[15]
Demographic profile of target population	The overall age-standardised incidence rate was 4.30 and 3.32 per 100,000 person-years for men and women, respectively, in the Düsseldorf MDS Registry. The incidence rate ratio comparing men to women was 1.78.[2] Using data from the Düsseldorf MDS Registry, in 2003 the median age of prevalent male and female patients was 69 and 78 years, respectively.[2] In an analysis of data from the North American Association of Central Cancer Registries, age adjusted incidence of MDS was significantly higher among males and a sharp increase was observed with age; rates were 5 times greater among those aged 80 years and older (35.5 per 100,000) compared with those aged 60 to 69 years (7.1 per 100,000).[16]
Main treatment options	TD patients with lower-risk MDS have limited treatment options that overcome the burdens and risks associated with chronic red blood cell (RBC) transfusions. Erythropoiesis-stimulating agents (ESAs) are used as first-line treatment option for anaemia in lower-risk MDS patients without del(5q).[13,17] Lenalidomide (Revlimid®, BMS) is indicated as monotherapy for the treatment of adult patients with TD 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.[18] The major favourable prognostic factors for response to ESAs are low or no RBC transfusion requirement (< 2 units/month) and a baseline serum erythropoietin (EPO) level < 500 U/L.[13] The European ESA scoring system uses a serum EPO level of ≤ 200 U/L as a prognostic factor for ESA responsiveness.[19] Eprex® is the only approved ESA, and is approved via Mutual Recognition Procedure in a number of EU countries. It is indicated for the treatment of symptomatic anaemia in adults with low- or intermediate-1-risk primary MDS who have low serum EPO (< 200 U/L).[20] Approximately 70% of patients will eventually become unresponsive to ESAs.[21] The second-line treatment options are restricted to aggressive disease-modifying agents, which include anti-lymphocyte globulin and anti-thymocyte globulin (immunosuppressive therapies), azacitidine and decitabine (hypomethylating agents) and lenalidomide. Outcomes remain suboptimal despite the use of these second-line treatment options, and many patients will ultimately require long-term RBC transfusions.[13,17] RBC transfusions remain the mainstay of treatment in patients with lower-risk MDS and anaemia but are associated with risk.[22,23,24]). 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.[22,23,24] In addition, long-term RBC transfusion dependence has other clinical consequences.[22] These include a potentially negative impact on quality of life, the development of iron overload and its associated complications, and the development of immune-related disorders and increased risk of infection.[25,26,22] There is a need for additional therapies to treat the MDS-associated anaemia in patients with lower-risk MDS, whose disease does not yet need treatment with more intensive and less well-tolerated drugs.

Table 2.1.2.1-1: Epidemiology of Patients with Myelodysplastic Syndromes

Important co-morbidities	Anaemia[27,28] Neutropenia and infections[28,29] Thrombocytopenia and bleeding[28,29] Other neoplasms, including progression to AML and solid tumours[10,30 ,31] Endocrine/diabetes[30,31] Cardiac disease[30, 31] Pulmonary disease[30,31] Renal disease[30, 31] Cerebrovascular disease[30,31] Hepatic disease[30,31] Rheumatologic disease[30,31] Gastrointestinal disease[31] Obesity[31] Psychiatric disease[31]

Table 2.1.2.1-2: Epidemiology of Patients with β-thalassaemia

Indication/target population	• In adults for the treatment of anaemia associated with TD and NTD β-thalassaemia.
Incidence of target indication	The annual incidence at birth of symptomatic β-thalassaemia is estimated at 1 in 100,000 worldwide, and 1 in 10,000 in the EU.[32] Incidence is highest in the Mediterranean region, the Middle East, and South East Asia (particularly India, Thailand, and Indonesia; this region accounts for approximately 50% of affected births) and incidence is increasing worldwide (eg, Europe, the Americas and Australia) as a result of migration.[33,34]
Prevalence of target indication	It is estimated that about 80 to 90 million people (~1.5% of the global population) are carriers of β-thalassaemia with approximately 60,000 symptomatic individuals born annually.[32] Some 23,000 children are born with TD β-thalassaemia each year, while a smaller, ill-defined number have NTD forms. NTD is most commonly found in parts of the Eastern Mediterranean and Africa, where β+ thalassaemia predominates.[34,35,36,37] The highest prevalence of the structural variant haemoglobin E is observed in the Indian subcontinent and East and Southeast Asia, where carrier frequencies may reach as high as 80%[38,39,37] Haemoglobin E/β-thalassaemia currently affects around 1,000,000 people worldwide[40] and more than 19,000 affected children are born each year, with half having TD and the other half NTD[34,37]

Table 2.1.2.1-2: Epidemiology of Patients with β-thalassaemia

Natural history, including mortality and morbidity	β-thalassaemia comprises a number of different phenotypes with varying severity, including: • TD: includes patients with β-thalassaemia major or severe forms of β-thalassaemia intermedia or haemoglobin E/β-thalassaemia, which require regular RBC transfusions. • NTD: includes patients with mild-to-moderate β-thalassaemia intermedia or haemoglobin E/β-thalassaemia who may require infrequent transfusions to manage the disease and its complications. • β-thalassaemia trait (minor): heterozygous patients with mild, usually asymptomatic anaemia that generally does not require treatment (excluded from the luspatercept target patient population). β-thalassaemia major usually presents between 6 and 24 months of age when the normal switch from γ-chains to β-chains does not occur. These individuals are TD, and if left untreated, will die by the age of 5 years from infections and cachexia.[32] Individuals with thalassaemia intermedia present between the ages of 2 and 6 years old.[32] Individuals with thalassaemia minor usually have excellent prognosis.[32] In some resource-limited settings, the clinical picture in patients who are untreated or poorly transfused, is characterised by growth retardation, pallor, jaundice, poor musculature, genu valgum, hepatosplenomegaly, leg ulcers, development of masses from EMH, and skeletal changes resulting from expansion of the bone marrow.[32] Many children who are adequately transfused and are fully compliant with iron chelation therapy develop normally up to 10 to 12 years. TD patients may suffer from the side effects of chronic transfusions, namely transfusion-associated infections, (particularly hepatitis B and C and in some populations human immunodeficiency virus [HIV]), and organ damage due to iron overload (including liver, heart, and endocrine glands).[32] The primary cause of death in adult TD patients remains cardiac events due to iron overload mainly caused by RBC transfusions[41,42] although recent studies show that liver disease is also becoming a leading cause of morbidity and mortality.[43] The average life expectancy of an individual with β-thalassaemia was 17 years in 1970, 27 years in 1980, and 37 years in 1990. Since 2000, greater than 80% of patients have a life expectancy of > 40 years.[44] In NTD β-thalassaemia patients, treatment strategy is focused in part on iron overload-related complications, but also on several complications of the disease itself. If left untreated, the clinical sequelae of NTD β-thalassaemia patients are due principally to the combined effect of ineffective erythropoiesis, chronic anaemia, and iron overload.[45] As a result of the ineffective RBC production by the bone marrow (ineffective erythropoiesis), a forced expansion of the haematopoietic tissue outside the marrow medulla appears and leads to haematopoietic compensatory involvement, mostly in the form of masses in other regions in the body; this phenomenon is termed EMH.[46,47] In addition to EMH, ineffective erythropoiesis is also associated with skeletal deformities, osteopenia/osteoporosis, and bone pain attributed to erythroid expansion in the bone marrow.[47] Ineffective erythropoiesis also leads to increased intestinal iron absorption, peripheral haemolysis, and a hypercoagulable state.[35] Additional complications that are thus commonly seen in NTD β-thalassaemia include liver disease, cholelithiasis, endocrinopathy, thrombosis, and pulmonary hypertension with right-sided heart failure, all of which have been associated with iron overload, hypercoagulability, or both. Despite frequently presenting with anaemia, patients

Table 2.1.2.1-2: Epidemiology of Patients with β-thalassaemia

	with NTD β-thalassaemia are by definition not dependent on regular transfusion for survival, a characteristic that distinguishes NTD β-thalassaemia from TD β-thalassaemia. Given the current lack of safe and effective drug therapies, there is significant unmet medical need for the development of new therapies that specifically address the underlying pathophysiology of both TD β-thalassaemia and NTD β-thalassaemia including anaemia and complications of ineffective erythropoiesis.
Risk factors for the disease	Family history is a strong risk factor for β-thalassaemia. Mutations in the β-globin gene can be passed on from each of the two carrier parents to affected offspring in a recessive Mendelian manner.[35]
Demographic profile of target population	β-thalassaemia has no gender predilection and affects both sexes equally. β-thalassaemia is prevalent in individuals of Mediterranean, Middle Eastern, Central Asian, Indian, Southern Chinese, Far Eastern, coastal North African and South American descent have the highest incidence of β-thalassaemia.[32] β-thalassaemia major usually manifests between the ages of 6 and 24 months. Individuals with thalassaemia intermedia present between the ages of 2 and 6 years old. Patients with thalassaemia minor may be asymptomatic and may not require treatment.[32]
Main treatment options	Current treatment options for β-thalassaemia are limited. Blood transfusions remain the main component of the β-thalassaemia standard of care, but the practice is attended by a significant number of risks, primarily driven by secondary iron overload and associated organ failure (heart, liver, and endocrine glands).[42,35,36,48] Patients who receive regular blood transfusions are also at risk of a variety of other serious complications including development of alloantibodies, which may lead to decreased lifespan of transfused blood cells and results in difficulty in obtaining compatible blood for transfusion, as well as transfusion reactions including nonhaemolytic febrile transfusions reactions, allergic reactions, acute haemolytic reactions, delayed transfusion reactions, and autoimmune haemolytic anaemia. Furthermore, though rare, these patients are likewise exposed to the serious risks of infectious agent transmission, transfusion-related acute lung injury, transfusion-induced graft versus host disease, and transfusion-associated circulatory collapse.[26] Although the survival of patients with NTD β-thalassaemia is not dependent on regular transfusion, transfusion requirements may change over time. Early in disease, transfusions may be intermittently required due to events such as pregnancy, splenomegaly, or infections.[49] Patients with NTD β-thalassaemia may be placed on regular transfusions to manage specific disease complications. There is no available therapy that is widely used to address the underlying ineffective erythropoiesis and anaemia of β-thalassaemia. The only approved therapies in Europe and the US for both TD and NTD β-thalassaemia are iron chelating agents for the treatment of iron overload.[42,35,48] Data support the efficacy of iron chelators in removing iron from the liver and heart of patients with TD β-thalassaemia; however, recent data indicate that optimal control of iron overload in the global population of TD β-thalassaemia has not yet been achieved.[50] Iron chelators are also associated with several known side effects, which require close clinical and laboratory monitoring, adding to the burden of a chronic disease requiring lifelong therapy.[42,35,48] Splenectomy, as a transfusion sparing procedure, is also primarily restricted to patients with symptomatic splenomegaly or hypersplenism because of the concurrent high risk of infections and vascular disease, in particular thromboembolism, following the procedure.[42,51,36]

Table 2.1.2.1-2: Epidemiology of Patients with β-thalassaemia

	Haematopoietic stem cell transplantation is the only available curative therapy for patients with β-thalassaemia; however, several factors continue to limit its acceptability: an overall mortality risk of 12% within 2 years of transplantation, acute and chronic graft versus host disease and graft failure, and the need for complete myeloablation that can result in infertility and other toxicities.[52,42,36] Haematopoietic stem cell transplantation is not appropriate in patients exhibiting severe iron overload, and in patients with liver pathologies such as severe hepatomegaly or fibrosis.[42] Zynteglo™ has recently been approved for a small subset of patients with TD β-thalassemia as a potential curative therapy: Betibeglogene autotemcel is approved for the treatment of patients 12 years and older with TD β-thalassaemia who do not have a β0/β0 genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen-matched related haematopoietic stem cell donor is not available. Because β-thalassemia patients are at increased rate of thromboembolic complications, patients with certain risk factors such as splenectomy with elevated platelet counts or cardiac disorders should be considered for prophylactic anticoagulant therapy such as low-dose aspirin.[53]
Important co-morbidities/ complications	Organ damage due to iron overload (intrinsic iron overload and the cumulative impact of iron overload related to transfusions):[54] • Liver disease (cirrhosis, hepatocellular carcinoma, hepatic failure). • Cardiac (left-sided heart failure, cardiac siderosis). • Endocrine damage (diabetes mellitus, hypothyroidism, hypoparathyroidism). • Pituitary damage (hypogonadism, growth retardation, delayed puberty). Skeletal malformations (long bone deformities and typical craniofacial changes)[42] EMH[55,56,57,58] Thromboembolic events (TEEs)[42] Osteoporosis[54] Splenomegaly[54] Splenectomy complications (sepsis, thrombophilia, pulmonary hypertension, iron overload)[42,51] Malignancies[59,60] Transfusion-associated: • Infections (hepatitis B and C, HIV)[54] • Alloimmunisation[42] • Allergic reactions[42] • Acute lung injury[42] • Immune haemolytic anaemia[42]

2.2 Nonclinical Part of the Safety Specification

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 2.2-1.

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Toxicity Studies	
• Single and Repeat-dose Toxicity	
Single-dose toxicity studies have not been conducted with luspatercept. Repeat-dose toxicology studies have been performed with luspatercept in rats and monkeys, dosing SC every 2 weeks for up to 3 (rats) or 6 (monkeys) months. Increases in measures of RBC mass (RBC, haematocrit, and haemoglobin) were observed in both species. In addition, EMH was noted in the mandibular and axillary lymph nodes at all dose levels in the monkey 6-month study. This is a common background finding in cynomolgus monkeys of this age. Decreased heart and lung weights with no associated histology findings, adrenal gland necrosis/congestion, liver necrosis, thymus congestion and mineralisation of the glandular portion of the stomach were observed in rats. A clinical observation of swollen hindlimbs/feet was noted in several studies in rats and rabbits (including juvenile and reproductive toxicity studies). In 1 juvenile rat, this correlated histopathologically with new bone formation, fibrosis, and inflammation. Mixed inflammatory cell infiltrate in the interstitium, including the blood vessels, of the choroid plexus was observed in monkeys. Immunohistochemistry of the choroid plexus revealed increased complement (C3) granularity in the interstitium. This finding was not considered diagnostic for, but was consistent with, increased handling of complement components, most likely as immune complexes by the foamy macrophages. The above findings were generally reversible after a recovery period.	Consistent with the expected pharmacologic action of luspatercept, a first-in-class erythroid maturation agent, it restores effective erythropoiesis, and is thereby indicated in the treatment of different chronic anaemias such as β-thalassaemia, MDS and myelofibrosis. Findings in rats were considered rodent-specific, as they were not observed in monkeys. Additionally, no evidence of similar toxicity, as assessed by routine monitoring, has been observed in humans in the BMS-sponsored clinical trials. The microscopic changes in the choroid plexus in monkeys were not considered adverse, are similar to background changes known to occur in cynomolgus monkeys,[61] would not be expected to interfere with choroid plexus function, and were not associated with any central nervous system clinical signs. EMH masses have been observed during treatment with luspatercept in Study ACE-536-B-THAL-002 and patients should be monitored for signs and symptoms of EMH masses, including any complications resulting from the EMH masses, and treated according to standard clinical guidelines.
• Reproductive and Developmental Toxicity	
Embryo-foetal developmental toxicology studies were conducted in the pregnant Sprague Dawley rat and New Zealand White rabbit. Luspatercept was a selective developmental toxicant (dam not affected; foetus affected) in the rat and a maternal and foetal developmental toxicant (doe and foetus affected) in the rabbit. In both species, effects included increased resorptions and postimplantation loss, and decreased litter size. There was also an increased incidence of skeletal variations in both rats and rabbits. In both species, effects of luspatercept were observed at the lowest dose tested (5 mg/kg), which corresponds to an estimated exposure in rats and rabbits of approximately 2.7 and 5.5 times greater, respectively, than the estimated clinical exposure.	Luspatercept is contraindicated during pregnancy. Women of childbearing potential (WCBP) have to use effective contraception during treatment with luspatercept and for at least 3 months after the last dose. Prior to starting treatment with luspatercept, a pregnancy test has to be performed for WCBP. Treatment with luspatercept should not be started if the woman is pregnant. If a patient becomes pregnant, luspatercept should be discontinued.
In a fertility and early embryonic development study in rats, there were significant reductions in the average numbers of corpora lutea, implantations, and viable embryos in luspatercept-treated females. There was no effect on mating,	The effect of luspatercept on fertility in humans is unknown. Based on findings in animals, luspatercept may compromise female fertility.

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
fertility, or litter parameters when males treated with luspatercept were mated with untreated females. The maternal no observed adverse effect level (NOAEL) was 3 mg/kg (estimated exposure multiple of 1.5 times higher than 1.75 mg/kg clinical dose), and the paternal NOAEL was the highest dose tested, 15 mg/kg (estimated exposure multiple of 7 times higher than 1.75 mg/kg clinical dose). Effects on fertility in female rats were reversible after a 14-week recovery period. In a pre- and postnatal developmental toxicity study, decreased body weights and adverse kidney findings were observed in the first filial generation (F1) at all dose levels, but the NOAEL for effects on behavioural indices, fertility, or reproductive parameters was the highest dose tested, 30 mg/kg (estimated exposure multiple of 15 times higher than 1.75 mg/kg clinical dose).	Lactation is discussed in the "Other Toxicity-related Information" row.
• Nephrotoxicity Adverse findings in rats included membrano-proliferative glomerulonephritis. Adverse findings in monkeys included membrano-proliferative glomerulonephritis, interstitial tubular haemorrhage, tubular atrophy and degeneration, fibrosis/fibroplasias, and mixed inflammatory cell infiltrates in the kidney. The kidney findings were presumed to be a direct drug effect, although a contribution to the changes by immune complex deposition could not be excluded. Variables associated with the kidney pathology were minimal increases in blood urea nitrogen and creatinine. Increases in potassium and inorganic phosphorous were also noted in females at 60 mg/kg in the 1-month rat study, as well as increases in urinary albumin-to-creatinine (ACR) ratio in individual monkeys in the 6-month study.	In the luspatercept clinical studies, renal injury was evaluated by assessing luspatercept with respect to its renal adverse event (AE) profile, its impact on renal function (creatinine clearance [CrCl]), and its impact on proteinuria. Among luspatercept-treated patients with events of renal impairment, renal function generally recovered substantially while the patient remained on luspatercept, indicating negative re-challenge. Episodes of impaired renal function were typically preceded by the occurrence of another AE typically linked with the development of acute renal failure (eg, sepsis, decompensated congestive heart failure), or was preceded by the use of therapeutic agents known to be potentially nephrotoxic. Finally, mean ACR remained clinically stable over time, with no prolonged elevations of mean ACR in patients in the Phase 2 and Phase 3 trials. In summary, administration of luspatercept was not associated with prolonged or irreversible worsening of clinically important indicators of kidney injury over the course of treatment.
• Hepatotoxicity Not applicable as no separate studies were performed to investigate hepatotoxicity. The repeat-dose toxicity studies, described above did however assess all organ systems.	In the luspatercept clinical studies, all of the elevations in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and total bilirubin in these patients had alternative explanations, including pre-existing increased bilirubin, concurrent treatment-emergent AEs (TEAEs), history of cirrhosis and/or hepatitis C, and use of concomitant medication capable of causing liver injury.

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
• Genotoxicity Genotoxicity studies have not been conducted with luspatercept, as is typical for biologics, in accordance with International Council for Harmonisation S6 guidance.	Not applicable.
• Carcinogenicity Carcinogenicity studies have not been conducted with luspatercept, as these studies are not appropriate for biotechnology-derived therapeutics. In the definitive toxicity study conducted in juvenile rats, haematologic malignancies were observed in 3 animals (one incidence each of lymphoma, myeloid leukaemia, and lymphoid leukaemia) out of a total of 44 examined in the highest dose group (10 mg/kg). Although lymphoma and leukaemia are common in rats at the end of 2 years, the presence of these tumours in rats < 26 weeks of age in the high-dose group is unusual and the relationship to luspatercept therapy cannot be ruled out. In addition, during the 3-month study in rats, an adult female rat in the high-dose (15 mg/kg) group was found dead during study Week 11, with a diagnosis of disseminated pleomorphic lymphoma. This tumour was considered a spontaneous occurrence and not related to luspatercept. No other tumour findings have been seen in studies with luspatercept in adult rats or monkeys. A pharmacokinetic (PK) comparison of juvenile rats to adult patients indicates a 4.4-fold difference in exposure between the juvenile rats dosed at 10 mg/kg and adult human patients at the highest recommended clinical dose (1.75 mg/kg every 3 weeks). No other proliferative or pre-neoplastic lesions, attributable to luspatercept have been observed in any species from the battery of nonclinical safety studies, including the 6-month study in monkeys.	In luspatercept clinical studies, patients who experienced progression to AML within the MDS population had relevant risk factors for developing AML based on their baseline disease characteristics, and no effect of luspatercept was observed in the randomised Phase 3 studies (ACE-536-MDS-001 and ACE-536-MDS-002). Although there was no imbalance in malignancies in the MDS clinical programme and no malignancies reported in luspatercept-treated patients in the TD β-thalassaemia population up until the data cut-offs in this RMP, long-term data are limited. No malignancies have been reported in luspatercept-treated NTD β-thalassemia patients in Study ACE-536-B-THAL-002.

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
General Safety Pharmacology • Cardiovascular Stand-alone safety pharmacology studies with luspatercept have not been performed. However, safety pharmacology parameters were incorporated into the 1- and 3-month toxicology studies in monkeys. Parameters evaluated for both studies included cardiovascular assessments (heart rate, blood pressure, body temperature, and qualitative electrocardiograms), respiratory (respiration rate) and neurologic (general attitude, behaviour, motor function [cranial nerves II though XII], proprioception, postural reactions, and spinal nerves). There were no luspatercept-related findings for any of the above safety pharmacology parameters at any dose levels evaluated in the 1-month study (30 mg/kg, SC or 10 mg/kg intravenous) or in the 3-month study (30 mg/kg, SC).	In ACE-536-MDS-001 and in TD β-thalassaemia patients in controlled luspatercept clinical studies, patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of 5 mmHg from baseline. In ACE-536-MDS-002, luspatercept treatment led to no mean increase in SBP from baseline and a ≤ 3 mm Hg increase from baseline DBP. In Study ACE-536-B-THAL-002, mean blood pressure values were generally higher in the luspatercept group than the placebo group, but remained within the normal range. In the luspatercept treatment group, shifts in systolic and diastolic blood pressure (≥ 20 mm Hg from baseline) were reported in 33.3% and 27.1% patients, respectively. Treatment must be started only if blood pressure is adequately controlled. Blood pressure should be monitored prior to each luspatercept administration. Dose adjustment may be required and, in case of persistent hypertension or exacerbations of pre-existing hypertension, patients should be treated for hypertension as per current clinical guidelines.
• Immunogenicity Immunogenicity was assessed in rat, rabbit, and monkey toxicity studies. In the rat, anti-luspatercept antibodies were observed in 63.8% and 16.7% of animals in the 3-month toxicology study and definitive embryo-foetal development studies, respectively. High-titre antibodies had a significant negative effect on serum levels of luspatercept in the 3-month rat study. Antibodies to luspatercept were also detected in 2 of 9 rabbits (22.2%) in the definitive embryo-foetal development rabbit study. The presence of antibodies decreased maternal and foetal luspatercept concentrations in these animals compared to other litters in the respective dose groups. In the definitive juvenile rat study, the incidence of a positive anti-drug antibody (ADA) response was low (7.8%), and in the non-Good Laboratory Practice rat renal toxicity study, ADA were measurable in 25% of luspatercept-treated animals, and in 33% of RAP-536-treated animals. In the monkey, 9.5%, 9.1%, and 3.3% of animals in the 1-, 3-, and 6-month luspatercept toxicology studies, respectively, had ADAs detected. The presence of low-titre antibodies to luspatercept in the monkey toxicology studies did not affect the individual serum PK profiles with an exception of a single ADA-positive monkey in the 6-month monkey study after Day 183.	Of the 260 MDS patients in ACE-536-MDS-001, the 175 MDS patients in ACE-536-MDS-002, and 380 β-thalassaemia patients (TD and NTD) who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies, 23 (8.8%) MDS patients in ACE-536-MDS-001, 13 (7.4%) MDS patients in ACE-536-MDS-002, and 7 (1.84%) β-thalassaemia patients tested positive for treatment-emergent anti-luspatercept antibodies, including (among those tested) 9 (3.5%) MDS patients in ACE-536-MDS-001, 12 (6.9%) MDS patients in ACE-536-MDS-002, and 5 (1.3%) β-thalassaemia patients who had neutralising antibodies against luspatercept. Luspatercept serum concentration tended to decrease in the presence of neutralising antibodies. There was no apparent loss of the drug's effectiveness except for a single isolated case. There were no severe systemic hypersensitivity reactions reported for patients with anti-luspatercept antibodies. There was no association between hypersensitivity type reactions or injection site reactions and presence of ADA. The presence of

Table 2.2-1: Nonclinical Risks and Relevance to Human Use

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Characterisation of antibodies generated against luspatercept in the 1-month rat study revealed that the antibodies were specific to epitopes on the human immunoglobulin G1 fragment crystallisable domain of the molecule and not to the extracellular domain of the activin receptor type IIB receptor.	ADA therefore had a minimal effect on patients across the 2 indications.
Mechanisms for Drug Interactions	
Not applicable for biotherapeutics.	Not applicable. No formal clinical interaction studies have been performed. Concurrent use of iron-chelating agents had no effect on luspatercept PK.
Other Toxicity-related Information	
Following SC dosing in pregnant Sprague Dawley rats, luspatercept was transferred into milk, with mean milk to serum concentrations of approximately 12% over the time points tested. In the pre- and postnatal development study, mean ratios of foetal to maternal serum luspatercept concentrations were 18% and 9% after 8 and 24 hours, respectively, indicating that luspatercept can cross the placenta.	It is unknown whether luspatercept or its metabolites are excreted in human milk. Luspatercept is transferred through the placenta of pregnant rats and rabbits and is excreted into the milk of lactating rats. Because of the unknown adverse effects of luspatercept in new-borns/infants, a decision must be made whether to discontinue breast-feeding during therapy with luspatercept and for 3 months after the last dose or to discontinue luspatercept therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

2.3 Clinical Trial Exposure

2.3.1 Clinical Study Information

An overview of the luspatercept clinical program summarized in this RMP supporting the safe and effective use of luspatercept is in Table 2.3.1-1.

Table 2.3.1-1: Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number [Indication]	Study Title	Data Cut off Date	Number Treated Subjects
Pivotal Clinical Studies			
ACE-536-MDS-001/ (MEDALIST)[62] [MDS][a]	A Phase 3, double-blind, randomised study to compare the efficacy and safety of luspatercept (ACE 536) versus placebo for the treatment of anaemia due to International Prognostic Scoring System-Revised (IPSS R) very low-, low- or intermediate-risk MDS in subjects with ring sideroblasts who require RBC transfusions.	08-May-2018	luspatercept arm: 153

Table 2.3.1-1: Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number [Indication]	Study Title	Data Cut off Date	Number Treated Subjects
Pivotal Clinical Studies			
ACE-536-MDS-002/ (COMMANDS)[63] [MDS]	Phase 3, open-label, randomized, study to compare the efficacy and safety of luspatercept (BMS-986346, ACE 536) versus epoetin alfa for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in ESA naïve subjects who require RBC transfusions	31-Mar-2023	luspatercept arm: 182
ACE-536-B-THAL-001/ (BELIEVE)[64] [β-thalassaemia][a]	A Phase 3, double-blind, randomised, placebo controlled, multicentre study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in adults who require regular RBC transfusions due to β thalassaemia.	11-May-2018	luspatercept arm: 181 Subjects from placebo arm that crossed over to luspatercept treatment after the study was unblinded: 92
ACE-536-B-THAL-002/ (BEYOND)[65]/ [NTD β-thalassaemia]	NTD β-thalassaemia Double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in adults with non-transfusion dependent β-thalassemia	14-Sep-2020	Luspatercept arm: 96
Phase 2 single-arm studies			
Study A536-03[66]/ [MDS]	Open label, ascending-dose study of luspatercept (ACE0536) for the treatment of anaemia in patients with low or intermediate-1-risk MDS.	01-Mar-2019	luspatercept arms: 116
Study A536-05[67]/ [MDS]	Open label extension study to evaluate the long-term effects of luspatercept (ACE-536) for the treatment of anemia in patients with low or intermediate-1 risk MDS previously enrolled in Study A536-03	13-Oct-2017	luspatercept arm: 39
Study A536-04[68]/ [β-thalassaemia]	Open label, ascending-dose study to evaluate the effects of luspatercept (ACE-536) in patients with β-thalassaemia intermedia	30-Jun-2016	luspatercept arms: 64
Study A536-06[69]/ [β-thalassaemia]	Open label extension study to evaluate the long-term effects of luspatercept (ACE-536) in patients with β-Thalassemia previously enrolled in Study A536-04	31-Aug-2017	luspatercept arm: 30

[a] Currently, there are no more patients participating in Studies ACE-536-MDS-001 and ACE-536-B-THAL-001. All patients who were willing to continue with the study have been rolled over to ACE-536-LTFU-001.

2.3.2 Patient Exposure

An overview of exposure to luspatercept is provided in a pooled fashion for Studies A536-02, A536-03, A536-04, A536-05, A536-06, ACE-536-MDS-001, and ACE-536-B-THAL-001 (luspatercept data pool) and on an individual study basis for Studies ACE-536-B-THAL-002 and ACE-536-MDS-002. Subsequently, tabular summaries of exposure by duration, dose, age group, sex, and race are provided for the pivotal Phase 3 studies, ACE-536-MDS-001, ACE-536-MDS-002, ACE-536-B-THAL-001, and ACE-536-B-THAL-002 (Table 2.3.2-1 to Table 2.3.2-4).

In the luspatercept data pool, 571 subjects received at least 1 dose of luspatercept, representing an overall exposure of 601.66 person-years, compared with 193 subjects who received at least 1 dose of placebo, representing an overall exposure of 168.24 person-years. The 2:1 randomisation scheme (luspatercept:placebo) used in studies ACE-536-MDS-001 and ACE-536-B-THAL-001 contributes to the person-year difference observed. The median duration of treatment was higher in the pooled luspatercept treatment group than in the pooled placebo treatment group (55.1 versus 49.7 weeks, respectively). Similarly, subjects in the pooled luspatercept treatment group received more doses of luspatercept than subjects in the pooled placebo treatment group (median 18.0 versus 16.0 doses, respectively). In both treatment groups, the median length of cycle between doses was 21.0 days, which is consistent with the every 3-week dosing regimen.

In Study ACE-536-B-THAL-002 in NTD β-thalassaemia, the median treatment duration was longer in the luspatercept treatment group compared with the placebo treatment group (99.7 versus 61.1 weeks). The median number of doses received was 28.5 in the luspatercept treatment group and 20.0 in the placebo treatment group. The median length of cycle between doses was 22.4 days in the luspatercept treatment group and 21.7 days in the placebo treatment group, which is consistent with the every 3-week dosing regimen. A total of 96 subjects received at least 1 dose of luspatercept for an overall cumulative exposure of 172.91 patient-years, compared with 49 subjects who received at least 1 dose of placebo for an overall cumulative exposure of 61.96 patient-years.

In Study ACE-536-MDS-002, 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. A total of 182 subjects received at least 1 dose of luspatercept for an overall cumulative exposure of 230.7 patient-years, compared with 179 subjects who received at least 1 dose of epoetin alfa for an overall cumulative exposure of 178.1 patient-years.

Table 2.3.2-1: Duration of Exposure (by Indication)

Indication (Study) Duration of exposure (at least)	Persons, n (%)	Person-years
MDS (Study ACE-536-MDS-001)		
1 month	153 (100)	136.7
3 months	147 (96.1)	135.7

Table 2.3.2-1: Duration of Exposure (by Indication)

Indication (Study) Duration of exposure (at least)	Persons, n (%)	Person-years
6 months	100 (65.4)	116.2
12 months	63 (41.2)	85.1
Total	153 (100)	136.7
Median exposure (min-max)	49.0 weeks (4.9-113.9 weeks)	
MDS (Study ACE-536-MDS-002)		
1 month	179 (98.4)	230.6
3 months	171 (94.0)	229.0
6 months	157 (86.3)	223.6
12 months	89 (48.9)	175.6
18 months	56 (30.8)	133.7
24 months	36 (19.8)	97.9
30 months	22 (12.1)	66.0
36 months	10 (5.5)	33.2
42 months	1 (0.5)	3.7
Total	182 (100.0)	230.7
Median exposure (min-max)	51.3 weeks (3-196 weeks)	
TD β-thalassaemia (Study ACE-536-B-THAL-001)		
1 month	221 (99.1)	259.7
3 months	217 (97.3)	259.3
6 months	210 (94.2)	256.6
12 months	161 (72.2)	211.1
Total	223 (100)	259.8
Median exposure (min-max)	63.3 weeks (1.7-93.7 weeks)	
NTD β-thalassaemia (Study ACE-536-B-THAL-002)		
1 month	96 (100)	172.9
3 months	96 (100)	172.9
6 months	92 (95.8)	171.6
12 months	83 (86.4)	163.5
Total	96 (100)	172.9
Median exposure (min-max)	99.7 weeks (15.0-132.1 weeks)	

Table 2.3.2-2: Exposure by Dose (by Indication)

Dose of exposure (at least)	Persons, n (%)	Person-years
MDS (Study ACE-536-MDS-001)		
At least 1 dose	153 (100)	136.7
At least 10 doses	94 (61.4)	112.4
At least 20 doses	48 (31.4)	68.9
At least 30 doses	5 (3.3)	96
Total	153 (100)	136.7
MDS (Study ACE-536-MDS-002)		
At least 1 dose	182 (100)	230.7
At least 10 doses	138 (75.8)	212.7
At least 20 doses	75 (41.2)	158.3
At least 30 doses	44 (24.2)	112.7
Total	182 (100)	230.7
TD β-thalassaemia (Study ACE-536-B-THAL-001)		
At least 1 dose	223 (100)	259.8
At least 10 doses	208 (93.3)	255.2
At least 20 doses	136 (61.0)	182.7
At least 30 doses	1 (0.4)	3.5
Total	223 (100)	259.8
NTD β-thalassaemia (Study ACE-536-B-THAL-002)		
At least 1 dose	96 (100)	172.9
At least 10 doses	88 (91.7)	166.9
At least 20 doses	70 (72.9)	142.8
At least 30 doses	44 (45.8)	97.7
Total	96 (100)	172.9

Table 2.3.2-3: Exposure by Age Group and Sex (by Indication)

	Persons, n (%)		Person-years	
Age Group	**Male**	**Female**	**Male**	**Female**
MDS (Study ACE-536-MDS-001)				
< 65 years	14 (48.3)	15 (51.7)	16.4	16.9
≥ 65 years	80 (64.5)	44 (35.5)	65.3	38.0
Total	94 (61.4)[a]	59 (38.6)[a]	81.7	55.0

Table 2.3.2-3: Exposure by Age Group and Sex (by Indication)

	Persons, n (%)		Person-years	
Age Group	**Male**	**Female**	**Male**	**Female**
MDS (Study ACE-536-MDS-002)				
< 64 years	13 (11.9)	14 (19.2)	13.8	20.9
65 - 74 years	41 (37.6)	27 (37.0)	49.0	31.6
≥ 75 years	55 (50.5)	32 (43.8)	76.3	39.2
Total	109 (100)[b]	73 (100)[b]	139.1	91.7
TD β-thalassaemia (Study ACE-536-B-THAL-001)				
≤ 32 years	56 (43.4)	73 (56.6)	66.9	82.4
> 32 years[c]	35 (37.2)	59 (62.8)	38.5	72.0
Total	91 (40.8)[a]	132 (59.2)[a]	105.4	154.4
NTD β-thalassaemia (Study ACE-536-B-THAL-002)				
≤ 32 years	13 (37.1)	22 (62.9)	26.1	36.3
> 32 years[d]	27 (44.3)	34 (55.7)	47.2	63.4
Total	40 (41.7)[a]	56 (58.3)[a]	73.3	99.6

a Denominator based on combined total for both sex categories.
b Denominator based on the total for this sex category only
c One patient was ≥ 65 years.
d Three patients were ≥ 65 years.

Table 2.3.2-4: Exposure by Race (by Indication)

Race	Persons, n (%)	Person-years
MDS (Study ACE-536-MDS-001)		
White	107 (69.9)	100.6
Black or African American	1 (0.7)	1.0
Other	1 (0.7)	0.1
Not collected or reported	44 (28.8)	35.0
Total	153 (100)	136.7

Table 2.3.2-4: Exposure by Race (by Indication)

Race	Persons, n (%)	Person-years
MDS (Study ACE-536-MDS-002)		
White	146 (80.2)	181.7
Asian	19 (10.4)	24.7
Black or African American	2 (1.1)	2.8
Not collected or reported	15 (8.2)	21.6
Total	182 (100.0)	230.7
TD β-thalassaemia (Study ACE-536-B-THAL-001)		
White	121 (54.3)	140.8
Asian	81 (36.3)	93.5
Black or African American	1 (0.4)	1.8
Other	15 (6.7)	17.0
Not collected or reported	5 (2.2)	6.7
Total	223 (100)	259.8
NTD β-thalassaemia (Study ACE-536-B-THAL-002)		
White	59 (61.5)	107.0
Asian	31 (32.3)	56.6
Other	6 (6.3)	9.4
Total	96 (100)	172.9

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Important exclusion criteria in pivotal clinical studies are presented in Table 2.4.1-1.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? If No, rationale
Malignancy or history of malignancy (except for treated [ie, determined to be cured] basal-cell or squamous cell in situ skin carcinomas and treated [ie, determined to be cured] cervical intraepithelial neoplasia or carcinoma in situ of the cervix). In the MDS Phase 3 studies, history of malignancy was allowed only for subjects free of disease for ≥ 5 years. A history of or concurrent incidental histologic finding of prostate cancer (T1a or T1b using the TNM clinical staging system) was also allowed.	These concomitant conditions could influence the interpretation of the study results.	• Not considered to be missing information. • The safety of luspatercept in patients with a history of malignancy has not been established in clinical practice and no carcinogenicity or mutagenicity studies have been conducted as luspatercept is a biologic. MDS is a malignant disease with great propensity to progress to other malignancies. Based on analyses of the pivotal registration studies, there is no evidence that luspatercept increases the risk of malignancies. • Although there was no imbalance in malignancies in the MDS clinical programme and no malignancies reported in luspatercept-treated patients in the TD β-thalassaemia population up until the data cut-offs in this RMP, long-term data are limited. No malignancies have been reported in luspatercept-treated patients in Study ACE-536-B-THAL-002. • Haematologic malignancy (including AML) is considered an important potential risk.
Known history of positive human immunodeficiency virus or congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease) or bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of screening. Any treatment for such infections must have been completed at least 4 weeks prior to screening	These concomitant conditions could influence the interpretation of the study results. MDS patients experience impaired immune responses due to their underlying diseases. The majority of β-thalassaemia patients had a splenectomy, making this population at an even greater risk of infections due to compromised cell-mediated immunity.	• Not considered to be missing information. • The safety of luspatercept in these patients has not been established in clinical practice. There is no evidence that luspatercept increases the overall risk of infections or causes immunosuppression. These patients may benefit from treatment with luspatercept by reducing the number of transfusions and improvement of underlying anaemia.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? If No, rationale
Cardiac history of uncontrolled hypertension: > Grade 1 (β-thalassaemia); > Grade 3 (MDS) OR stroke/deep vein thrombosis (DVT)/pulmonary embolism/myocardial infarction/heart failure (ejection fraction < 35%), uncontrolled arrhythmia within the prior 6 months.	Significant uncontrolled cardiac disease was an exclusion criterion for all luspatercept studies to avoid interference with the study endpoints.	• Not considered to be missing information. • No effects on left ventricular ejection fraction, electrocardiogram variables, or vital signs have been observed in studies with luspatercept. No patient had a TEAE in the Cardiac disorders system organ class that led to discontinuation of luspatercept. TEAEs generally correlated with the cardiac medical history of the studied population and with what could be expected in the population of older patients with haematologic malignancies. • TEE is considered an important identified risk in the TD and NTD β-thalassaemia population with splenectomy. • Overall, the safety profile of luspatercept does not suggest a need for its limitation in patients with significant cardiac disease.
Impaired hepatic function: • ALT ≥ 3 × upper limit of normal (ULN). • AST ≥ 3 × ULN (MDS population only). • Total bilirubin ≥ 2 × ULN (MDS population only). • Active hepatitis B/C.	These concomitant conditions could influence the interpretation of the study results.	• Not considered to be missing information. • Population PK analysis for luspatercept included patients with normal hepatic function, mild hepatic impairment, moderate hepatic impairment, or severe hepatic impairment as defined by the National Cancer Institute criteria of hepatic dysfunction. • Effects of hepatic function categories, elevated liver enzymes and elevated total bilirubin on luspatercept clearance were not observed. No clinically significant difference in mean steady state maximum concentration (Cmax) and area under the concentration-time curve (AUC) was found across hepatic function groups. • No starting dose adjustment is required for patients with total bilirubin > ULN and/or ALT or AST < 3 × ULN. No specific dose recommendation can be made for patients with ALT or AST ≥ 3 × ULN or liver injury Common Terminology Criteria for Adverse Events Grade ≥ 3 due to lack of clinical data.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? If No, rationale
Impaired renal function: • TD β-thalassaemia: CrCl < 60 mL/min. • TD β-thalassaemia: proteinuria ≥ Grade 3. • NTD β-thalassaemia: estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. • MDS: CrCl < 40 mL/min. • MDS: eGFR < 40 mL/min/1.73 m^2	These concomitant conditions could influence the interpretation of the study results. For β-thalassaemia studies, these exclusion criteria have been implemented to exclude patients at risk of developing new or worsening kidney disease/ abnormalities.	• Not considered to be missing information. • Luspatercept is not expected to be excreted into urine due to its large molecular mass that is above the glomerular filtration size exclusion threshold. Population PK analysis for luspatercept included patients with normal renal function, mild renal impairment, or moderate renal impairment. • No clinically significant difference in mean steady state Cmax and AUC was found across renal function groups. PK data are not available for patients with severe renal impairment or end stage kidney disease. • Overall, the safety profile of luspatercept does not suggest a need for its limitation in patients with renal impairment.
Pulmonary function (β-thalassaemia): clinically significant pulmonary fibrosis or pulmonary hypertension Grade ≥ 3 (Grade 3 pulmonary fibrosis defined as severe hypoxaemia, evidence of right-sided heart failure, and radiographic pulmonary fibrosis > 50% to 75%).	These concomitant conditions could influence the interpretation of the study results.	• Not considered to be missing information. • In β-thalassaemia studies, the PK of luspatercept has not been evaluated in patients with clinically significant pulmonary fibrosis or pulmonary hypertension Grade ≥ 3. • Overall, the safety profile of luspatercept does not suggest a need for its limitation in patients with impaired pulmonary function.
Thrombocytosis (β-thalassaemia): platelet count > 1000 × 10^9/L.	These concomitant conditions could influence the interpretation of the study results.	• Not considered to be missing information. • In β-thalassaemia studies, patients with platelets > 1000 × 10^9/L have been excluded to decrease the risk of patients exposed to risk of TEEs during treatment. In the TD β-thalassaemia data pool, 14.6% of luspatercept-treated patients and 9.2% of placebo-treated patients had platelet counts ≥ 1000 × 10^9 cells/L that occurred during treatment. • None of the patients with platelet count ≥ 1000 × 10^9 cells/L had a concurrent TEE. • In Study ACE-536-B-THAL-002 (NTD β-thalassaemia patients), 5 patients in each treatment group (16.7% and 19.2% of patients in the luspatercept and placebo treatment groups, respectively) had postbaseline values ≥ 1000 × 10^9/L. • Overall, the safety profile of luspatercept does not suggest a need for its limitation in β-thalassaemia patients with thrombocytosis. However, TEE is considered an important identified risk in the TD

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? If No, rationale
		and NTD β-thalassaemia population with splenectomy. Thrombocytosis is often a complication of splenectomy and it is an added risk factor for TEEs and should be evaluated in this context.
Chronic steroid use	Chronic steroid use can further compromise the immune system, putting the patient at risk of infections. Such concomitant medications could influence the interpretation of the study data.	• Not considered to be missing information. • In β-thalassaemia studies, chronic systemic glucocorticoids ≤ 12 weeks prior to randomisation (physiologic replacement therapy for adrenal insufficiency is allowed) has been implemented to clarify the adrenal insufficiency exclusion criteria, as per the original protocol. • These patients may benefit from treatment with luspatercept and so should not be excluded from treatment with luspatercept. • As luspatercept is a biologic, it is unlikely that it would interact with other medicinal products.
Pregnant or lactating females	Pregnant and lactating females are excluded to avoid potential harm to the unborn foetus or breast-feeding new-born.	• Not considered to be missing information. • Luspatercept is contraindicated during pregnancy. Women of childbearing potential have to use effective contraception during treatment with luspatercept and for at least 3 months after the last dose. Prior to starting treatment with luspatercept, a pregnancy test has to be performed for WCBP. Treatment with luspatercept should not be started if the woman is pregnant. If a patient becomes pregnant, luspatercept should be discontinued. • Because of the unknown adverse effects of luspatercept in new-borns/infants, a decision must be made whether to discontinue breast-feeding during therapy with luspatercept and for 3 months after the last dose or to discontinue luspatercept therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

2.4.2 Limitations of Adverse Drug Reaction Detection in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

To ensure patient safety, specific populations of patients were excluded from the pivotal and supportive studies. Thus, experience in these populations is limited (Table 2.4.3-1).

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Pregnant and lactating women were excluded from the study population and throughout the development programme. Women of childbearing potential were required to use protocol-approved, effective means of contraception 5 weeks prior to and for the duration of their participation in luspatercept trials and for at least 84 days thereafter. Similarly, male study patients who engaged in sexual activity from which conception was possible were also required to use condoms for the duration of their participation in luspatercept trials and for at least 84 days thereafter. There are no adequate and well controlled studies of luspatercept in pregnant women. As of the data lock points of 08-May-2018 for Study ACE-536-MDS-001, 31-Mar-2023 for Study ACE-536-MDS-002, 11-May-2018 for Study ACE-536-B-THAL-001, and 14-Sep-2020 for ACE-536-B-THAL-002, there have been no reports of pregnancy in females treated with luspatercept.
Lactating women	It is unknown whether luspatercept or its metabolites are excreted in human milk. There have been no studies conducted in humans evaluating the effects of luspatercept on the reproductive capacity or foetal outcomes. There have been no reports of patients breast-feeding whilst on treatment with luspatercept.
Paediatric population	There is no relevant use of luspatercept in the paediatric population for the indication of MDS or in paediatric patients less than 6 years of age in β-thalassaemia. The safety and efficacy of luspatercept in paediatric patients aged from 6 years to less than 18 years have not been established in β-thalassaemia. There is an agreed PIP (EMEA-001521-PIP-01-13) for luspatercept in β-thalassaemia patients from 6 years to less than 18 years of age. The currently agreed PIP consists of the following 2 clinical studies in β-thalassaemia: • Study to evaluate safety and PK of luspatercept in paediatric patients from 6 years to less than 18 years of age with TD and NTD β-thalassaemia (on going) As of 24-Jun-2022, 8 adolescent subjects < 18 years have been exposed. • Double-blind, randomised, placebo-controlled trial to evaluate safety and efficacy of luspatercept in paediatric patients from 6 years to less than 12 years of age with TD and NTD β-thalassaemia. The same PIP EMEA-001521-PIP-01-013 includes a full product-specific waiver for pediatric development in the treatment of MDS.

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Elderly population	In Study ACE-536-MDS-001, 124 (81.0%) patients exposed to luspatercept were ≥ 65 years of age. In Study ACE-536-MDS-002, 68 (37.4%) subjects exposed to luspatercept were 65 to 75 years of age, and 87 (47.8%) were ≥ 75 years of age. Population PK analysis for luspatercept included patients with ages ranging from 18 to 95 years old, with a median age of 72 years for patients with MDS and of 33 years for patients with β-thalassaemia. No clinically significant difference in AUC or clearance was found across age groups in MDS patients (< 65, 65 to 74, and ≥ 75 years) or in β-thalassaemia patients (18 to 71 years). There was no notable effect of age on the overall incidence of patients who reported TEAEs. The incidence of serious TEAEs and TEAEs leading to drug withdrawal was higher in luspatercept- and placebo-treated patients ≥ 65 years of age compared with those < 65 years of age, but the difference between age groups was more pronounced in active-treated patients than placebo patients. The majority of most frequently reported serious AEs (SAEs) were age- and/or disease-related. Patient age had no clinically significant effect on luspatercept exposure or clearance. No starting dose adjustment is required for elderly patients.
Patients with relevant comorbidities:	
Patients with renal impairment	Population PK analysis for luspatercept included patients with normal renal function (eGFR ≥ 90 mL/min; n = 463), mild renal impairment (eGFR 60 to 89 mL/min; n = 273), moderate renal impairment (eGFR 30 to 59 mL/min; n = 91), or severe renal impairment (eGFR < 30 mL/min; n = 1)[70] as defined by the Modification of Diet in Renal Disease (MDRD) formula. No clinically significant difference in mean steady state Cmax and AUC was found across renal function groups. PK data are not available for patients with end stage kidney disease.
Patients with hepatic impairment	Population PK analysis for luspatercept included patients with normal hepatic function (bilirubin, ALT, and AST ≤ ULN; n = 361), mild hepatic impairment (bilirubin > 1 to 1.5 × ULN, or ALT or AST > ULN; n = 213), moderate hepatic impairment (bilirubin > 1.5 to 3 × ULN, any ALT or AST; n = 187), or severe hepatic impairment (bilirubin > 3 × ULN, any ALT or AST; n = 74) as defined by the NCI-ODWG criteria of hepatic dysfunction.[70] Effects of hepatic function categories, elevated liver enzymes (ALT or AST, up to 3 × ULN) and elevated total bilirubin (4 to 246 µmol/L) on luspatercept clearance were not observed. No clinically significant difference in mean steady state C_{max} and AUC was found across hepatic function groups. Pharmacokinetic data are insufficient for patients with liver enzymes (ALT or AST) ≥ 3 × ULN.
Patients with cardiovascular impairment	No formal studies have been conducted. In Studies ACE-536-MDS-001, ACE-536-MDS-002, ACE-536-B-THAL-001, and ACE-536-B-THAL-002, 59 (38.6%), 73 (40.1%), 42 (18.8%), and 15 (15.6%) luspatercept-treated patients, respectively, had a medical history within the system organ class of cardiac disorders.
Immunocompromised patients	No formal studies have been conducted. No luspatercept-treated patients in Studies ACE536-MDS-001, ACE-536-MDS-002, and ACE-536-B-THAL-001 had a medical history preferred term (PT) of immunosuppression. A total of 2 (1.3%) luspatercept-treated patients in Study ACE-536-MDS-001 and 4 (2.2%) luspatercept-

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	treated subjects in Study ACE-536-MDS-002 were receiving concomitant immunosuppressants.
Patients with a disease severity different from inclusion criteria in clinical trials	No formal studies have been conducted.
Population with relevant different ethnic origin	In the MDS Data Pool, 82.3% of luspatercept-treated patients were White and 0.4% were Black or African-American. In the TD β-thalassaemia Data Pool, 63.8% of luspatercept-treated patients were White, 28.6% were Asian, and 0.7% were Black or African-American. In Study ACE-536-MDS-001, 107 (69.9%) patients exposed to luspatercept were White, 1 (0.7%) patient each were Black or African American and "Other" race, and data were not collected or reported for 44 (28.8%) patients. In Study ACE-536-MDS-002, 146 (80.2%) subjects exposed to luspatercept were White, 19 (10.4%) were Asian, and 2 (1.1%) were Black or African American; data were not collected or unknown for 15 (8.2%) subjects. In Study ACE-536-B-THAL-001, 121 (54.3%) patients exposed to luspatercept were White, 81 (36.3%) patients were Asian, 15 (6.7%) patients were of "Other" race, 1 (0.4%) patient was Black or African American, and data were not collected or reported for 5 (2.2%) patients. Race (Asian versus White) had no clinically significant effect on luspatercept AUC or clearance. In Study ACE-536-B-THAL-002, 59 (61.5%) patients exposed to luspatercept were White, 31 (32.3%) patients were Asian, and 6 (6.3%) patients were of "Other" race.
Subpopulations carrying relevant genetic polymorphisms	In Study ACE-536-B-THAL-001, determination of β-thalassaemia genotype grouping showed that 68/224 (30.4%) luspatercept-treated patients were β0/β0, which is indicative of a greater severity of disease; 155/224 (69.2%) luspatercept-treated patients were non-β0/β0 and 1/224 (0.4%) luspatercept-treated patient had missing data. There was no clinically significant effect on luspatercept clearance in β0/β0 versus non-β0/β0 patients.
Other relevant comorbidity	In the MDS and β-thalassaemia pivotal registration studies, a wide range of patients were enrolled, and the reported medical histories of patients were consistent with the disease population and known comorbidities, and were also generally comparable between treatment groups. The safety profile of luspatercept did not change when luspatercept was given alone or in combination with medications used for a wide range of comorbid conditions.

2.5 Postauthorisation Experience

2.5.1 Postauthorisation Exposure

Overall, the estimated cumulative commercial exposure to luspatercept as of 24-Jun-2023 is approximately 27,159 patients. The estimated commercial exposure to luspatercept for the interval of this report (25-Dec-2022 to 24-Jun-2023) is approximately 18,871 patients.[71]

2.5.1.1 Method Used to Calculate Exposure

The methodology for estimating commercial patient exposure utilizes up to 2 data sources[71]:

1. The Company's Sales/Shipment Data – this data consists of all shipments of the Company product to all applicable countries and includes commercial and free-of-charge units for both branded and generic product (as applicable). The data are used to determine the units (eg, milligrams) of a product that was sold to a geography to estimate the number of patients who would have been exposed to that product, based on expected dosing in the geography. Shipment data are used to estimate the active patients for a period of time by dividing the total units sold by the average units per patient (note that average units per patient is derived from epidemiologic or market research).

2. Claims Data – this data consists of 2 distinct sources of electronic health care claims data in the USA: Optum Clinformatics Datamart and Symphony Claims for Hem/Onc. Claims data consisting of distinct patient IDs and prescription fill rates for each product are used to understand usage patterns. For newly approved products, until sufficient claims data are available, patterns are based on discontinuation rates derived from clinical trial experience.

2.5.1.2 Exposure

Estimated cumulative exposure by region is provided in Table 2.5.1.2-1.[71]

Table 2.5.1.2-1: Summary of Worldwide Commercial Exposure

Region	Cumulative (08-Nov-2019 to 24-Jun-2023)
[redacted]	[redacted]
EEA[a]	7,297
[redacted]	[redacted]
ROW[c]	2,462
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TOTAL	**27,159**

EEA, European Economic Area; ROW, Rest of World; [redacted]

[a] Includes the 27 EU countries plus Iceland, Liechtenstein, and Norway.

[b] Includes estimated exposure from special access programs.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

No potential for drug dependence, misuse or abuse has been noted for luspatercept in any of the clinical studies. However, there is the potential that luspatercept could be illicitly used as a doping agent to artificially increase the amount of RBC mass in the body which allows the body to transport more oxygen to muscles and therefore increase stamina in an attempt to improve athletic performance. Luspatercept is subject to restricted medical prescription and administration.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns in the initial RMP submission (Version 1.0) are summarised in Table 2.7.1-1.

Table 2.7.1-1: Summary of Safety Concerns in the Initial RMP Submission

Important identified risk:	TEEs (only in the β-thalassaemia population with splenectomy)
Important potential risks:	Haematologic malignancies (including AML)
	Off-label use in paediatric patients (developmental toxicity of luspatercept)
	Use during pregnancy and lactation
Missing information:	Long-term safety

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Identified and potential risks not considered important and the reasons for not including them in the list of safety concerns in the RMP are presented in Table 2.7.1.1-1.

Table 2.7.1.1-1: Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Risk	Justification
Risks with Minimal Clinical Impact on Patients (in Relation to the Severity of the Indication Treated) • Identified Risk: Hypersensitivity type reactions and immunogenicity	Luspatercept is contraindicated in patients with hypersensitivity to luspatercept or to any of the excipients. Hypersensitivity type reactions (including eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, and drug eruption) and injection site reactions (including injection site erythema, injection site pruritus, injection site swelling, and injection site rash) are commonly reported ADRs in patients treated with luspatercept. Immunogenicity type reaction AEs were reported in 16.3% and 10.5% of luspatercept- and placebo-treated MDS patients, respectively, in Study ACE-536-MDS-001, and in 23.3% and 19.3% of β-thalassaemia patients, respectively, in Study ACE-536-B-THAL-001. No anaphylactic reactions have been reported in the luspatercept clinical programme. In clinical studies, all events were Grade 1 or 2. One (0.4%) β-thalassaemia patient in Study ACE-536-B-THAL-001 discontinued luspatercept due to a hypersensitivity event. In ACE-536-MDS-002, immunogenicity hypersensitivity-type reactions (all grades) were reported in a higher proportion of MDS patients in the luspatercept arm (3.8%) than the epoetin alfa arm (1.7%). No Grade 3/4 TEAEs of immunogenicity hypersensitivity-type reactions were reported in the luspatercept arm. In clinical studies in MDS, an analysis of 260 MDS patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 23 (8.8%) MDS patients tested positive for treatment-emergent anti-luspatercept antibodies, including 9 (3.5%) MDS patients who had neutralising antibodies against luspatercept. In clinical studies in β-thalassaemia, an analysis of 284 β-thalassaemia patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 4 (1.4%) β-thalassaemia patients tested positive for treatment-emergent anti-luspatercept antibodies, including 2 (0.7%) β-thalassaemia patients who had neutralising antibodies against luspatercept. Luspatercept serum concentration tended to decrease in the presence of neutralising antibodies. There were no severe systemic hypersensitivity reactions reported for patients with anti-luspatercept antibodies. There was no association between hypersensitivity type reactions or injection site reactions and presence of ADA.

Table 2.7.1.1-1: Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Risk	Justification
Risks with Minimal Clinical Impact on Patients (in Relation to the Severity of the Indication Treated) • Identified Risk: Hypertension	Patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of up to 5 mmHg from baseline. Hypertension (including essential hypertension, hypertension, and hypertensive crisis) is commonly reported in patients treated with luspatercept. Hypertension was reported in 8.5% and 9.2% of luspatercept- and placebo-treated MDS patients, respectively, in Study ACE-536-MDS-001, and in 8.1% and 3.7% of luspatercept- and placebo-treated β-thalassaemia patients, respectively, in Study ACE-536-B-THAL-001. In ACE-536-MDS-002, the proportion of MDS patients with TEAEs of hypertension was higher in luspatercept-treated patients (15.9%; EAIR: 14.5 per 100 PY) compared with epoetin alfa-treated patients (9.5%; EAIR: 10.4 per 100 PY). Grade 3 TEAEs of hypertension were reported in 11.0% of MDS patients in the luspatercept arm. 2 (1.1%) serious events were reported in the luspatercept arm. Grade 3 TEAEs were reported in 5.0% of subjects in the epoetin alfa arm. No serious events were reported in the epoetin alfa arm. No Grade 4 TEAEs of hypertension were reported in either arm. In ACE-536-MDS-001, Grade 3 events were reported for 5 patients (3.3%) treated with luspatercept and in 3 patients (3.9%) receiving placebo. In β-thalassaemia patients, Grade 3 events were reported for 4 patients (1.8%) treated with luspatercept (0% placebo). There were no Grade 4 events, no serious events, and no hypertension events leading to treatment discontinuation. Blood pressure should be monitored prior to each luspatercept administration. In case of new-onset hypertension or exacerbations of pre-existing hypertension, patients should be treated for hypertension as per current clinical guidelines. Hypertension is easily treatable and does not impact the risk-benefit profile of luspatercept. Events of hypertension will be monitored as per local standard of care and routine pharmacovigilance activities including signal detection activities apply.
Known Risks that Require No Further Characterisation and are Followed up via Routine Pharmacovigilance Namely through Signal Detection and Adverse Reaction Reporting, and for which the Risk Minimisation Messages in the Product Information are Adhered by Prescribers (eg, Actions Being Part of Standard Clinical Practice in each EU Member State where the Product is Authorised) • Identified Risk: Syncope	Syncope has been reported with luspatercept. In Study ACE-536-MDS-001, syncope/presyncope was reported in 6.5% of patients treated with luspatercept and 1.3% with placebo. A total of 5 luspatercept-treated patients and 1 placebo-treated patient in Study ACE-536-MDS-001 experienced Grade 3 syncope. Three events were reported as SAEs; 1 was associated with an orthostatic dysregulation, 1 described as a vasovagal episode and 1 was associated with intercurrent heart failure. All events resolved and did not reoccur despite treatment continuation. In Study ACE-536-MDS-002, syncope was reported in 4.4% of luspatercept-treated patients and 2.8% of epoetin alfa-treated patients. A total of 7 luspatercept-treated patients and 1 epoetin alfa-treated patient experienced Grade 3 syncope. No events were reported as SAEs. All events resolved. Presyncope was reported in 1.6% of luspatercept-treated patients and 1.7% of epoetin alfa-treated patients. One luspatercept-treated patient and no epoetin alfa-treated patients experienced Grade 3 presyncope. The event was not reported as an SAE and resolved. In Study ACE-536-B-THAL-001, syncope/presyncope was reported in 3.6% of patients treated with luspatercept and 0.9% with placebo. Four patients experienced Grade 3 syncope, none of which was considered serious, all transient and recovering in the same day and not reoccurring despite treatment continuation at the same dose level.

Table 2.7.1.1-1: Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Risk	Justification
Known Risks that do Not Impact the Risk-benefit Profile	Bone pain is a very commonly experienced ADR on treatment with luspatercept, especially in β-thalassaemia patients. Bone pain may occur more frequently at the start of treatment (during the first 4 cycles; 12 weeks).
• Identified Risk: Bone pain	Bone pain was reported in 19.7% and 8.3% of luspatercept- and placebo-treated β-thalassaemia patients, respectively, in Study ACE-536-B-THAL-001, and in 2.6% and 3.9% of MDS patients, respectively, in Study ACE-536-MDS-001. In β-thalassaemia patients treated with luspatercept, bone pain was most common in the first 3 months (16.6%) compared to Months 4 to 6 (3.7%). Most events (41/44 events) were Grade 1 or 2; 3 events were Grade 3. One event led to treatment discontinuation. In ACE-536-MDS-002, bone pain was reported in 2.2% and 2.8% of luspatercept- and epoetin alfa-treated MDS patients, respectively. All events were Grade 1 or Grade 2. No events were Grade 3.
• Potential Risk: Kidney Injury	In the pivotal BMS-sponsored phase 3 studies (ACE-536-MDS-001 and ACE-536-B-THAL-001), kidney injury has been observed in 9.8% and 3.6% of luspatercept-treated MDS and β-thalassaemia patients, respectively, and 5.3% and 2.8% of placebo-treated patients, respectively. There were no SAEs of kidney injury in luspatercept-treated patients with β-thalassaemia; 2.0% of luspatercept-treated MDS patients experienced an SAE of kidney injury. Administration of luspatercept was not associated with prolonged or irreversible worsening of clinically important indicators of kidney injury, including CrCl and ACR measurements, over the course of treatment. No mean changes of clinical concern were observed in CrCl during Study ACE-536-B-THAL-001 and there was no clinically important difference between luspatercept- and placebo-treated patients or change in mean ACR over time in the β-thalassaemia population. In ACE-MDS-002, kidney injury was reported in 8.8% and 6.7% of luspatercept- and epoetin alfa-treated MDS patients, respectively. Of the subjects in the luspatercept arm with TEAEs of kidney injury no SAEs or Grade 4 AEs of kidney injury type events were reported. 3 luspatercept-treated subjects had 3 Grade 3 kidney type events (renal impairment, acute kidney injury, and GFR decrease). Of the subjects in the epoetin alfa arm with TEAEs of kidney injury, a Grade 4 renal event of renal failure and 2 serious events of kidney injury (acute kidney injury and tubulointerstitial nephritis) were reported. In summary, no adverse effect of luspatercept on renal function was observed in clinical studies, and hence there is no impact on the risk-benefit profile. Patients with renal impairment at baseline should be closely monitored for renal function as per standard of care. Events of kidney injury will be monitored as per local standard of care through routine adverse reaction reporting, including during the BMS-sponsored long-term follow-up Study ACE-536-LTFU-001.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Important Identified Risks

Important Identified Risks	Risk-benefit Impact
TEEs (only in the β-thalassaemia population with splenectomy)	TEEs are common complications of thalassaemia especially in splenectomised patients. In Study ACE-536-B-THAL-001, embolic and thrombotic events and thrombophlebitis were observed in a greater proportion of luspatercept-treated patients with β-thalassaemia (4.0%) compared to placebo-treated patients with β-thalassaemia (0.9%). Device occlusion does not clinically qualify as a TEE. Excluding the device occlusion, there were 8 patients (3.6%) in the luspatercept treatment group who reported TEE events. Six (2.7%) luspatercept-treated patients experienced thromboembolic SAEs, 2 of whom experienced Grade 3 or 4 events. TEEs were restricted to splenectomised patients with multiple risk factors for the reported embolic/thrombotic event including thrombocytosis, relevant cardiovascular history (heart failure, cardiac siderosis, hypertension, coronary artery disease, atrial fibrillation, tricuspid insufficiency, mitral valve stenosis, pulmonary hypertension) for developing cerebrovascular accident or transient ischaemic attack, thromboembolism risk factors (smoking, diabetes, obesity, glucose-6-phosphate dehydrogenase deficiency, sedentary lifestyle), and hormonal replacement therapy for the development of DVT, pulmonary embolism, and other thrombotic event. No patient had concurrent hypertension at the time of the TEE. The risk of TEEs is higher in splenectomised patients with β-thalassaemia. Further data are being collected during the BMS-sponsored long-term follow-up Study ACE-536-LTFU-001.

Table 2.7.1.2-2: Important Potential Risks

Important Potential Risks	Risk-benefit Impact
Haematologic malignancies (including AML)	Malignancies in general may result in significant morbidity and mortality, depending on the type, and impact on the patient's activities of daily living. Haematologic malignancies (PT of progression to AML only) were observed in 2.0% of luspatercept-treated MDS patients and 1.3% of placebo-treated patients in Study ACE-536-MDS-001 (exposure-adjusted incidence rate [EAIR] was 2.2 per 100,000 person-years for both groups). All events were serious and of Grade 3 or 4 severity. There was no observed incremental risk associated with luspatercept administration for haematologic malignancies. In Study ACE-536-MDS-002, haematologic malignancies (PTs of AML, transformation to AML, BCL, and CMML) were observed in 2.2% of luspatercept-treated MDS patients; the follow-up adjusted incidence rate was 1.7 per 100,000 person-years. Haematologic malignancies (PTs of transformation to AML, and large granular lymphocytosis) was observed in 1.1% of epoetin alfa-treated patients, the follow-up adjusted incidence rate was 1.1 per 100,000 person-years. There was no observed incremental risk associated with luspatercept administration for haematologic malignancies. No haematologic malignancies have been observed with luspatercept in the β-thalassaemia population as of the data lock point of this submission. One event of erythroleukaemia (AML M6) was reported in Study ACE-536-B-THAL-001 in Nov 2018. Due to the difficulty in diagnosing AML M6 against a background of β-thalassaemia, an independent expert haematopathologist was engaged to review extensive morphologic and genetic analyses in this case. The independent expert haematopathologist concluded that a diagnosis of AML M6 in

Table 2.7.1.2-2: Important Potential Risks

Important Potential Risks	Risk-benefit Impact
	this patient was very unlikely. The independent data monitoring committee considered the case to be consistent with β-thalassaemia major complicated by splenomegaly, neutropenia, and sepsis, possibly triggered by deferiprone therapy. The patient subsequently died. Although there was no imbalance in malignancies in the MDS clinical programme and no malignancies reported in the β-thalassaemia population up until the data cut-off, the data set is limited and therefore haematologic malignancy (including AML) is considered an important potential risk. Further data will be collected during the BMS-sponsored long-term follow-up Study ACE-536-LTFU-001.
Off-label use in paediatric patients (developmental toxicity of luspatercept)	The target population is adults as reflected in the luspatercept SmPC. Studies in animals have shown developmental toxicity following luspatercept administration; however, the relevance of the juvenile nonclinical findings in rats to development in paediatric patients is unknown. There is no relevant use of luspatercept in the paediatric population for the indication of MDS or in paediatric patients less than 6 months of age in β-thalassaemia. The safety and efficacy of luspatercept in paediatric patients aged from 6 months to less than 18 years have not yet been established in β-thalassaemia. There are currently no available data from the use of luspatercept in paediatric patients.
Use during pregnancy and lactation	Studies in animals have shown reproductive toxicity following luspatercept administration. Luspatercept was detected in the milk of lactating rats, and based on findings in animals, luspatercept may compromise female fertility. There are no data from the use of luspatercept in pregnant women, it is unknown whether luspatercept or its metabolites are excreted in human milk, and the effect of luspatercept on fertility in humans is unknown. Luspatercept is contraindicated during pregnancy. Women of childbearing potential have to use effective contraception during treatment with luspatercept and for at least 3 months after the last dose. Prior to starting treatment with luspatercept, a pregnancy test has to be performed for WCBP. Treatment with luspatercept should not be started if the woman is pregnant. If a patient becomes pregnant, luspatercept should be discontinued.

Table 2.7.1.2-3: Missing Information

Missing Information	Risk-benefit Impact
Long-term safety	Long-term follow-up in the clinical development programme is limited. Further data are being collected during the BMS-sponsored long-term follow-up Study ACE-536-LTFU-001.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns or reclassification with the submission of the updated RMP.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The RMP search criteria have been defined for each BMS-sponsored study based on the Medical Dictionary of Regulatory Activities (MedDRA) version as noted in Table 2.7.3-1. The important identified and potential risks of luspatercept are summarised in the following tables (Table 2.7.3.1-1 to Table 2.7.3.2-4) for the study cut-off dates listed in Section 2.3. Missing information for luspatercept is presented in Table 2.7.3.3-1.

Table 2.7.3-1: RMP Search Criteria

Study	MedDRA Version Used to Define RMP Search Criteria	MedDRA Version Used to Code AEs in Clinical Database	Data Lock Point
ACE-536-MDS-001 (MEDALIST)	Version 20.0	Version 20.0	08-May-2018
ACE-536-MDS-002 (COMMANDS)	Version 25.0	Version 25.0	31-Mar-2023
ACE-536-B-THAL-001 (BELIEVE)	Version 20.0	Version 20.0	11-May-2018
ACE-536-B-THAL-002 (BEYOND)	Version 23.0	Version 23.0	14-Sep-2020
ACE-536-LTFU-001[a]	Version 23.0	Version 23.0	13-Dec-2021

[a] For the safety concern of EMH (In the TD β-thalassaemia population) only.

2.7.3.1 Presentation of Important Identified Risks

Table 2.7.3.1-1: Important Identified Risk: Thromboembolic Events (Only in the TD and non TD β thalassaemia Population with Splenectomy)

Thromboembolic Events (Only in the TD and NTD β-thalassaemia Population with Splenectomy)
Potential Mechanisms No mechanism by which luspatercept may cause TEEs has been identified.
Evidence Source(s) and Strength of Evidence There is a known risk of TEEs in patients with splenectomy (Natesirinilkul, 2016).[51] In Study ACE-536-B-THAL-001, embolic and thrombotic events and thrombophlebitis were observed in a greater proportion of luspatercept-treated patients (4.0%) compared to placebo-treated patients (0.9%) with TD β-thalassaemia. Device occlusion does not clinically qualify as a TEE. Excluding the device occlusion, there were 8 TD β-thalassaemia patients (3.6%) in the luspatercept treatment group who reported TEE events. All cases of TEEs were consistent with the literature and reported in patients who have had a splenectomy and who had at least 1 other risk factor for developing a TEE (including history of thrombocytosis or hormone replacement therapy). The occurrence of TEEs was not correlated with elevated haemoglobin levels. No patient had concurrent hypertension at the time of the TEE.
Characterisation of the Risk **Frequency with 95% CI**

Table 2.7.3.1-1: Important Identified Risk: Thromboembolic Events (Only in the TD and non TD β thalassaemia Population with Splenectomy)

Thromboembolic Events (Only in the TD and NTD β-thalassaemia Population with Splenectomy)

TD β-thalassaemia

Embolic and Thrombotic Events and Thrombophlebitis	Luspatercept (N = 223)	Control (N = 109)
Patients with ≥ 1 AE, n (%)	9 (4.0)[a]	1 (0.9)
Patients with ≥ 1 SAE, n (%)	6 (2.7)	0
Incidence (%) of Patients with ≥ 1 AE (95% CI)	4.0 (1.9, 7.5)	0.9 (0.0, 5.0)
Exposure-adjusted Incidence Rate/100 Person-Years	3.5	0.8

a Device occlusion does not clinically qualify as a TEE. Excluding the device occlusion, there were 8 patients (3.6%) in the luspatercept treatment group who reported TEE events.

In Study ACE-536-B-THAL-001, the proportion of patients experiencing at least 1 TEE was greater among luspatercept-treated patients compared to patients receiving placebo (relative risk = 4.4 [95% CI = 0.5 to 42.5]). Reported PTs in luspatercept-treated patients were DVT (3 patients), cerebrovascular accident and thrombophlebitis superficial (2 patients each), and device occlusion (not clinically consistent with TEEs), ischaemic stroke, portal vein thrombosis and pulmonary embolism (1 patient each).

NTD β-thalassaemia

In Study ACE-536-B-THAL-002, no TEE events have been reported in either treatment group.

Seriousness/Outcomes

TD β-thalassaemia

In Study ACE-536-B-THAL-001, serious TEEs were experienced by 6 (2.7%) luspatercept-treated patients; PTs reported in the luspatercept group included cerebrovascular accident and DVT (2 patients each), and portal vein thrombosis, pulmonary embolism, and thrombophlebitis superficial (1 patient each).

The outcomes of these SAEs are summarised below.

Outcome	Number (%) of Patients
Death	0
Ongoing at Death	0
Not Recovered/Not Resolved	2 (0.9)
Recovered/Resolved with Sequelae	1 (0.4)
Recovered/Resolved	3 (1.3)
Unknown/Not Provided	0
Total	6 (2.7)

Severity and Nature of Risk

TD β-thalassaemia

Embolic and Thrombotic Events and Thrombophlebitis	Luspatercept (N = 223)	Control (N = 109)
All AEs, n (%)	9 (4.0)[a]	1 (0.9)
Grade 3 or 4, n (%)	2 (0.9)	0
AEs Leading to Discontinuation, n (%)	4 (1.8)	0
AEs Leading to Dose Reduction, n (%)	0	0

Table 2.7.3.1-1: Important Identified Risk: Thromboembolic Events (Only in the TD and non TD β thalassaemia Population with Splenectomy)

Thromboembolic Events (Only in the TD and NTD β-thalassaemia Population with Splenectomy)		
AEs Leading to Dose Interruption, n (%)	2 (0.9)	0

a Device occlusion does not clinically qualify as a TEE. Excluding the device occlusion (nonserious Grade 1 event that did not lead to discontinuation or dose modification), there were 8 patients (3.6%) in the luspatercept treatment group who reported TEE events.

In Study ACE-536-B-THAL-001, Grade 3 or Grade 4 events were experienced in 2 luspatercept-treated patients (PTs: cerebrovascular accident and pulmonary embolism). A total of 4 (1.8%) luspatercept-treated patients discontinued study treatment due to embolic and thrombotic events and thrombophlebitis (DVT [2 patients] and portal vein thrombosis, pulmonary embolism, and thrombophlebitis superficial [1 patient each]).

Risk Groups and Risk Factors

TEEs are common complications of thalassaemia, especially thalassaemia intermedia. The increased risk of TEEs is likely due to abnormalities in platelet, RBC, endothelial cell, and thrombin activation which all contribute to hypercoagulable state (Thiersch, 2017;[72] Taher, 2010a;[73] Taher, 2010b[74]).

In addition to these haematological abnormalities, splenectomy has also been shown to be a major risk factor contributing to hypercoagulability among patients with thalassaemia (Natesirinilkul, 2016).[51]

Additional risk factors for TEEs in β-thalassaemia include age, iron overload, thrombocytosis, hormone replacement therapy, cardiac and endocrine disease, all common in this patient population. Furthermore, patients may also be at risk of TEEs due to other conventional risk factors similar to the nonthalassaemia population (Taher, 2010a;[73] Taher, 2010b[74]).

Preventability

Due to the risk of TEEs in splenectomised patients with β-thalassaemia, it is prudent to inform treating physicians about this identified risk, so they can work with patients to address modifiable risk factors. The potential benefit of treatment with luspatercept should be weighed against the identified risk of TEEs in β-thalassaemia patients with a splenectomy and other risk factors for developing a TEE. Thromboprophylaxis according to current clinical guidelines should be considered in patients with β-thalassaemia at higher risk.

Impact on the Risk-benefit Balance of the Product

TEEs are common complications of thalassaemia. There is a known risk of TEEs in patients with splenectomy (Natesirinilkul, 2016).[51]

Public Health Impact

The annual incidence of venous TEEs is more than one per thousand in the general population (Cushman, 2007).[75]

In one study, 22.5% of splenectomised patients developed TEEs compared to 3.5% in nonsplenectomised patients, and the relative risk of developing a TEE was 6.59 (95% CI, 3.09 to 14.05) compared to the nonsplenectomised patients. The rate (prevalence) of TEEs in TD β-thalassaemia patients varies between 5.2% and 6.3% (Moratelli, 1998;[76] Taher, 2010c[77]).

MedDRA Terms

Sub-standardised MedDRA queries (SMQs) for embolic and thrombotic events and thrombophlebitis.

Table 2.7.3.1-2: Important Identified Risk: EMH Masses (In the TD and NTD β thalassaemia Population)

EMH Masses (In the TD and NTD β-thalassaemia Population)

Potential Mechanisms

The mechanism of action of the potential connection between luspatercept (either direct or indirect) and EMH is not known, but could be associated with the increased production of endogenous erythropoietin. As a result of ineffective red blood cell production by the bone marrow (ineffective erythropoiesis) in ß-thalassaemia, a forced expansion of the hematopoietic tissue outside the marrow medulla appears and leads to hematopoietic compensatory involvement, mostly in the form of masses in other regions in the body; this phenomenon is termed EMH.

Evidence Source(s) and Strength of Evidence

In TD β–thalassaemia patients, EMH masses were observed in 3.2% (10/315) of patients treated with luspatercept in the pivotal study and in the long-term follow-up study (Study ACE-536-B-THAL-001/ACE-536-LTFU-001). Spinal cord compression symptoms due to EMH masses occurred in 1.9% (6/315) of patients treated with luspatercept.

In NTD β–thalassaemia patients, EMH masses were observed in 6.3% (6/96) of patients treated with luspatercept in the pivotal study. Spinal cord compression due to EMH masses occurred in 1.0% (1/96) of patients treated with luspatercept. During the open-label portion of the study, EMH masses were observed in 2 additional patients for a total of 8/134 (6.0%) of patients.

Characterisation of the Risk

Frequency with 95% CI

MDS

As of the data lock points of 08-May-2018 and 31-Mar-2023 for Studies ACE-536-MDS-001 and ACE-536-MDS-002, respectively, no EMH masses have been observed.

TD β-thalassaemia

As of the data lock point of 11-May-2018 for Study ACE-536-B-THAL-001, no EMH masses have been observed. However, EMH masses were observed in patients from Study ACE-536-B-THAL-001 who transferred into ACE-536-LTFU-001, presented below.

EMH Masses	Luspatercept (N = 315)
Patients with ≥ 1 AE, n (%)	10 (3.2)
Patients with ≥ 1 SAE, n (%)	4 (1.3)
Incidence (%) of Patients with ≥ 1 AE (95% CI)	3.2 (1.5, 5.8)
Exposure-adjusted Incidence Rate/100 Person-Years (95% CI)	1.1 (0.6, 2.0)

Note: ACE-536-LTFU-001 has no control arm.

NTD β-thalassaemia

EMH Masses	Luspatercept (N = 96)	Control (N = 49)
Patients with ≥ 1 AE, n (%)	6 (6.3)	1 (2.0)
Patients with ≥ 1 SAE, n (%)	0[a]	1 (2.0)
Incidence (%) of Patients with ≥ 1 AE (95% CI)	6 (6.3) (2.3, 13.1)	1 (2.0) (0.1, 10.9)
Exposure-adjusted Incidence Rate/100 Person-Years (95% CI)	3.5 (1.6, 7.9)	1.7 (0.2, 11.8)

[a] Although no SAE was reported based on the MEDRA PT used for EMH masses, SAE of spinal cord compression due to EMH masses was reported as a separate PT.

Table 2.7.3.1-2: Important Identified Risk: EMH Masses (In the TD and NTD β thalassaemia Population)

EMH Masses (In the TD and NTD β-thalassaemia Population)

In Study ACE-536-B-THAL-002, the proportion of patients experiencing at least 1 event of EMH was higher among luspatercept-treated patients compared to patients receiving placebo (relative risk = 3.1 [95% CI = 0.6 to 14.9]).

Seriousness/Outcomes

TD β-thalassaemia

In Study ACE-536-B-THAL-001/ACE-536-LTFU-001, among the 10 of 315 luspatercept-treated patients experiencing EMH masses, 4 (1.3%) were serious in nature.

The outcomes of these SAEs are summarised below.

Outcome	Number (%) of Patients
Not Recovered/Not Resolved	2 (0.6)
Recovered/Resolved with Sequelae	2 (0.6)
Total	4 (1.3)

Table represents patients from Study ACE-536-B-THAL-001 that transferred into ACE-536-LTFU-001. ACE-536-LTFU-001 has no control arm.

NTD β-thalassaemia

In Study ACE-536-B-THAL-002, no serious events of EMH were experienced by luspatercept-treated patients.

Table 2.7.3.1-2: Important Identified Risk: EMH Masses (In the TD and NTD β thalassaemia Population)

EMH Masses (In the TD and NTD β-thalassaemia Population)

Severity and Nature of Risk

TD β-thalassaemia

EMH Masses	Luspatercept (N = 315)
All AEs, n (%)	10 (3.2)
Grade 3 or 4, n (%)	5 (1.6)
AEs Leading to Discontinuation, n (%)	5 (1.6)
AEs Leading to Dose Reduction, n (%)	2 (0.6)
AEs Leading to Dose Interruption, n (%)	0 (0.0)

Table represents patients from Study ACE-536-B-THAL-001 that transferred into ACE-536-LTFU-001. ACE-536-LTFU-001 has no control arm.

Grade 3 or Grade 4 events were experienced in 5 luspatercept-treated patients. A total of 5 (1.6%) luspatercept-treated patients discontinued study treatment due to EMH masses.

NTD β-thalassaemia

EMH	Luspatercept (N = 96)	Control (N = 49)
All AEs, n (%)	6 (6.3)	1 (2.0)
Grade 3 or 4, n (%)	0	1 (2.0)
AEs Leading to Discontinuation, n (%)	1 (1.0)	0
AEs Leading to Dose Reduction, n (%)	0	0
AEs Leading to Dose Interruption, n (%)	0	1 (2.0)

In Study ACE-536-B-THAL-002, no Grade 3 or Grade 4 EMH events were experienced in luspatercept-treated patients.

Table 2.7.3.1-2: Important Identified Risk: EMH Masses (In the TD and NTD β thalassaemia Population)

EMH Masses (In the TD and NTD β-thalassaemia Population)
Risk Groups and Risk Factors Extramedullary haemopoiesis is among the 3 most common complications, and prevalence of EMH masses has been reported as approximately 20% to 25% (Taher, 2010c;[77] Winichakoon, 2015[78]). Among patients with no previous transfusions, approximately 60.0% have disease-related complications of extramedullary haemopoiesis, whereas among patients with regular transfusions (TD β-thalassaemia), approximately 4.0% have disease-related complications of extramedullary haemopoiesis (Taher, 2010b).[74] Extramedullary haemopoiesis is a complication due to ineffective erythropoiesis or inadequate bone marrow function and is seen to occur in patients with β-thalassaemia and other chronic haematologic disorders. In patients with such disorders, the ineffective erythropoiesis or inadequate bone marrow function can potentially precipitate extra marrow production of blood elements (ie, extramedullary haemopoiesis) (Orphanidou-Vlachou, 2014).[79] Expansion of the erythron in the bone marrow in NTD β-thalassaemia during ineffective erythropoiesis is associated with homing and proliferation of erythroid precursors in the spleen and liver as a physiologic compensatory phenomenon, which leads to hepatosplenomegaly. Ineffective erythropoiesis in NTD β-thalassaemia patients also forces expansion of the hematopoietic tissue in areas other than the liver and spleen, mostly in the form of masses termed extramedullary hematopoietic pseudotumours (Rivella, 2009;[80] Rivella, 2012).[81] Risk factors associated with β-thalassaemia EMH include: males, splenectomy, IVS-I-6 either in homozygosity or compound heterozygosity, higher levels of GDF15 and erythropoietin, and fewer red blood cell transfusions (Ricchi, 2014;[55] Sousos, 2017;[58] Ricchi, 2015[56]). Chronic anaemia has been shown to lead to increased levels of erythropoietin and overstimulation of early stage erythropoiesis. For patients with β-thalassaemia, this may result in EMH, primarily in the spleen (Sleiman, 2018).[82]
Preventability The potential benefit of treatment with luspatercept should be weighed against the potential risk for EMH masses complications in TD and NTD β-thalassaemia patients. Luspatercept is contraindicated in patients requiring treatment to control the growth of EMH masses. Patients with EMH masses may experience worsening of these masses and complications during treatment. Signs and symptoms may vary depending on anatomical location. Patients should be monitored at initiation and during treatment for symptoms and signs or complications resulting from the EMH masses, and be treated according to clinical guidelines. Treatment with luspatercept must be discontinued in case of serious complications due to EMH masses.
Impact on the Risk-benefit Balance of the Product Extramedullary hematopoietic pseudotumours can occur anywhere in the body and can cause great health risks especially when surrounding vital structure like the spinal cord, as they can lead to permanent damage and disability (Haidar, 2010),[47] if not diagnosed and managed acutely. A paraspinal location for the hematopoietic tissue occurs in 11% to 15% of cases with EMH Paraspinal EMH mainly presents as pseudotumours, which may cause a variety of neurological symptoms due to spinal compression. More than 80% of cases may remain asymptomatic and the lesions are discovered incidentally by imaging. The development of neurologic symptoms depends on the chronicity of the disease with neurologic symptoms most frequently being reported during the third and fourth decades of life (Haidar, 2010).[47] Based on the cumulative review of the available safety information across all β-thalassaemia studies, the reported EMH-type events appear to be mainly associated with the patients' pre-existing β-thalassaemia and less with the administration of luspatercept.

Table 2.7.3.1-2: Important Identified Risk: EMH Masses (In the TD and NTD β thalassaemia Population)

EMH Masses (In the TD and NTD β-thalassaemia Population)
MedDRA Terms
PTs: Cutaneous extramedullary haemopoiesis and Extramedullary haemopoiesis.

2.7.3.2 Presentation of Important Potential Risks

Table 2.7.3.2-1: Important Potential Risk: Haematologic Malignancies (Including AML)

Haematologic Malignancies (Including AML)
Potential Mechanisms
No mechanism whereby luspatercept may cause haematological malignancies (including AML) has been identified for patients in the MDS and β-thalassaemia populations.
Evidence Source(s) and Strength of Evidence
In a toxicity study conducted in juvenile rats, 3 of the 44 rats examined in the highest dose group (10 mg/kg) had haematologic malignancies (one incidence each of lymphoma, myeloid leukaemia, and lymphoid leukaemia). In Study ACE-536-MDS-001, haematologic malignancies (PTs of transformation to AML only) were observed in 2.0% of luspatercept-treated MDS patients; the follow-up-adjusted incidence rate was 1.68 (95% CI, 0.54 to 5.22 per 100,000 person-years). In Study ACE-536-MDS-002, haematologic malignancies (PTs of AML, transformation to AML, BCL, and CMML) were observed in 2.2% of luspatercept-treated MDS patients; the follow-up adjusted incidence rate was 1.7 per 100,000 person-years. Haematologic malignancies (PTs of transformation to AML, and large granular lymphocytosis) was observed in 1.1% of epoetin alfa-treated patients; the follow-up adjusted incidence rate was 1.1 per 100,000 person-years. There was no observed incremental risk associated with luspatercept administration for haematologic malignancies. No haematologic malignancies have been observed with luspatercept in the TD and NTD β-thalassaemia population as of the data lock point. One event of erythroleukaemia (AML M6) was reported in Study ACE-536-B-THAL-001 in [redacted] An independent expert haematopathologist concluded that a diagnosis of AML M6 in this patient was very unlikely. The independent data monitoring committee considered the clinical course to be consistent with β-thalassaemia major complicated by splenomegaly, neutropenia, and sepsis, possibly triggered by deferiprone therapy. The patient subsequently died. Available clinical data do not suggest a relationship of transformation/development of higher risk MDS/AML with luspatercept treatment.
Characterisation of the Risk **Frequency with 95% CI**

MDS

Haematologic Malignancies (Including AML)		
Study MDS-001	**Luspatercept (N = 153)**	**Control (N = 76)**
Patients with ≥ 1 SAE, n (%)[a]	3 (2.0)	1 (1.3)
Incidence (%) of Patients with ≥ 1 AE (95% CI)	2.0 (0.4, 5.6)	1.3 (0, 7.1)
Follow-up-adjusted Incidence Rate/100 Person-Years	1.68	1.13
Study ACE-536-MDS-002	**Luspatercept (N = 182)**	**Epoetin Alfa (N = 179)**

Table 2.7.3.2-1: Important Potential Risk: Haematologic Malignancies (Including AML)

Haematologic Malignancies (Including AML)

Patients with ≥ 1 SAE, n (%)[a]	4 (2.2)[b]	2 (1.1)
Incidence (%) of Patients with ≥ 1 AE (95% CI)	2.2 (0.6, 5.5)	1.1 (0.1, 4.0)
Follow-up-adjusted Incidence Rate/100 Person-Years	1.7	1.1

a All reported events of haematologic malignancies were SAEs.

b 1 subject in the luspatercept arm had AML and transformation to AML.

In Study ACE-536-MDS-001, the proportion of patients experiencing at least 1 event of haematologic malignancy (PTs of transformation to AML only) was similar among luspatercept-treated patients compared to patients receiving placebo (relative risk = 1.5 [95% CI = 0.2 to 13.6]). In Study ACE-536-MDS-002, the proportion of patients experiencing at least 1 event of haematologic malignancy (PTs of AML, BCL, large granular lymphocytosis, transformation to AML, and CMML) was similar among luspatercept-treated patients compared to patients receiving epoetin alfa (relative risk = 2.0 [95% CI = 0.2 to 19.2]).

TD β-thalassaemia

No haematologic malignancies have been observed with luspatercept in the TD β-thalassaemia population as of the data lock point of this submission. One event of erythroleukaemia (AML M6) was reported in Study ACE-536-B-THAL-001 in [redacted]. Due to the difficulty in diagnosing AML M6 against a background of β-thalassaemia, an independent expert haematopathologist was engaged to review extensive morphologic and genetic analyses in this case. The independent expert haematopathologist concluded that a diagnosis of AML M6 in this patient was very unlikely. The independent data monitoring committee considered the clinical course to be consistent with β-thalassaemia major complicated by splenomegaly, neutropenia, and sepsis, possibly triggered by deferiprone therapy. The patient subsequently died.

NTD β-thalassaemia

No haematologic malignancies have been observed with luspatercept in the NTD β-thalassaemia population as of the data lock point of this submission.

Haematologic Malignancies (Including AML)	Luspatercept (N = 96)	Control (N = 49)
Patients with ≥ 1 AE, n (%)	0	2 (4.1)
Patients with ≥ 1 SAE, n (%)	0	2 (4.1)
Incidence (%) of Patients with ≥ 1 AE (95% CI)	0	2 (4.1) (0.5, 14.0)
Exposure-adjusted Incidence Rate/100 Person-Years (95% CI)	0	3.2 (0.8, 12.9)

Seriousness/Outcomes

MDS

In Study ACE-536-MDS-001, serious events of haematologic malignancy (PTs of transformation to AML only) were experienced by 3 luspatercept-treated patients. All events were reported as not recovered/not resolved. In Study ACE-536-MDS-002, serious events of haematologic malignancy (PTs of AML, BCL, transformation to AML, and CMML) were experienced by 4 luspatercept-treated patients. The event of AML was reported as fatal. The events of BCL, transformation to AML and CMML were reported as not recovered/not resolved.

Table 2.7.3.2-1: Important Potential Risk: Haematologic Malignancies (Including AML)

Haematologic Malignancies (Including AML)

Severity and Nature of Risk

MDS

Haematologic Malignancy (Including AML)		
Study MDS-001	**Luspatercept (N = 153)**	**Control (N = 76)**
All AEs, n (%)	3 (2.0)	1 (1.3)
Grade 3 or 4, n (%)	3 (2.0)	1 (1.3)
AEs Leading to Discontinuation, n (%)	2 (1.3)	1 (1.3)
AEs Leading to Dose Reduction, n (%)	0	0
AEs Leading to Dose Interruption, n (%)	0	0
Study ACE-536-MDS-002	**Luspatercept (N = 182)**	**Epoetin Alfa (N = 179)**
All AEs, n (%)	4 (2.2)[a]	2 (1.1)
Grade 3 or 4, n (%)	4 (2.2)	1 (0.6)
Fatal	1 (0.5)	0 (0.0)
AEs Leading to Discontinuation, n (%)	3 (1.6%)	1 (0.6)
AEs Leading to Dose Reduction, n (%)	0	0
AEs Leading to Dose Interruption, n (%)	0	0

a 1 subject in the luspatercept arm had AML and transformation to AML.

In Study ACE-536-MDS-001, 2 patients discontinued treatment with luspatercept due to haematologic malignancy (PTs of transformation to AML only). In Study ACE-536-MDS-002, 3 patients discontinued treatment with luspatercept due to haematologic malignancy (PTs of transformation to AML and CMML).

Table 2.7.3.2-1: Important Potential Risk: Haematologic Malignancies (Including AML)

Haematologic Malignancies (Including AML)
Risk Groups and Risk Factors Progression to AML is well known as part of the progression of the disease (up to 25% of patients) and is associated with baseline factors.[83] Steensma et al. studied risk stratification according to the IPSS in 816 patients and found a time to 25% leukaemia progression being 9.4 years for IPSS low-risk, 3.3 years for IPSS intermediate-1-risk, 1.1 years for IPSS intermediate-2 risk, and 0.2 years for IPSS high risk.[28] Thus, assuming a linear progression, the 1-year risk of AML in MDS is approximately 2.6% (IPSS low-risk) to 7.6% (IPSS intermediate-1-risk). Using the WHO classification system, Malcovati[84] assessed the role of the main prognostic factors for progression to leukaemia and overall survival (OS) in 476 patients first diagnosed with de novo MDS in Italy between 1992 and 2002. Malcovati reported a negative effect of developing a transfusion requirement on OS in patients with refractory anaemia, refractory anaemia with ring sideroblasts or MDS with del(5q) (hazard ratio [HR] = 3.46). In a further development of the WHO Classification-Based Prognostic Scoring System a learning cohort of 426 Italian MDS patients and a validation cohort of 193 evaluable German MDS patients was reported by Malcovati.[85] In a multivariable analysis of the Italian patients stratified by WHO subgroups, cytogenetics and transfusion requirement significantly affected OS (HR = 1.48 and HR = 2.53, respectively) and risk of AML (HR = 1.3 and HR = 2.4, respectively). In a multivariable analysis of the German MDS patients stratified by WHO subgroups, cytogenetics and transfusion dependency retained a significant effect on both OS (HR = 1.84 and HR = 1.85, respectively) and risk of AML (HR = 2.27 and HR = 2.25, respectively). Mallo[86] reported the results of a cooperative study designed to assess prognostic factors for OS and progression to AML in 541 patients with de novo MDS and del 5q. In multivariate analyses the most important predictors of both OS and AML progression were number of chromosomal abnormalities ($p < 0.001$ for both outcomes), platelet count ($p < 0.001$ and $p = 0.001$, respectively) and proportion of bone marrow blasts ($p < 0.001$ and $p = 0.016$, respectively). Transfusion burden was not addressed in this study. In a multicentre study conducted in Iran between 2002 and 2007, haematologic malignancy in patients with β-thalassaemia was evaluated. The proportion of patients with cancer was higher in those with β-thalassaemia intermedia compared with β-thalassaemia major. Cancer was diagnosed in patients aged 0 to 39 years, but not in any of the older patients.[59]
Preventability Prescribers should consider the potential risk of haematologic malignancies (including AML) prior to treatment initiation and to detect haematologic malignancies as early as possible so that appropriate therapy can be provided to improve outcome.
Impact on the Risk-benefit Balance of the Product Haematologic malignancy (including AML) may result in significant morbidity and mortality. It impacts the patient's activities of daily living.

Table 2.7.3.2-1: Important Potential Risk: Haematologic Malignancies (Including AML)

Haematologic Malignancies (Including AML)
Public Health Impact
Haematologic malignancies (including AML) may result in significant morbidity and mortality depending on the type. They impact the patient's activities of daily living. Prior tumours have been reported as a comorbidity in approximately 15% of patients with MDS.[30,31] Follow-up-adjusted incidence rates were used to evaluate the background rate of progression to AML in similar populations from 4 lenalidomide studies in patients with lower-risk (IPSS low- to intermediate-1-risk) MDS.[87,88,89,90] Three of these lenalidomide studies included patients with the del(5q) cytogenetic abnormality. Study CC-5013-MDS-005 included a patient population who had IPSS low- or intermediate-1-risk MDS and did not have the del(5q) cytogenetic abnormality; therefore, this patient population most closely matched the patient population of the pivotal BMS-sponsored Phase 3 luspatercept Study ACE-536-MDS-001 in terms of risk of progression to AML. In Study CC-5013-MDS-005, the follow-up-adjusted incidence of AML progression was 1.91 per 100 person-years (95% CI, 0.80 to 4.59) and 2.46 per 100 person-years (95% CI, 0.79 to 7.64) for patients who received lenalidomide and placebo, respectively. The Düsseldorf MDS registry has been collecting data since 1982 when the French-American-British classification was published as a first robust tool for the diagnosis and classification of myeloid malignancies with < 30% medullary blasts and dysplasia in blood and marrow. Data from about 7400 patients are available with follow-up and description of diagnosis, karyotyping, progression, treatment, and causes of death (internal BMS report). About 5% of the patients were lost to follow-up. From the Düsseldorf MDS registry, there were 2485 patients with IPSS low- or intermediate-1-risk category who were captured in the registry, of which 2458 patients were evaluable for the analysis of progression to AML. In these 2458 patients with IPSS low- or intermediate-1-risk category, the follow-up-adjusted incidence rate of AML progression was 2.82 per 100 person-years (95% CI, 2.48 to 3.20). When the patients in the Düsseldorf MDS registry were analysed by IPSS-R very low- or low-risk category (N = 613), similar to the patient population of Study ACE-536-MDS-001 in terms of risk of progression to AML, the follow-up-adjusted incidence rate of AML progression was 2.37 per 100 person-years (95% CI, 1.86 to 2.99). Dayyani[91] described causes of death among 273 US patients with low-risk MDS. In this series of deceased patients, progression to AML occurred in 15% of patients. The association between β-thalassaemia and haematologic malignancies has been investigated in 2 large scale cohort studies, both of which proposed an increased risk compared with the population.[59,60] In the Taiwanese cohort study,[60] a 5.32-fold increased risk for haematologic malignancies was noted in patients with β-thalassaemia when compared with an age- and gender-matched control cohort. Furthermore, patients with β-thalassaemia with transfusion exhibited a 9.31-fold increased risk for developing haematological malignancy compared with patients who did not receive transfusion. The incidences of any cancer (except metastatic cancer) were reported as 3.96 and 2.60/1000 person-years for the β-thalassaemia and matched comparison cohorts, respectively. The overall incidence of cancer was 52% higher in the β-thalassaemia cohort than in the comparison cohort, with an adjusted HR of 1.54 (95% CI 1.15 to 2.07).
MedDRA Terms
Malignancy SMQ and subsequent determination of what clinically constitutes a haematologic malignancy.

Table 2.7.3.2-2: Important Potential Risk: Off label Use in Paediatric Patients (Developmental Toxicity of Luspatercept)

Off-label Use in Paediatric Patients (Developmental Toxicity of Luspatercept)
Potential Mechanisms The exact mechanism of developmental toxicity of luspatercept when used off-label in paediatric patients has not been studied.
Evidence Source(s) and Strength of Evidence In a study in juvenile rats, luspatercept was administered from postnatal day 7 to 91 at 0, 1, 3, or 10 mg/kg. Luspatercept-related findings unique to juvenile rats included tubular atrophy/hypoplasia of the kidney inner medulla, delays in the mean age of sexual maturation in males, effects on reproductive performance (lower mating indices), and nonadverse decreases in bone mineral density in both male and female rats. The effects on reproductive performance were observed after a greater than 3-month recovery period, suggesting a permanent effect. Although reversibility of the tubular atrophy/hypoplasia was not examined, these effects are also considered to be irreversible. Adverse effects on the kidney and reproductive system were observed at clinically relevant exposure levels and seen at the lowest dose tested and, thus, a NOAEL was not established. In addition, haematological malignancies were observed in 3 out of 44 rats examined in the highest dose group (10 mg/kg). These findings are all considered potential risks in paediatric patients.
Characterisation of the Risk There is no relevant use of luspatercept in the paediatric population for the indication of MDS or in paediatric patients less than 6 years of age in β-thalassaemia. The safety and efficacy of luspatercept in paediatric patients aged from 6 years to less than 18 years have not yet been established in β-thalassaemia. There are currently limited data from the use of luspatercept in paediatric patients.
Risk Groups and Risk Factors Paediatric patients exposed to luspatercept.
Preventability The target population is adults, as reflected in the luspatercept SmPC.
Impact on the Risk-benefit Balance of the Product The relevance of the juvenile nonclinical findings in rats to development in paediatric patients is unknown. Studies in animals have shown developmental toxicity following luspatercept administration. Based on findings in animals, luspatercept may cause developmental toxicities when used off-label in paediatric patients. There are limited data from the use of luspatercept in paediatric patients.
Public Health Impact In children with β-thalassaemia, growth and development are retarded. Luspatercept may have a potential impact of developmental toxicity in children.
MedDRA Terms The subset of paediatric patient population will be identified by searching for cases reporting patients between 0 days and <18 years of age. <u>Developmental toxicity:</u> MedDRA PTs: Bone development abnormal, Cartilage development disorder, Developmental delay, Developmental regression, Disorder of sex development, Motor developmental delay, Tooth development disorder, Abnormal organ growth, Growth disorder, Growth failure, Growth retardation, Delayed puberty, Developmental delay, Fine motor delay, Motor developmental delay <u>Off label use:</u> MedDRA PTs: Drug effective for unapproved indication, Drug ineffective for unapproved indication, Off label use, Product use in unapproved indication, Therapeutic product effective for unapproved indication, Therapeutic product ineffective for unapproved indication and Unintentional use for unapproved indication.

Table 2.7.3.2-3: Important Potential Risk: Use During Pregnancy and Lactation

Use During Pregnancy and Lactation
Potential Mechanisms The exact mechanism of foetal toxicity has not been studied. It is unknown whether luspatercept or its metabolites are excreted in human milk.
Evidence Source(s) and Strength of Evidence Luspatercept is transferred through the placenta of pregnant rats and rabbits and is excreted into the milk of lactating rats. In a fertility study in rats, administration of luspatercept to females at doses higher than the currently recommended highest human dose reduced the average number of implantations and viable embryos. No such effects were observed when exposure in animals was at 1.5 times the clinical exposure. Administration of luspatercept to male rats at doses higher than the currently recommended highest human dose had no adverse effect on male reproductive organs or on their ability to mate and produce viable embryos. The highest dose tested in male rats yielded an exposure approximately 7 times the clinical exposure. Luspatercept was a selective developmental toxicant (dam not affected; foetus affected) in the rat and a maternal and foetal developmental toxicant (doe and foetus affected) in the rabbit. Embryo-foetal effects were seen in both species and included reductions in numbers of live foetuses and foetal body weights, increases in resorptions, post-implantation loss and skeletal variations, and in rabbit foetuses, malformations of the ribs and vertebrae. In a peri- and post-natal development study, with dose levels of 3, 10, or 30 mg/kg administered once every 2 weeks from gestational day 6 through post-natal day 20, adverse findings at all doses consisted of lower F1 pup body weights in both sexes at birth, throughout lactation, and post weaning; lower body weights during the early premating period (Week 1 and 2) in the F1 females (adverse only at 30 mg/kg/dose) and lower body weights in F1 males during the premating, pairing, and post-mating periods; and microscopic kidney findings in F1 pups. Additionally, no adverse findings included delayed male sexual maturation at 10- and 30 mg/kg/dose. There was no effect on behavioural indices, fertility, or reproductive parameters at any dose level in either sex in the F1 animals.
Characterisation of the Risk No cases of pregnancy or lactation have been reported in patients exposed to luspatercept in Studies ACE-536-MDS-001, ACE-536-B-THAL-001 and ACE-536-B-THAL-002.
Risk Groups and Risk Factors Pregnant or lactating females exposed to luspatercept.
Preventability Luspatercept is contraindicated during pregnancy. Women of childbearing potential have to use effective contraception during treatment with luspatercept and for at least 3 months after the last dose. Prior to starting treatment with luspatercept, a pregnancy test has to be performed for WCBP. Treatment with luspatercept should not be started if the woman is pregnant. If a patient becomes pregnant, luspatercept should be discontinued. Because of the unknown adverse effects of luspatercept in new-borns/infants, a decision must be made whether to discontinue breast-feeding during therapy with luspatercept and for 3 months after the last dose or to discontinue luspatercept therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Impact on the Risk-benefit Balance of the Product Clinical implications are potentially foetal loss or teratogenicity. Studies in animals have shown reproductive toxicity following luspatercept administration. Luspatercept was detected in the milk of lactating rats. Based on findings in animals, luspatercept may also compromise female fertility. There are no data from the use of luspatercept in pregnant women.
Public Health Impact

Table 2.7.3.2-3: Important Potential Risk: Use During Pregnancy and Lactation

Use During Pregnancy and Lactation
Major foetal abnormalities, if detected, will have a major impact on quality of life or could be fatal in utero.
MedDRA Terms
Broad scope Sub-SMQ Foetal disorders, Broad scope of Sub-SMQ Normal pregnancy conditions and outcomes, Broad scope Sub-SMQ Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth), Narrow scope of Sub-SMQ Termination of pregnancy and risk of abortion and ad hoc PTs; Broad scope of Sub-SMQ Neonatal disorders; Combination of the Pregnancy related, Teratogenicity, Lactation, and Neonatal Strategies; Narrow scope of Sub-SMQ Congenital, familial and genetic disorders; Narrow scope of Sub-SMQ Functional lactation disorders and Narrow scope of Sub-SMQ Neonatal exposures via breast milk.

Table 2.7.3.2-4: Important Potential Risk: Bone Fractures

Bone Fractures
Potential Mechanisms
No mechanism whereby luspatercept may contribute to the risk of bone fractures has been identified for patients.
Evidence Source(s) and Strength of Evidence
In Study ACE536-B-THAL-002, traumatic bone fractures were observed in a greater proportion of luspatercept-treated patients compared to placebo treated patients with NTD β thalassaemia. 8.3% of luspatercept-treated patients reported an event of traumatic fracture. 2.1% of the events were mild and 2.1% of the events were moderate in severity. 4 (4.2%) events were Grade 3 (severe) with none being Grade 4 or fatal. 1 (2.0%) placebo-treated patient reported a Grade 3 (severe) event of traumatic fracture. No Grade 4 or fatal events were reported at the data lock point of this submission. In addition, 1 single event of pathologic fracture (1.0%) in a luspatercept -treated subject and none on placebo was reported in the study. The pathologic fracture was non-serious Grade 1 and involved a subject who also reported a traumatic fracture. No other type of fracture or specific fracture location was reported in the study. The addition of traumatic bone fracture as an ADR to the SmPC is based on the numerical imbalance favoring the placebo arm in the NTD β-thalassaemia indication . In both the ACE-536-MDS-001 and ACE-536-MDS-002 studies, there is no imbalance in the frequency of treatment-emergent bone fractures in the luspatercept vs placebo (7.2% vs 9.2%) or epoetin alfa (8.8% vs 10.1%) arms, respectively. In ACE-536-MDS-001, serious treatment-emergent bone fractures were reported in 3.3% of luspatercept-treated subjects vs 6.6% of placebo-treated subjects. In ACE-536-MDS-002, serious treatment-emergent bone fractures were reported in 5.5% of the luspatercept-treated subjects vs 5.0% of the epoetin alfa-treated subjects. Advanced age, risk factors, and medical history relevant to fracture risk, including osteopenia, osteoporosis, prior fractures, and vertigo/dizziness, were noted among these subjects.

Table 2.7.3.2-4: Important Potential Risk: Bone Fractures

Bone Fractures

Characterisation of the Risk

Frequency with 95% CI

NTD β-thalassaemia

System Organ Class Preferred Term	Luspatercept (N=96) n (%) (95% CI)	Placebo (N=49) n (%) (95% CI)
Subjects with at Least One Specified TEAE	8 (8.3) (3.7, 15.8)	1 (2.0) (0.1, 10.9)
Injury, poisoning and procedural complications	8 (8.3) (3.7, 15.8)	1 (2.0) (0.1, 10.9)
Traumatic fracture	8 (8.3) (3.7, 15.8)	1 (2.0) (0.1, 10.9)
Musculoskeletal and connective tissue disorders	1 (1.0) (0.0, 5.7)	0 (0.0) NA
Pathological fracture	1 (1.0) (0.0, 5.7)	0 (0.0) NA

In Study ACE-536-B-THAL-002, the proportion of NTD β-thalassaemia patients experiencing at least 1 event of traumatic fractures was higher among luspatercept-treated patients (8.3%) compared to patients receiving placebo (2.0%).

System Organ Class Preferred Term	Luspatercept (N=96) n (%) (95% CI)	Placebo (N=49) n (%) (95% CI)
Subjects with at Least One Specified Serious TEAE	5 (5.2) (1.7, 11.7)	1 (2.0) (0.1, 10.9)
Injury, poisoning and procedural complications	5 (5.2) (1.7, 11.7)	1 (2.0) (0.1, 10.9)
Traumatic fracture	5 (5.2) (1.7, 11.7)	1 (2.0) (0.1, 10.9)

MDS

Preferred Term	n (%) (95% CI)	n (%) (95% CI)
Study ACE-536-MDS-001	**Luspatercept (N = 153)**	**Placebo (N = 76)**
Subjects with at Least One Specified TEAE	11 (7.2) (3.6, 12.5)	7 (9.2) (3.8, 18.1)
Humerus fracture	2 (1.3) (0.2, 4.6)	1 (1.3) (0.0, 7.1)
Femur fracture	2 (1.3) (0.2, 4.6)	0 (0.0) (0.0, 0.0)
Spinal fracture	2 (1.3) (0.2, 4.6)	0 (0.0) (0.0, 0.0)
Hip fracture	1 (0.7) (0.0, 3.6)	3 (3.9) (0.8, 11.1)
Clavicle fracture	1 (0.7) (0.0, 3.6)	0 (0.0) (0.0, 0.0)

Table 2.7.3.2-4: Important Potential Risk: Bone Fractures

Bone Fractures		
Foot fracture	1 (0.7) (0.0, 3.6)	0 (0.0) (0.0, 0.0)
Fracture pain	1 (0.7) (0.0, 3.6)	0 (0.0) (0.0, 0.0)
Spinal compression fracture	1 (0.7) (0.0, 3.6)	0 (0.0) (0.0, 0.0)
Rib fracture	0 (0.0) (0.0, 0.0)	2 (2.6) (0.3, 9.2)
Ankle fracture	0 (0.0) (0.0, 0.0)	1 (1.3) (0.0, 7.1)
Thoracic vertebral fracture	0 (0.0) (0.0, 0.0)	1 (1.3) (0.0, 7.1)
Upper limb fracture	0 (0.0) (0.0, 0.0)	1 (1.3) (0.0, 7.1)
Study ACE-536-MDS-002	**Luspatercept (N = 182)**	**Epoetin Alfa (N = 179)**
Subjects with at Least One Specified TEAE	16 (8.8) (5.1, 13.9)	18 (10.1) (6.1, 15.4)
Pelvic fracture	4 (2.2) (0.6, 5.5)	0 (0.0) (0.0, 0.0)
Rib fracture	3 (1.6) (0.3, 4.7)	4 (2.2) (0.6, 5.6)
Spinal fracture	2 (1.1) (0.1, 3.9)	4 (2.2) (0.6, 5.6)
Lumbar vertebral fracture	2 (1.1) (0.1, 3.9)	0 (0.0) (0.0, 0.0)
Spinal compression fracture	2 (1.1) (0.1, 3.9)	0 (0.0) (0.0, 0.0)
Hip fracture	1 (0.5) (0.0, 3.0)	3 (1.7) (0.3, 4.8)
Upper limb fracture	1 (0.5) (0.0, 3.0)	2 (1.1) (0.1, 4.0)
Femur fracture	1 (0.5) (0.0, 3.0)	1 (0.6) (0.0, 3.1)
Wrist fracture	1 (0.5) (0.0, 3.0)	1 (0.6) (0.0, 3.1)
Clavicle fracture	1 (0.5) (0.0, 3.0)	0 (0.0) (0.0, 0.0)
Femoral neck fracture	1 (0.5) (0.0, 3.0)	0 (0.0) (0.0, 0.0)
Foot fracture	1 (0.5) (0.0, 3.0)	0 (0.0) (0.0, 0.0)
Fractured sacrum	1 (0.5) (0.0, 3.0)	0 (0.0) (0.0, 0.0)
Hand fracture	0 (0.0) (0.0, 0.0)	2 (1.1) (0.1, 4.0)
Acetabulum fracture	0 (0.0) (0.0, 0.0)	1 (0.6) (0.0, 3.1)
Facial bones fracture	0 (0.0) (0.0, 0.0)	1 (0.6) (0.0, 3.1)
Fracture displacement	0 (0.0) (0.0, 0.0)	1 (0.6) (0.0, 3.1)
Thoracic vertebral fracture	0 (0.0) (0.0, 0.0)	1 (0.6) (0.0, 3.1)

Preferred Term	n (%) (95% CI)	n (%) (95% CI)
Study ACE-536-MDS-001	**Luspatercept (N = 153)**	**Placebo (N = 76)**
Subjects with at Least One Specified Serious TEAE	5 (3.3) (1.1, 7.5)	5 (6.6) (2.2, 14.7)
Femur fracture	2 (1.3) (0.2, 4.6)	0 (0.0) (0.0, 0.0)

Table 2.7.3.2-4: Important Potential Risk: Bone Fractures

Bone Fractures		
Hip fracture	1 (0.7) (0.0, 3.6)	3 (3.9) (0.8, 11.1)
Humerus fracture	1 (0.7) (0.0, 3.6)	1 (1.3) (0.0, 7.1)
Clavicle fracture	1 (0.7) (0.0, 3.6)	0 (0.0) (0.0, 0.0)
Ankle fracture	0 (0.0) (0.0, 0.0)	1 (1.3) (0.0, 7.1)
Thoracic vertebral fracture	0 (0.0) (0.0, 0.0)	1 (1.3) (0.0, 7.1)
Study ACE-536-MDS-002	**Luspatercept (N = 182)**	**Epoetin Alfa (N = 179)**
Subjects with at Least One Specified Serious TEAE	10 (5.5) (2.7, 9.9)	9 (5.0) (2.3, 9.3)
Pelvic Fracture	4 (2.2) (0.6, 5.6)	0 (0.0) (0.0, 0.0)
Spinal Fracture	2 (1.1) (0.1, 3.9)	3 (1.7) (0.3, 4.8)
Rib Fracture	2 (1.1) (0.1, 3.9)	0 (0.0) (0.0, 0.0)
Hip fracture	1 (0.5) (0.0, 3.0)	2 (1.1) (0.1, 4.0)
Femur fracture	1 (0.5) (0.0, 3.0)	1 (0.6) (0.0, 3.1)
Clavicle fracture	1 (0.5) (0.0, 3.0)	0 (0.0) (0.0, 0.0)
Femoral neck fracture	1 (0.5) (0.0, 3.0)	0 (0.0) (0.0, 0.0)
Spinal compression fracture	1 (0.5) (0.0, 3.0)	0 (0.0) (0.0, 0.0)
Acetabulum fracture	0 (0.0) (0.0, 0.0)	1 (0.6) (0.0, 3.1)
Hand fracture	0 (0.0) (0.0, 0.0)	1 (0.6) (0.0, 3.1)
Thoracic vertebral fracture	0 (0.0) (0.0, 0.0)	1 (0.6) (0.0, 3.1)

Seriousness/Outcomes

NTD β-thalassaemia

In Study ACE-536-B-THAL-002, serious TEAE of traumatic fracture were experienced by 5 (5.2%) luspatercept treated patients. Serious events of traumatic fracture were considered resolved in 4 of the luspatercept treated patients and ongoing in 1 luspatercept treated patient. Serious TEAEs of traumatic fracture (verbatim terms: traumatic right hip fracture and traumatic right olecranon fracture) were reported in 1 (2.0%) patient receiving placebo. The event of traumatic right hip fracture was considered resolved with sequalae and the event of traumatic right olecranon fracture was considered resolved. These events were considered to be 2 temporally separate events with no further circumstances reported.

MDS

The outcomes of these SAEs reported in ACE-536-MDS-001 and ACE-536-MDS-002 are summarised below.

Preferred Term AE Outcome	**n (%)**	**n (%)**
Study ACE-536-MDS-001	**Luspatercept (N = 153)**	**Placebo (N = 76)**
Femur Fracture	**2 (1.3)**	**0 (0.0)**
Resolved	2 (1.3)	0 (0.0)

Table 2.7.3.2-4: Important Potential Risk: Bone Fractures

Bone Fractures		
Clavicle fracture	**1 (0.7)**	**0 (0.0)**
Resolved	1 (0.7)	0 (0.0)
Hip Fracture	**1 (0.7)**	**3 (3.9)**
Resolved	1 (0.7)	1 (1.3)
Not Recovered/Not Resolved	0 (0.0)	1 (1.3)
Resolved with Sequelae	0 (0.0)	1 (1.3)
Humerus Fracture	**1 (0.7)**	**1 (1.3)**
Resolved	1 (0.7)	0 (0.0)
Resolved with Sequelae	0 (0.0)	1 (1.3)
Ankle Fracture	**0 (0.0)**	**1 (1.3)**
Not Recovered/Not Resolved	0 (0.0)	1 (1.3)
Thoracic vertebral fracture	**0 (0.0)**	**1 (1.3)**
Resolved	0 (0.0)	1 (1.3)
Study ACE-536-MDS-002	**Luspatercept (N = 182)**	**Epoetin Alfa (N = 179)**
Pelvic Fracture	**4 (2.2)**	**0 (0.0)**
Recovered/Resolved	2 (1.1)	0 (0.0)
Not Recovered/Not Resolved	1 (0.5)	0 (0.0)
Recovering/Resolving	1 (0.5)	0 (0.0)
Spinal Fracture	**2 (1.1)**	**3 (1.7)**
Not Recovered/Not Resolved	1 (0.5)	1 (0.6)
Recovered/Resolved with Sequelae	1 (0.5)	0 (0.0)
Recovered/Resolved	0 (0.0)	2 (1.1)
Recovering/Resolving	0 (0.0)	1 (0.6)
Rib Fracture	**2 (1.1)**	**0 (0.0)**
Not Recovered/Not Resolved	1 (0.5)	0 (0.0)
Recovered/Resolved	1 (0.5)	0 (0.0)
Clavicle fracture	**1 (0.5)**	**0 (0.0)**
Not Recovered/Not Resolved	1 (0.5)	0 (0.0)
Femoral neck fracture	**1 (0.5)**	**0 (0.0)**
Not Recovered/Not Resolved	1 (0.5)	0 (0.0)
Femur fracture	**1 (0.5)**	**1 (0.6)**
Recovered/Resolved with Sequelae	1 (0.5)	0 (0.0)

Table 2.7.3.2-4: Important Potential Risk: Bone Fractures

Bone Fractures		
Recovered/Resolved	0 (0.0)	1 (0.6)
Hip Fracture	**1 (0.5)**	**2 (1.1)**
Recovered/Resolved	1 (0.5)	0 (0.0)
Recovered/Resolved with Sequelae	0 (0.0)	2 (1.1)
Spinal compression fracture	**1 (0.5)**	**0 (0.0)**
Recovering/Resolving	1 (0.5)	0 (0.0)
Acetabulum fracture	**0 (0.0)**	**1 (0.6)**
Recovered/Resolved	0 (0.0)	1 (0.6)
Hand fracture	**0 (0.0)**	**1 (0.6)**
Not Recovered/Not Resolved	0 (0.0)	1 (0.6)
Thoracic vertebral fracture	**0 (0.0)**	**1 (0.6)**
Not Recovered/Not Resolved	0 (0.0)	1 (0.6)

Table 2.7.3.2-4: Important Potential Risk: Bone Fractures

Bone Fractures

Severity and Nature of Risk

NTD β-thalassaemia

Bone Fracture (PT Traumatic fracture)	Luspatercept (N = 96)	Control (N = 49)
All AEs, n (%)	8 (8.3)	1 (2.0)
Grade 3 or 4, n (%)	4 (4.2)	1 (2.0)
AEs Leading to Discontinuation, n (%)	0	0
AEs Leading to Dose Reduction, n (%)	0	0
AEs Leading to Dose Delay, n (%)	2 (2.1)	1 (2.0)

No Grade 4 or 5 events of traumatic fracture were reported in Study ACE-536-B-THAL-002.

MDS

Study MDS-001	Luspatercept (N = 153)	Control (N = 76)
All AEs, n (%)	11 (7.2)	7 (9.2)
Grade 3 or 4, n (%)	4 (2.6)	4 (5.3)
AEs Leading to Dose Interruption, n (%)	2 (1.3)	0 (0.0)
Study ACE-536-MDS-002	**Luspatercept (N = 182)**	**Epoetin Alfa (N = 179)**
All AEs, n (%)	16 (8.8)	18 (10.1)
Grade 3 or 4, n (%)	10 (5.5)	9 (5.0)
AEs Leading to Discontinuation, n (%)	1 (0.5)	1 (0.6)
AEs Leading to Dose Interruption, n (%)	4 (2.2)	8 (4.5)

No Grade 5 events of traumatic fracture were reported in Study ACE-536-MDS-001 or ACE-536-MDS-002.

No traumatic fracture events led to dose discontinuation in Study ACE-536-MDS-001.

Table 2.7.3.2-4: Important Potential Risk: Bone Fractures

Bone Fractures
Risk Groups and Risk Factors Vogiatzi et al.[92] estimated the prevalence of fractures in a sample of North American patients with β-thalassemia. Age was a significant independent predictor of fracture history in a model that only included age, diagnosis, gender and race. Fracture prevalence was higher among older subjects (odds ratio for a 5-year increase 1.45, 95% CI 1.30 to 1.62, P<0.001). Age distribution in the β-thalassemia intermedia group was reported as follows: 0.0% in the 0-11 age group, 6.7% in the 11-20 age group and 22.9% in 20+ age group. Other risk factors included, lower lumbar bone mass, decreased lower bone mineral density, and hypogonadism. Another risk factor for bone fracture is type of thalassemia. A systematic review and meta-analysis by Charoenngam et al.[93] that included 25 studies with 4934 patients showed that the pooled prevalence of fracture was 18% (95%CI, 16-19%; I2 = 89.0%) among patients with TD thalassemia, and 7% (95%CI, 4-10%; I2 = 94.2%) among patients with NTD thalassemia. This risk may relate to the fact that patients with TD thalassemia have lower bone mineral density than NTD thalassemia and may experience lifelong fracture rates as high as 71%. The pathogenesis of thalassemia-associated osteoporosis (TAO) is multifactorial with anemia and iron overload playing crucial role in its development. Results for bone loss in the NTD population vary in the literature by type of NTD β-Thalassemia. A study by Nakavachara et al. 2018 determined that the prevalence of low bone mass among adolescents with NTD Hb E/β-Thalassemia was relatively low (1.7-10.2%).[94] In the study by Vogiatzi, fracture prevalence, regardless of thalassemia type, increased with age and among patients who have lower lumbar bone mass. The average BMD Z and T scores were 0.85 SD lower among patients with a history of fractures (mean Z/T score −2.78 vs. −1.93, 95% CI for the difference −0.49 to −1.22 SD, P = 0.02) implying that fractures in thalassemia are primarily the result of decreased bone mass.[92] Within the MDS population, there is insufficient evidence of a direct association between MDS and the bone fracture risk. However, it is known that femur and pelvic fractures are prevalent in the MDS patient demographic. In 2018, according to the Behavioral Risk Factor Surveillance System, 27.5% of adults aged ≥ 65 years reported at least one fall in the past year (35.6 million falls), and 10.2% reported a fall-related injury (8.4 million fall-related injuries).[95] In general, the elderly population can sustain isolated rami or sacral fractures due to minor trauma and osteopenia, compared to younger populations. In addition, with increasing age, there is a higher risk of osteoporosis in the MDS patient population compared to the general population.[96] Risk factors for pelvic fractures include low bone mass, smoking, hysterectomy, older age, and a propensity to fall.[97] With respect to femur fractures, mostly involving the hip, major risk factors include osteoporosis and falls. It is estimated that approximately 30% to 60% of community-dwelling older adults fall each year.[98] Approximately 90% of hip fractures in older patients occur from a simple fall from the standing position.[99] Women sustain hip fractures more often due to their higher prevalence of osteoporosis. The lifetime risk of hip fracture is 17.5% for women and 6% for men.[100] The average ages for femoral neck fracture are 77 years old in women and 72 years old in men.[101] Taken together, there is a lack of literature supporting an association between MDS and fracture risk, which is concordant with the findings in BMS-sponsored trials ACE-536-MDS-001 and ACE-536-MDS-002. These trials suggest that patients treated with luspatercept are not at an elevated risk of fracture. Rather, the MDS patient population has a higher prevalence of those characteristics that are associated with increased fracture risk (e.g., older age and history of osteoporosis).[102]

Table 2.7.3.2-4: Important Potential Risk: Bone Fractures

Bone Fractures
Preventability Due to the potential risk of traumatic fractures in patients, it is prudent to inform treating physicians about this risk, so they can work with patients to address modifiable risk factors in a population that is prone to sustain fractures.
Impact on the Risk-benefit Balance of the Product There is a higher incidence of traumatic fractures reported in the luspatercept treatment group than in the placebo treatment group in the NTD pivotal ACE-536-B-THAL-002 study. Most of these traumatic fractures were due to accidental falls with no further circumstances reported, none of these were reported as spontaneous fractures, and most subjects had underlying osteoporosis or osteopenia. All luspatercept subjects who reported traumatic fractures had stable T-scores from baseline until the time of the fracture. All TEAEs of traumatic fractures were considered by the investigator as not related to study treatment and due to other causes. However, given the numerical imbalance favoring placebo, traumatic fracture was added as an adverse drug reaction to the SmPC. For patients treated with and who are responsive to luspatercept, clinical benefit will manifest through reduction in cumulative transfusion burden over time. Given the lifelong chronic anemia, its significant impact on morbidity and mortality, and lack of treatment options available for NTD β-thalassemia patients, the MAH believes luspatercept offers an important and much-needed treatment option for patients in this indication and the risk of traumatic fractures can be effectively mitigated by routine pharmacovigilance.
Public Health Impact Fractures have important functional consequences and reductions in quality of life. The economic impact of fractures may result in temporary disability and significant health care resources are required for diagnosis and treatment most fractures. Overall, patients with β-thalassemia are known to be at higher risk of bone loss which can lead to fractures though no studies have been conducted that compare bone loss or fracture risk in the NTD β-thalassemia population compared to the general population. Similarly, the risk factors of bone fractures (e.g., older age and history of osteoporosis) are prevalent in the MDS patient demographic.
MedDRA Terms Fracture, Acetabulum fracture, Ankle fracture, Atypical femur fracture, Atypical fracture, Avulsion fracture, Cervical vertebral fracture, Chance fracture, Clavicle fracture, Comminuted fracture, Complicated fracture, Compression fracture, Costal cartilage fracture, Craniofacial fracture, Depressed fracture, Epiphyseal fracture, Facial bones fracture, Femoral neck fracture, Femur fracture, Fibula fracture, Foot fracture, Forearm fracture, Fracture blisters, Fracture delayed union, Fracture displacement, Fracture infection, Fracture malunion, Fracture nonunion, Fracture of clavicle due to birth trauma, Fractured coccyx, Fractured sacrum, Fractured skull depressed, Greenstick fracture, Hand fracture, Hip fracture, Humerus fracture, Ilium fracture, Impacted fracture, Jaw fracture, Limb fracture, Lisfranc fracture, Lower limb fracture, Lumbar vertebral fracture, Maisonneuve fracture, Metaphyseal corner fracture, Multiple fractures, Neurogenic fracture, Open fracture, Osteochondral fracture, Osteophyte fracture, Osteoporotic fracture, Patella fracture, Pathological fracture, Pelvic fracture, Periprosthetic fracture, Pseudofracture, Radius fracture, Rib fracture, Sacroiliac fracture, Scapula fracture, Skull fracture, Skull fractured base, Spinal compression fracture, Spinal fracture, Spinal fusion fracture, Sternal fracture, Stress fracture, Subchondral insufficiency fracture, Thoracic vertebral fracture, Tibia fracture, Torus fracture, Traumatic fracture, Ulna fracture, Upper limb fracture, Wrist fracture.

2.7.3.3 Presentation of the Missing Information

Table 2.7.3.3-1: Missing Information – Long-term Safety

Long-term Safety

Table 2.7.3.3-1: Missing Information – Long-term Safety

Evidence Source:
Comprehensive long-term safety of luspatercept treatment has not yet been obtained from the ongoing clinical studies. It is not anticipated that the safety profile will be different over time.
Population in Need of Further Characterisation:
As there is limited follow-up in the ongoing clinical trials, patients treated with luspatercept need to be followed up to establish the long-term safety of luspatercept. Further data are being collected during the BMS-sponsored long-term follow-up Study ACE-536-LTFU-001.

2.8 Summary of the Safety Concerns

2.8.1 Summary - Ongoing Safety Concerns

Important identified and potential risks, together with missing information, are summarised in Table 2.8.1-1.

Table 2.8.1-1: 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
Missing information	• Long-term safety

3 PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

3.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance activities in BMS as described in the BMS Pharmacovigilance System Master File and Drug Safety's Standard Operating Procedures are in accordance with "Good Pharmacovigilance Practices in the European Union." BMS's Routine Pharmacovigilance System is detailed in the current version of the BMS Pharmacovigilance System Master File.

In addition to expedited reporting, BMS diligently undertakes follow-up on all AEs, including serious AEs that are provided to health authorities to ensure that all details of the case are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the AEs.

Emerging potential safety signals can be detected by periodic and if appropriate, cumulative evaluation of the AEs. The results will be compiled in the periodic safety update report (PSUR),

in accordance with Guidelines on Good Pharmacovigilance Practices in the EU/EEA. Periodicity of the PSUR submissions is defined by the date of the first US Food and Drug Administration approval/international birth date of 08-Nov-2019.

In addition, data regarding the important identified and potential risks will be presented in the PSUR. The data presentation will include all case reports collected during the period covered by the PSUR together with cumulative data.

Using the data obtained from this plan, the risk-benefit profile of luspatercept will be re-evaluated on a periodic basis via the PSUR. If necessary, the related sections of the RMP will be updated accordingly.

3.1.1 Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

3.1.1.1 Specific AE Follow-up Forms

AE follow-up forms for haematologic malignancies (including progression to AML in MDS and targeted questions for follow-up of haematologic malignancy), TEEs, EMH masses, and pregnancy and infant follow-up are presented in Annex 4 (see Annex 4).

3.1.1.2 Other Forms of Routine Pharmacovigilance Activities

None proposed.

3.1.2 Additional Pharmacovigilance Activities

3.1.2.1 Study ACE-536-LTFU-001

A BMS-sponsored Phase 3b, open label, single-arm, rollover study to evaluate long-term safety of luspatercept in patients who have participated in Acceleron or BMS-sponsored luspatercept (ACE-536) clinical trials is ongoing (Study ACE-536-LTFU-001; Table 3.1.2.1-1).

Table 3.1.2.1-1: Study ACE-536-LTFU-001

Study Short Name and Title	Rationale and Study Objectives	Study Design	Study Population	Milestones
Phase 3b, open label, single-arm, rollover study to evaluate long-term safety in subjects who have participated in other luspatercept (ACE-536) clinical trials ACE-536-LTFU-001	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.	Phase 3b, open label, single-arm, rollover study.	Patients who have participated in luspatercept (ACE-536) clinical trials.	Final report: Q2 2029. Interim safety updates will be provided annually for the first 5 years.

All patients entering into Study ACE-536-LTFU-001 will continue to be followed for 5 years from Dose 1 of the parent protocol, or 3 years of post-treatment from the last dose of the parent protocol, whichever occurs later.

For information on exposure data up to the data cut-off and patients remaining on treatment at that time point, see Section 2.3 of the RMP.

3.2 Summary Table of the Additional Pharmacovigilance Activities

3.2.1 Ongoing and Planned Additional Pharmacovigilance Activities

A summary of the additional pharmacovigilance activities in included in Table 3.2.1-1.

Table 3.2.1-1: Category 1 to 3: Ongoing and Planned Studies/Activities in the Postauthorisation Pharmacovigilance Development Plan

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.

4 PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

4.1 Planned and Ongoing Postauthorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

There are no planned or ongoing postauthorisation efficacy studies for luspatercept.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Risk Minimisation Plan

5.1.1 Routine Risk Minimisation Measures

Summaries of the routine risk minimisation measures for each safety concern included in Section 2.8 are provided in Table 5.1.1-1.

Table 5.1.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
TEEs (only in the TD and NTD β-thalassaemia population with splenectomy)	**Routine risk communication:** TEEs (including DVT, portal vein thrombosis, ischaemic stroke, and pulmonary embolism) are included as undesirable effects in patients with TD β-thalassaemia in Section 4.8 of the SmPC. Stroke symptoms and blood clots in the veins are included as possible side effects in Section 4 of the package leaflet (PL). Warnings regarding luspatercept treatment in β-thalassaemia patients with a splenectomy are included in Section 4.4 of the SmPC and Section 2 of the PL. Incidence of TEEs and information on risk factors are also included in Section 4.4 of the SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Statement in Section 4.4 of the SmPC that thromboprophylaxis according to current clinical guidelines should be considered in higher risk patients. Advice regarding preventative measures and medications is included in Section 2 of the PL. Advice regarding interruption and dose modification of luspatercept treatment for persistent treatment-related Grade ≥ 3 adverse reactions until the toxicity has improved or returned to baseline is included in Section 4.2 of the SmPC. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.

Table 5.1.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
EMH masses (In the TD and NTD β-thalassaemia population)	**Routine risk communication:** Contraindication for patients requiring treatment to control the growth of EMH masses is included in Section 4.3 of the SmPC. A warning regarding this risk in patients with EMH masses is provided in Section 4.4 of the SmPC. EMH masses is included as undesirable effect in patients in Section 4.8 of the SmPC. A warning regarding EMH masses is provided in Section 4 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Statement in Section 4.4 of the SmPC that luspatercept is contraindicated in patients requiring treatment to control the growth of EMH masses. Patients with EMH masses may experience worsening of these masses and complications during treatment. Signs and symptoms may vary depending on anatomical location. Patients should be monitored at initiation and during treatment for symptoms and signs or complications resulting from the EMH masses, and be treated according to clinical guidelines. Treatment with luspatercept must be discontinued in case of serious complications due to EMH masses. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.
Important potential risks	
Haematologic malignancies (including AML)	**Routine risk communication:** Haematologic malignancies were observed in a study of juvenile rats (see Section 5.3 of the SmPC). **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Advice regarding interruption and dose modification of luspatercept treatment for persistent treatment-related Grade ≥ 3 adverse reactions until the toxicity has improved or returned to baseline is included in Section 4.2 of the SmPC. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.

Table 5.1.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Off-label use in paediatric patients (developmental toxicity of luspatercept)	**Routine risk communication:** The target population is adults as reflected in Section 4.1 of the SmPC. Section 4.2 of the SmPC includes a statement that there is no relevant use of luspatercept in the paediatric population for the indication of MDS, or in paediatric patients less than 6 years of age in β-thalassaemia. The safety and efficacy of luspatercept in the paediatric patients aged from 6 years to less than 18 years have not yet been established in β-thalassaemia. Section 5.3 of the SmPC includes the nonclinical findings regarding pre- and post-natal development and juvenile toxicity. Statement that luspatercept is not recommended for use in children and adolescents under 18 years is included in Section 2 of the PL. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Statement in Section 4.2 of the SmPC that luspatercept should be initiated by a physician experienced in treatment of haematological diseases. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.
Use during pregnancy and lactation	**Routine risk communication:** Contraindication during pregnancy is included in Section 4.3 of the SmPC. Instruction not to start luspatercept if the patient is pregnant, and to discontinue luspatercept if a patient becomes pregnant is included in Section 4.6 of the SmPC. Section 4.6 includes reference to nonclinical findings and Section 5.3 includes the nonclinical findings regarding reproductive toxicity, lactation, and fertility. Contraindication regarding luspatercept treatment during pregnancy and warnings and precautions regarding luspatercept therapy during breast-feeding are included in Section 2 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Instruction to use effective contraception during treatment with luspatercept and for at least 3 months after the last dose of luspatercept is included in Section 4.6 of the SmPC and Section 2 of the PL. A recommendation to have a pregnancy test prior to starting therapy with luspatercept and advice whether to discontinue breast-feeding or luspatercept therapy for 3 months after the last dose is included in Section 4.6 of the SmPC and Section 2 of the PL. Statement in Section 4.2 of the SmPC that luspatercept should be initiated by a physician experienced in treatment of haematological diseases. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.
Bone fractures	**Routine risk communication:**

Table 5.1.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	A warning regarding this risk in NTD β-thalassaemia patients is provided in Section 4.4 of the SmPC. Traumatic fracture is included as undesirable effect in patients in Section 4.8 of the SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.
Missing information	
Long-term safety	**Routine risk communication:** None proposed. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed. **Other routine risk minimisation measures beyond the Product Information:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.

5.1.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are presented in Table 5.1.2-1 (Patient Card) and Table 5.1.2-2 (HCP Checklist), and summarised in Annex 6.

Table 5.1.2-1: Patient Card (for Women of Childbearing Potential Only)

Patient Card (for Women of Childbearing Potential Only)
Objectives: Provision of information to WCBP for the risk of use during pregnancy and lactation.
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).

Table 5.1.2-1: Patient Card (for Women of Childbearing Potential Only)

Patient Card (for Women of Childbearing Potential Only)
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 5.1.2-2: 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.

5.1.3 Summary of Risk Minimisation Measures

A summary of the EU-RMP is outlined in Table 5.1.3-1.

Table 5.1.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
TEEs (only in the TD and NTD β-thalassaemia population with splenectomy)	**Routine risk minimisation measures:** SmPC Section 4.8 – TEEs (including DVT, portal vein thrombosis, ischaemic stroke, and pulmonary embolism) are included as undesirable effects in patients with TD β-thalassaemia. PL Section 4 – Stroke symptoms and blood clots in the veins are included as possible side effects. SmPC Section 4.4 – Incidence of TEEs, risk factors and advice to consider thromboprophylaxis in higher risk patients. PL Section 2 – Advice regarding preventative measures and medications. SmPC Section 4.4 and PL Section 2 – Warning regarding luspatercept treatment in β-thalassaemia patients with a splenectomy and other TEE risk factors. SmPC Section 4.2 - Advice regarding interruption and dose modification of luspatercept for persistent treatment-related Grade ≥ 3 adverse reactions until the toxicity has improved or returned to baseline. **Additional risk minimisation measures:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reaction. **Additional pharmacovigilance activities:** Study ACE-536-LTFU-001.
EMH masses (In the TD and NTD β-thalassaemia population)	**Routine risk minimisation measures:** SmPC Section 4.3- Contraindication for patients requiring treatment to control the growth of EMH masses. SmPC Section 4.8 – EMH masses is included as an undesirable effect. SmPC Section 4.4– Warning regarding the risk of EMH masses. PL Section 2 – Warning regarding luspatercept treatment in patients. **Additional risk minimisation measures:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reaction **Additional pharmacovigilance activities:** Study ACE-536-LTFU-001.
Important Potential Risks		

Table 5.1.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Haematologic malignancies (including AML)	**Routine risk minimisation measures:** SmPC Section 5.3 – Haematologic malignancies were observed in juvenile rats. SmPC Section 4.2 - Advice regarding interruption and dose modification of luspatercept for persistent treatment-related Grade ≥ 3 adverse reactions until the toxicity has improved or returned to baseline. **Additional risk minimisation measures:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reaction. **Additional pharmacovigilance activities:** Study ACE-536-LTFU-001.
Off-label use in paediatric patients (developmental toxicity of luspatercept)	**Routine risk minimisation measures:** SmPC Section 4.1 – Target population is adults. SmPC Section 4.2 – Statement that there is no relevant use of luspatercept in the paediatric population for the indication of MDS, or in paediatric patients less than 6 years of age in β-thalassaemia. The safety and efficacy of luspatercept in the paediatric patients aged from 6 years to less than 18 years have not yet been established in β-thalassaemia. SmPC Section 4.2 – Statement that luspatercept treatment should be initiated by a physician experienced in treatment of haematological diseases. SmPC Section 5.3 – Nonclinical findings regarding pre- and post-natal development and juvenile toxicity. PL Section 2 – Statement that luspatercept is not recommended for use in children and adolescents under 18 years. **Additional risk minimisation measures:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** None proposed.

Table 5.1.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use during pregnancy and lactation	**Routine risk minimisation measures:** SmPC Section 4.2 – Statement that luspatercept should be initiated by a physician experienced in treatment of haematological diseases. SmPC Section 4.3 – Contraindication in pregnancy. SmPC Section 4.6 – Instruction not to start luspatercept if the patient is pregnant, and to discontinue luspatercept if a patient becomes pregnant. SmPC Section 4.6 – Instructions to use effective contraception during and for at least 3 months after the last dose of luspatercept, and to have a pregnancy test prior to therapy. SmPC Section 4.6 – Advice whether to discontinue breast-feeding or luspatercept for 3 months after the last dose. SmPC Section 4.6 (cross-referencing to Section 5.3) – Nonclinical findings regarding reproductive toxicity, lactation, and fertility. PL Section 2 – Contraindication regarding luspatercept treatment during pregnancy, warnings and precautions regarding luspatercept therapy during breast-feeding, and advice regarding contraception usage. **Additional risk minimisation measures:** • Patient Card (for WCBP only). • HCP Checklist. **Legal status:** Luspatercept is subject to restricted medical prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reaction. **Additional pharmacovigilance activities:** None.
Bone fractures	**Routine risk minimisation measures:** SmPC Section 4.4– Warning regarding the risk of traumatic fracture in NTD β-thalassaemia patients. SmPC Section 4.8 – Traumatic fracture is included as an undesirable effect. **Additional risk minimisation measures:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Study ACE-536-LTFU-001.
Missing Information		
Long-term safety	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Table 5.1.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Legal status:	None proposed.
	Luspatercept is subject to restricted medical prescription.	**Additional pharmacovigilance activities:**
		Study ACE-536-LTFU-001.

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for REBLOZYL (luspatercept)

This is a summary of the risk management plan (RMP) for REBLOZYL. The RMP details important risks of REBLOZYL, how these risks can be minimised, and how more information will be obtained about REBLOZYL's risks and uncertainties (missing information).

REBLOZYL's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how REBLOZYL should be used.

This summary of the RMP for REBLOZYL should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of REBLOZYL's RMP.

I. The medicine and what it is used for

REBLOZYL is authorised in adults for the treatment of TD anaemia due to very low, low and intermediate-risk MDS and in adults for the treatment of anaemia associated with TD and NTD β-thalassaemia (see SmPC for the full indication). It contains luspatercept as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of REBLOZYL's benefits can be found in REBLOZYL's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

- https://www.ema.europa.eu/en/medicines/human/EPAR/reblozyl.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of REBLOZYL, together with measures to minimise such risks and the proposed studies for learning more about REBLOZYL's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including periodic safety update report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of REBLOZYL is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of REBLOZYL are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of REBLOZYL. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Important identified and potential risks, together with missing information, are summarised in the table below.

List of important risks and missing information

Important identified risks	• Thromboembolic events (TEEs; only in the TD and NTD β-thalassaemia population with splenectomy) • Extramedullary haematopoiesis (EMH) masses (In the TD and NTD β-thalassaemia population)
Important potential risks	• Haematologic malignancies (including acute myeloid leukaemia [AML]) • Off-label use in paediatric patients (developmental toxicity of luspatercept) • Use during pregnancy and lactation • Bone fractures
Missing information	• Long-term safety

II.B Summary of important risks

Thromboembolic Events (Only in the TD and NTD β-thalassaemia Population with Splenectomy)

Important Identified Risk: Thromboembolic Events (Only in the TD and NTD β-thalassaemia Population with Splenectomy)	
Evidence for linking the risk to the medicine	There is a known risk of TEEs in patients with splenectomy. In Study ACE-536-B-THAL-001, embolic and thrombotic events and thrombophlebitis were observed in a greater proportion of luspatercept-treated patients (4.0%) compared to placebo-treated patients (0.9%) with TD β-thalassaemia. Device occlusion does not clinically qualify as a TEE. Excluding the device occlusion, there were 8 TD β-thalassaemia patients (3.6%) in the luspatercept treatment group who reported TEE events. All cases of TEEs were consistent with the literature and reported in patients who have had a splenectomy and who had at least 1 other risk factor for developing a TEE (including history of thrombocytosis or hormone replacement therapy). The occurrence of TEEs was not correlated with elevated haemoglobin levels. No patient had concurrent hypertension at the time of the TEE.
Risk factors and risk groups	TEEs are common complications of thalassaemia, especially thalassaemia intermedia. The increased risk of TEEs is likely due to abnormalities in platelet, red blood cell, endothelial cell, and thrombin activation which all contribute to hypercoagulable state. In addition to these haematological abnormalities, splenectomy has also been shown to be a major risk factor contributing to hypercoagulability among patients with thalassaemia. Additional risk factors for TEEs in β-thalassaemia include age, iron overload, thrombocytosis, hormone replacement therapy, cardiac and endocrine disease, all common in this patient population. Furthermore, patients may also be at risk of TEEs due to other conventional risk factors similar to the nonthalassaemia population.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 – TEEs (including deep vein thrombosis, portal vein thrombosis, ischaemic stroke, and pulmonary embolism) are included as undesirable effects in patients with TD β-thalassaemia. PL Section 4 – Stroke symptoms and blood clots in the veins are included as possible side effects. SmPC Section 4.4 – Incidence of TEEs and risk factors and advice to consider thromboprophylaxis in higher risk patients. PL Section 2 – Advice regarding preventative measures and medications. SmPC Section 4.4 and PL Section 2 – Warning regarding luspatercept treatment in β-thalassaemia patients with a splenectomy and other TEE risk factors. SmPC Section 4.2 - Advice regarding interruption and dose modification of luspatercept for persistent treatment-related Grade ≥ 3 adverse reactions until the toxicity has improved or returned to baseline. **Additional risk minimisation measures:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.
Additional pharmacovigilance activities	Study ACE-536-LTFU-001. See Section II.C of this summary for an overview of the postauthorisation development plan.

Extramedullary haematopoiesis (EMH) Masses (In the TD and NTD β-thalassaemia Population)

Important Identified Risk: EMH Masses (In the TD and NTD β-thalassaemia Population)	
Evidence for linking the risk to the medicine	In TD β−thalassaemia patients, EMH masses were observed in 3.2% (10/315) of patients treated with luspatercept in the pivotal study and in the long-term follow-up study (Study ACE-536-B-THAL-001/ACE-536-LTFU-001). Spinal cord compression symptoms due to EMH masses occurred in 1.9% (6/315) of patients treated with luspatercept. In NTD β−thalassaemia patients, EMH masses were observed in 6.3% (6/96) of patients treated with luspatercept in the pivotal study. Spinal cord compression due to EMH masses occurred in 1.0% (1/96) of patients treated with luspatercept. During the open-label portion of the study, EMH masses were observed in 2 additional patients for a total of 8/134 (6.0%) of patients.
Risk factors and risk groups	Extramedullary haemopoiesis is among the 3 most common complications, and prevalence of EMH masses has been reported as approximately 20% to 25%. Among patients with no previous transfusions, approximately 60.0% have disease-related complications of extramedullary haemopoiesis, whereas among patients with regular transfusions (TD β-thalassaemia), approximately 4.0% have disease-related complications of extramedullary haemopoiesis. Extramedullary haemopoiesis is a complication due to ineffective erythropoiesis or inadequate bone marrow function and is seen to occur in patients with β-thalassaemia and other chronic hematologic disorders. In patients with such disorders, the ineffective erythropoiesis or inadequate bone marrow function can potentially precipitate extra marrow production of blood elements (ie, extramedullary haemopoiesis). Expansion of the erythron in the bone marrow in NTD β-thalassaemia during ineffective erythropoiesis is associated with homing and proliferation of erythroid precursors in the spleen and liver as a physiologic compensatory phenomenon, which leads to hepatosplenomegaly. Ineffective erythropoiesis in NTD β-thalassaemia patients also forces expansion of the hematopoietic tissue in areas other than the liver and spleen, mostly in the form of masses termed extramedullary hematopoietic pseudotumours. Risk factors associated with β-thalassaemia EMH include: males, splenectomy, IVS-I-6 either in homozygosity or compound heterozygosity, higher levels of GDF15 and erythropoietin, and fewer red blood cell transfusions. Chronic anaemia has been shown to lead to increased levels of erythropoietin and overstimulation of early stage erythropoiesis. For patients with thalassaemia, this may result in EMH, primarily in the spleen.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.3: Contraindication for patients requiring treatment to control the growth of EMH masses. SmPC Section 4.8 – EMH masses is included as an undesirable effect in patients. SmPC Section 4.4 – Warning regarding the risk of EMH masses in patients. Luspatercept is contraindicated in patients requiring treatment to control the growth of EMH masses. Patients with EMH masses may experience worsening of these masses and complications during treatment. Signs and symptoms may vary depending on anatomical location. Patients should be monitored at initiation and during treatment for symptoms and signs or complications resulting from the EMH masses, and be treated according to clinical guidelines. Treatment with luspatercept must be discontinued in case of serious complications due to EMH masses. PL Section 2 – Warning regarding luspatercept treatment in patients.

Extramedullary haematopoiesis (EMH) Masses (In the TD and NTD β-thalassaemia Population)

Important Identified Risk: EMH Masses (In the TD and NTD β-thalassaemia Population)	
	Additional risk minimisation measures: None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.
Additional pharmacovigilance activities	Study ACE-536-LTFU-001. See Section II.C of this summary for an overview of the postauthorisation development plan.

Blood Cancers (Haematologic Malignancies [Including AML])

Important Potential Risk: Haematologic Malignancies (Including AML)	
Evidence for linking the risk to the medicine	In a toxicity study conducted in juvenile rats, 3 of the 44 rats examined in the highest dose group (10 mg/kg) had haematologic malignancies (one incidence each of lymphoma, myeloid leukaemia, and lymphoid leukaemia) were reported. In Study ACE-536-MDS-001, haematologic malignancies (preferred terms of transformation to AML only) were observed in 2.0% of luspatercept-treated MDS patients; the follow-up-adjusted incidence rate was 1.68 (95% CI, 0.54 to 5.22 per 100,000 person-years). In Study ACE-536-MDS-002, haematologic malignancies (PTs of AML, transformation to AML, BCL and CMML) were observed in 2.2% of luspatercept-treated MDS patients; the follow-up adjusted incidence rate was 1.7 per 100,000 person-years). There was no observed incremental risk associated with luspatercept administration for haematologic malignancies. No haematologic malignancies have been observed with luspatercept in the TD and NTD β-thalassaemia population as of the data lock point of this submission. One event of erythroleukaemia (AML M6) was reported in Study ACE-536-B-THAL-001 in [redacted]. An independent expert haematopathologist concluded that a diagnosis of AML M6 in this patient was very unlikely. The independent data monitoring committee considered the clinical course to be consistent with β-thalassaemia major complicated by splenomegaly, neutropenia, and sepsis, possibly triggered by deferiprone therapy. The patient subsequently died. Available clinical data do not suggest a relationship of transformation/development of higher risk MDS/AML with luspatercept treatment.

Blood Cancers (Haematologic Malignancies [Including AML])

Important Potential Risk: Haematologic Malignancies (Including AML)	
Risk factors and risk groups	Progression to AML is well known as part of the progression of the disease (up to 25% of patients) and is associated with baseline factors. Steensma et al. studied risk stratification according to the International Prognostic Scoring System (IPSS) in 816 patients and found a time to 25% leukaemia progression being 9.4 years for IPSS low-risk, 3.3 years for IPSS intermediate-1-risk, 1.1 years for IPSS intermediate-2 risk, and 0.2 years for IPSS high risk. Thus, assuming a linear progression, the 1-year risk of AML in MDS is approximately 2.6% (IPSS low-risk) to 7.6% (IPSS intermediate-1-risk). Using the World Health Organization (WHO) classification system, Malcovati assessed the role of the main prognostic factors for progression to leukaemia and overall survival (OS) in 476 patients first diagnosed with de novo MDS in Italy between 1992 and 2002. Malcovati reported a negative effect of developing a transfusion requirement on OS in patients with refractory anaemia, refractory anaemia with ring sideroblasts or MDS with del(5q) (hazard ratio [HR] = 3.46). In a further development of the WHO Classification-Based Prognostic Scoring System a learning cohort of 426 Italian MDS patients and a validation cohort of 193 evaluable German MDS patients was reported by Malcovati. In a multivariable analysis of the Italian patients stratified by WHO subgroups, cytogenetics and transfusion requirement significantly affected OS (HR = 1.48 and HR = 2.53, respectively) and risk of AML (HR = 1.3 and HR = 2.4, respectively). In a multivariable analysis of the German MDS patients stratified by WHO subgroups, cytogenetics and transfusion dependency retained a significant effect on both OS (HR = 1.84 and HR = 1.85, respectively) and risk of AML (HR = 2.27 and HR = 2.25, respectively). Mallo reported the results of a cooperative study designed to assess prognostic factors for OS and progression to AML in 541 patients with de novo MDS and del 5q. In multivariate analyses the most important predictors of both OS and AML progression were number of chromosomal abnormalities ($p < 0.001$ for both outcomes), platelet count ($p < 0.001$ and $p = 0.001$, respectively) and proportion of bone marrow blasts ($p < 0.001$ and $p = 0.016$, respectively). Transfusion burden was not addressed in this study. In a multicentre study conducted in Iran between 2002 and 2007, haematologic malignancy in patients with β-thalassaemia was evaluated. The proportion of patients with cancer was higher in those with β-thalassaemia intermedia compared with β-thalassaemia major. Cancer was diagnosed in patients aged 0 to 39 years, but not in any of the older patients.
Risk minimisation measures	**Routine risk minimisation measures** SmPC Section 5.3 – Haematologic malignancies were observed in juvenile rats. SmPC Section 4.2 - Advice regarding interruption and dose modification of luspatercept for persistent treatment-related Grade ≥ 3 adverse reactions until the toxicity has improved or returned to baseline. **Additional risk minimisation measures:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.
Additional pharmacovigilance activities	Study ACE-536-LTFU-001. See Section II.C of this summary for an overview of the postauthorisation development plan.

Off-label Use in Paediatric Patients (Developmental Toxicity of Luspatercept)

Important Potential Risk: Off-label Use in Paediatric Patients (Developmental Toxicity of Luspatercept)	
Evidence for linking the risk to the medicine	In a study in juvenile rats, luspatercept was administered from postnatal day 7 to 91 at 0, 1, 3, or 10 mg/kg. Luspatercept-related findings unique to juvenile rats included tubular atrophy/hypoplasia of the kidney inner medulla, delays in the mean age of sexual maturation in males, effects on reproductive performance (lower mating indices), and nonadverse decreases in bone mineral density in both male and female rats. The effects on reproductive performance were observed after a greater than 3-month recovery period, suggesting a permanent effect. Although reversibility of the tubular atrophy/hypoplasia was not examined, these effects are also considered to be irreversible. Adverse effects on the kidney and reproductive system were observed at clinically relevant exposure levels and seen at the lowest dose tested and, thus, a no observed adverse effect level was not established. In addition, haematological malignancies were observed in 3 out of 44 rats examined in the highest dose group (10 mg/kg). These findings are all considered to be potential risks in paediatric patients.
Risk factors and risk groups	Paediatric patients exposed to luspatercept.
Risk minimisation measures	**Routine risk minimisation measures** SmPC Section 4.1 – The target population is adults. SmPC Section 4.2 – Statement that there is no relevant use of luspatercept in the paediatric population for the indication of MDS, or in paediatric patients less than 6 years of age in β-thalassaemia. The safety and efficacy of luspatercept in the paediatric patients aged from 6 years to less than 18 years have not yet been established in β-thalassaemia. SmPC Section 4.2 – Statement that luspatercept treatment should be initiated by a physician experienced in treatment of haematological diseases. SmPC Section 5.3 – Nonclinical findings regarding pre- and post-natal development and juvenile toxicity. PL Section 2 – Statement that luspatercept is not recommended for use in children and adolescents under 18 years. **Additional risk minimisation measures:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.

Use During Pregnancy and Lactation

Important Potential Risk: Use During Pregnancy and Lactation	
Evidence for linking the risk to the medicine	Luspatercept is transferred through the placenta of pregnant rats and rabbits and is excreted into the milk of lactating rats. In a fertility study in rats, administration of luspatercept to females at doses higher than the currently recommended highest human dose reduced the average number of implantations and viable embryos. No such effects were observed when exposure in animals was at 1.5 times the clinical exposure. Administration of luspatercept to male rats at doses higher than the currently recommended highest human dose had no adverse effect on male reproductive organs or on their ability to mate and produce viable embryos. The highest dose tested in male rats yielded an exposure approximately 7 times the clinical exposure. Luspatercept was a selective developmental toxicant (dam not affected; foetus affected) in the rat and a maternal and foetal developmental toxicant (doe and foetus affected) in the rabbit. Embryo-foetal effects were seen in both species and included reductions in numbers of live foetuses and foetal body weights, increases in resorptions, post-implantation loss and skeletal variations, and in rabbit foetuses, malformations of the ribs and vertebrae. In a peri- and post-natal development study, with dose levels of 3, 10, or 30 mg/kg administered once every 2 weeks from gestational day 6 through post-natal day 20, adverse findings at all doses consisted of lower first filial generation (F1) pup body weights in both sexes at birth, throughout lactation, and post weaning; lower body weights during the early premating period (Week 1 and 2) in the F1 females (adverse only at 30 mg/kg/dose) and lower body weights in F1 males during the premating, pairing, and post-mating periods; and microscopic kidney findings in F1 pups. Additionally, no adverse findings included delayed male sexual maturation at 10- and 30 mg/kg/dose. There was no effect on behavioural indices, fertility, or reproductive parameters at any dose level in either sex in the F1 animals.
Risk factors and risk groups	Pregnant or lactating females exposed to luspatercept.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 – Statement that luspatercept should be initiated by a physician experienced in treatment of haematological diseases. SmPC Section 4.3 – Contraindication in pregnancy. SmPC Section 4.6 – Instruction not to start luspatercept if the patient is pregnant, and to discontinue luspatercept if a patient becomes pregnant. SmPC Section 4.6 – Instructions to use effective contraception during and for at least 3 months after the last dose of luspatercept, and to have a pregnancy test prior to therapy. SmPC Section 4.6 – Advice whether to discontinue breast-feeding or luspatercept for 3 months after the last dose. SmPC Section 4.6 (cross-referencing to Section 5.3) – Nonclinical findings regarding reproductive toxicity, lactation, and fertility. PL Section 2 – Contraindication regarding luspatercept treatment during pregnancy, warnings and precautions regarding luspatercept therapy during breast-feeding, and advice regarding contraception usage. **Additional risk minimisation measures:** • Patient Card (for women of childbearing potential [WCBP] only). • HCP Checklist. **Legal status:**

Use During Pregnancy and Lactation

Important Potential Risk: Use During Pregnancy and Lactation	
	Luspatercept is subject to restricted medical prescription.
Additional pharmacovigilance activities	None proposed. See Section II.C of this summary for an overview of the postauthorisation development plan.

Bone fractures

Important Potential Risk: Bone fractures	
Evidence for linking the risk to the medicine	In Study ACE536-B-THAL-002, traumatic bone fractures were observed in a greater proportion of luspatercepttreated patients compared to placebo treated patients with NTD β thalassaemia. 8.3% of luspatercept-treated patients reported an event of traumatic fracture. 2.1% of the events were mild and 2.1% of the events were moderate in severity. 4 (4.2%) events were Grade 3 (severe) with none being Grade 4 or fatal. 1 (2.0%) placebo-treated patient reported a Grade 3 (severe) event of traumatic fracture. No Grade 4 or fatal events were reported at the data lock point of this submission. In addition, 1 single event of pathologic fracture (1.0%) in a luspatercept -treated subject and none on placebo was reported in the study. The pathologic fracture was non-serious Grade 1 and involved a subject who also reported a traumatic fracture. No other type of fracture or specific fracture location was reported in the study. The addition of traumatic bone fracture and an ADR to the SmPC is based on the numerical imbalance favoring the placebo arm in the NTD β-thalassaemia indication . In both the ACE-536-MDS-001 and ACE-536-MDS-002 studies, there is no imbalance in the frequency of treatment-emergent bone fractures in the luspatercept vs placebo (7.2% vs 9.2%) or epoetin alfa (8.8% vs 10.1%) arms, respectively. In ACE-536-MDS-001, serious treatment-emergent bone fractures were reported in 3.3% of luspatercept-treated subjects vs 6.6% of placebo-treated subjects. In ACE-536-MDS-002, serious treatment-emergent bone fractures were reported in 5.5% of the luspatercept-treated subjects vs 5.0% of the epoetin alfa-treated subjects. Advanced age, risk factors, and medical history relevant to fracture risk, including osteopenia, osteoporosis, prior fractures, and vertigo/dizziness, were noted among these subjects.

Risk factors and risk groups	Vogiatzi et al. estimated the prevalence of fractures in a sample of North American patients with β-thalassemia. Age was a significant independent predictor of fracture history in a model that only included age, diagnosis, gender and race. Fracture prevalence was higher among older subjects (odds ratio for a 5-year increase 1.45, 95% CI 1.30 to 1.62, P<0.001). Age distribution in the β-thalassemia intermedia group was reported as follows: 0.0% in the 0-11 age group, 6.7% in the 11-20 age group and 22.9% in 20+ age group. Other risk factors included, lower lumbar bone mass, decreased lower bone mineral density, and hypogonadism. Another risk factor for bone fracture is type of thalassemia. A systematic review and meta-analysis by Charoenngam et al. that included 25 studies with 4934 patients showed that the pooled prevalence of fracture was 18% (95%CI, 16-19%; I2 = 89.0%) among patients with TD thalassemia, and 7% (95%CI, 4-10%; I2 = 94.2%) among patients with NTD thalassemia. This risk may relate to the fact that patients with TD thalassemia have lower bone mineral density than NTD thalassemia and may experience lifelong fracture rates as high as 71%. The pathogenesis of thalassemia-associated osteoporosis (TAO) is multifactorial with anemia and iron overload playing crucial role in its development. Results for bone loss in the NTD population vary in the literature by type of NTD β-Thalassemia. A study by Nakavachara et al. 2018 determined that the prevalence of low bone mass among adolescents with NTD Hb E/β-Thalassemia was relatively low (1.7-10.2%). In the study by Vogiatzi, fracture prevalence, regardless of thalassemia type, increased with age and among patients who have lower lumbar bone mass. The average BMD Z and T scores were 0.85 SD lower among patients with a history of fractures (mean Z/T score −2.78 vs. −1.93, 95% CI for the difference −0.49 to −1.22 SD, P = 0.02) implying that fractures in thalassemia are primarily the result of decreased bone mass. Within the MDS population, there is insufficient evidence of a direct association between MDS and the bone fracture risk. However, it is known that femur and pelvic fractures are prevalent in the MDS patient demographic. In 2018 Moreland et al reported, according to the Behavioral Risk Factor Surveillance System, 27.5% of adults aged ≥ 65 years reported at least one fall in the past year (35.6 million falls), and 10.2% reported a fall-related injury (8.4 million fall-related injuries). In general, the elderly population can sustain isolated rami or sacral fractures due to minor trauma and osteopenia, compared to younger populations. In addition, Datzmann et al. reported that with increasing age, there is a higher risk of osteoporosis in the MDS patient population compared to that of the general population. Tomberg et al reported risk factors for pelvic fractures include low bone mass, smoking, hysterectomy, older age, and a propensity to fall. With respect to femur fractures, mostly involving the hip, major risk factors include osteoporosis and falls. Rubenstein et al reported it is estimated that approximately 30% to 60% of community-dwelling older adults fall each year. Approximately 90% of hip fractures in older patients occur from a simple fall from the standing position (Baumgaertner et al., 2002). According to Melton, women sustain hip fractures more often due to their higher prevalence of osteoporosis. The lifetime risk of hip fracture is 17.5% for women and 6% for men. Baumgaertner et al reported the average ages for femoral neck fracture are 77 years old in women and 72 years old in men. Taken together, there is a lack of literature supporting an association between MDS and fracture risk, which is concordant with the findings in BMS sponsored trials ACE-536-MDS-001 and ACE-536-MDS-002. These trials suggest that patients treated with luspatercept are not at an elevated risk of fracture. Rather, the MDS patient population has a higher prevalence of those characteristics that are associated with increased fracture risk (e.g., older age and history of osteoporosis).
Risk minimisation measures	**Routine risk minimisation measures:**

Bone fractures

Important Potential Risk: Bone fractures	
	SmPC Section 4.4– Warning regarding the risk of traumatic fracture in NTD β-thalassaemia patients. SmPC Section 4.8 – Traumatic fracture is included as an undesirable effect. **Additional risk minimisation measures:** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.
Additional pharmacovigilance activities	Study ACE-536-LTFU-001. See Section II.C of this summary for an overview of the postauthorisation development plan.

Long-term Safety

Missing Information: Long-term Safety	
Risk minimisation measures	**Routine risk minimisation measures** None proposed. **Additional risk minimisation measures** None proposed. **Legal status:** Luspatercept is subject to restricted medical prescription.
Additional pharmacovigilance activities	Study ACE-536-LTFU-001. See Section II.C of this summary for an overview of the postauthorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of luspatercept.

II.C.2 Other studies in post-authorisation development plan

ACE-536-LTFU-001 – A Phase 3b, Open Label, Single-arm, Rollover Study to Evaluate Long-term Safety in Subjects who have Participated in Other Luspatercept (ACE-536) Clinical Trials

Purpose of the study: 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.

APPENDIX 1: REFERENCES

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ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table 1: Specific AE Follow-up Questionnaires

Important Identified or Potential Risk	Draft Specific AE Follow-up Questionnaire Title
Thromboembolic events	Thromboembolism Questionnaire (Figure 1)
EMH Masses	Extramedullary Hematopoisis Mass Questionnaire (Luspatercept) (Figure 2)
Haematologic malignancies (including AML)	Luspatercept Progression to AML in MDS Questionnaire (Figure 3) Targeted Questions for Follow-up of Haematologic Malignancy for Luspatercept (Figure 4)
Use during pregnancy and lactation	Event-Specific Questionnaire for Healthcare Professionals – Pregnancy Follow-up (Figure 5) Event-Specific Questionnaire for Primary Care Physician or Paediatrician – Infant Follow-up (Figure 6)

Figure 1: Thromboembolism Questionnaire

THROMBOEMBOLISM (LUSPATERCEPT)

Baseline date:_____ Result:_____

Onset date:_____ Result:_____

Recovery date:_____ Result:_____

Ferritin level

Baseline date:_____ Result:_____

Onset date:_____ Result:_____

Recovery date:_____ Result:_____

5) Please provide documentation confirming the TEE such as Doppler/US/VQ/CT/MRI or any other imaging result and date:

_____
_____
_____
_____
_____

In case of cerebrovascular event, in addition to the radiological evidence, please provide:
-Detailed Clinical course of the event, including symptoms and signs:

_____
_____
_____
_____

6) Relevant medical history:

a. A history of thromboembolic events? If so, when, what was the treatment and outcome?

7)

a. History of relevant risk factors for TEE (Check all that apply):

Hormonal Replacement ..... ☐
Steroid Use..... ☐
Splenectomy..... ☐
Valve Disease ..... ☐
Hypertension ..... ☐
Coronary Artery Disease..... ☐
Cerebrovascular Disease (Stroke, TIA)..... ☐
Atrial Fibrillation..... ☐
Immobilization..... ☐

Work aid: Target Questions for Follow-up on Luspatercept EOI TEE
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THROMBOEMBOLISM (LUSPATERCEPT)

Trauma	☐
Surgery	☐
Smoking	☐
Dehydration	☐
Sedentary lifestyle	☐
Central venous access	☐
Clotting disorders	☐
Cardiac Siderosis	☐
Other	☐

Relevant details regarding risk factors above:

_____
_____
_____
_____
_____

8) Please provide relevant concomitant medications including corticosteroids/EPO/hormonal replacement/contraception with dose and dates.

_____
_____
_____
_____
_____
_____

9) Was the patient receiving anticoagulants/thromboprophylaxis prior to the **reported event**? If yes, which one(s)? Please include dates, doses and indications.

_____
_____
_____
_____
_____

10) What was the measure taken with respect to luspatercept treatment at the time of the event?

11) If luspatercept was stopped, was it reintroduced?

THROMBOEMBOLISM (LUSPATERCEPT)

12) If reintroduced, is the patient receiving anticoagulants/thromboprophylaxis concomitantly with luspatercept therapy? If yes, which ones(s)? Please provide type, dates and dosage.

_____

_____

_____

Figure 2: EMH Masses Questionnaire

EXTRAMEDULLARY HEMATOPOISIS MASS (LUSPATERCEPT)

1) Please provide indication for luspatercept use:

_____

2) Please provide luspatercept dose, frequency and therapy dates:

luspatercept dose: _____
luspatercept frequency: _____
therapy dates: _____

3) Is the patient RBC transfusion dependent? Yes _____ No _____

4) Please provide the frequency of the RBC transfusion:

5) Please provide last RBC transfusion date and number of units transfused (as applicable)

_____

6) Please provide the onset date, anatomical location and size of extramedullary hemopoietic (EMH) mass(es)

_____
_____
_____
_____

7) Please provide circumstances and/or symptoms leading to the diagnosis including signs and symptoms as well as eventual complications if any associated with the EMH mass(es)

_____
_____
_____

8) If applicable, please provide hospital admission date/diagnosis and discharge date/diagnosis/outcome/sequelae for the reported extramedullary hemopoietic (EMH) mass adverse event(s) and relevant treatment for the reported adverse event

_____
_____
_____

Work aid: Target Questions for Follow-up on Luspatercept EOI EMH Version 1.0 –22Sep2021

EXTRAMEDULLARY HEMATOPOISIS MASS (LUSPATERCEPT)

9) Please provide laboratory data including:

Hemoglobin and Hematocrit at the time of the adverse event (date)
_____

Baseline (at the time of study therapy start) date: _____

Result (with units): _____

Normal range (with units): _____

Red Blood Cell at the time of the adverse event (date):
_____

Baseline (at the time of study therapy start) date: _____

Result (with units): _____

Normal range (with units): _____

10) Please provide documentation confirming the EMH mass(es) including anatomical location and size such as Imaging (ultrasound, Xray CT scan, MRI or any other imaging result (s) and date (s):

_____
_____
_____
_____
_____

In case of EMH mass(es) with neurologic symptoms suggestive of spinal compression, in addition to the radiological evidence, please provide:

-Detailed clinical course of the adverse event, including symptoms and signs, neurological examination results, treatment and outcome including the date of improvement/recovery:

_____
_____
_____
_____

EXTRAMEDULLARY HEMATOPOISIS MASS (LUSPATERCEPT)

11) Relevant medical history:

a. A history of EMH mass event(s)? If so, please provide anatomical location, date of diagnosis, what was the treatment and outcome?

b. Signs and symptoms of previous EMH mass such as radicular pain (if applicable)

	Location date	Onset date	Size based on MRI/X-ray CT scan	Clinical symptoms, and signs if applicable	Resolution date
EHM prior to Luspatercept therapy					
Current EHM					

12) History of relevant risk factors for EMH mass(es) (Check all that apply):

- Splenectomy ☐
- Splenomegaly ☐
- Hepatomegaly ☐
- Chronic Anemia ☐
- EMH Masses ☐
- Other ☐

Relevant details regarding risk factors above:

EXTRAMEDULLARY HEMATOPOISIS MASS (LUSPATERCEPT)

13) Please provide relevant concomitant medications including hydroxyurea with dose and dates.

_____
_____
_____
_____
_____
_____

14) What was the measure taken with respect to luspatercept treatment at the time of the adverse event?

15) If luspatercept was stopped did EMH abate or showed signs of improvement?

_____
_____
_____

16) Was luspatercept reintroduced? If so, did the adverse event recur? Please provide dates and dosage.

_____
_____
_____

17) If reintroduced, is the patient receiving concomitant treatment with luspatercept therapy? If yes, which ones (s)? Please provide type, dates and dosage.

_____
_____
_____

Figure 3: Luspatercept Progression to AML in MDS Questionnaire

Luspatercept Progression to AML in MDS Questionnaire

1) Please provide the date MDS was initially diagnosed:

2) MM/DD/YYYY_____

3) IPSS-R classification at initial diagnosis of MDS: MM/DD/YYYY _____

IPSS-R Very Low ☐

IPSS-R Low ☐

IPSS-R Intermediate ☐

4) IPSS-R classification at time of luspatercept start of therapy: :

MM/DD/YYYY _____

IPSS-R Very Low ☐

IPSS-R Low ☐

IPSS-R Intermediate ☐

5) Date of progression to High Risk MDS, Very High Risk or AML : MM/DD/YYYY

_____

6) Please provide bone marrow results including molecular genetics as well as cytogenetics at baseline and at the time of progression to AML:

MUTATIONS AT BASELINE (CIRCLE ALL THAT APPLY)	MUTATIONS AT ONSET OF AML (CIRCLE ALL THAT APPLY)
SF3B1	SF3B1
TP53	TP53
ASXL1	ASXL1
RUNX1	RUNX1
ETV6	ETV6
EZH2	EZH2

Work aid: Target Questions for Follow-up on Luspatercept EOI AML
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Bone Marrow Analysis Findings at Baseline			Bone Marrow Analysis Findings at Time of Event		
Cytogenetic (Dates DD/MM/YYYY)	Morphology (Dates DD/MM/YYYY)	Molecular (Dates DD/MM/YYYY)	Cytogenetic (Dates DD/MM/YYYY)	Morphology (Dates DD/MM/YYYY)	Molecular (Dates DD/MM/YYYY)

_____
_____
_____

7) Please provide the following relevant lab results:

BASELINE RBC TRANSFUSIONS BURDEN (NUMBER OF TRANSFUSIONS IN THE LAST 6 WEEKS):

_____

BASELINE FERRITIN LEVEL: _____

BASELINE EPO LEVEL: _____

BASELINE BLASTS BONE MARROW: _____

BASELINE BLASTS PERIPHERAL: _____

BASELINE RING SIDEROBLAST: _____

PRIOR ESA TREATMENT AND DATES: _____

_____
_____
_____

PRIOR TREATMENT FOR MDS OTHER THAN ESA:
_____
_____
_____

COMPLETE BLOOD COUNT

WBC:_____
PLQ :_____
HB: _____

BLASTS AT TIME OF AML DIAGNOSIS (BONE MARROW): _____

BLASTS AT TIME OF AML DIAGNOSIS (PERIPHERAL): _____

RING SIDEROBLAST AT TIME OF AML DIAGNOSIS:

ADDITIONAL INFO:
RELEVANT CONMEDS, TRANSFUSION INFO, DOSE ADJUSTMENT INFO, INTERVENTION ETC.

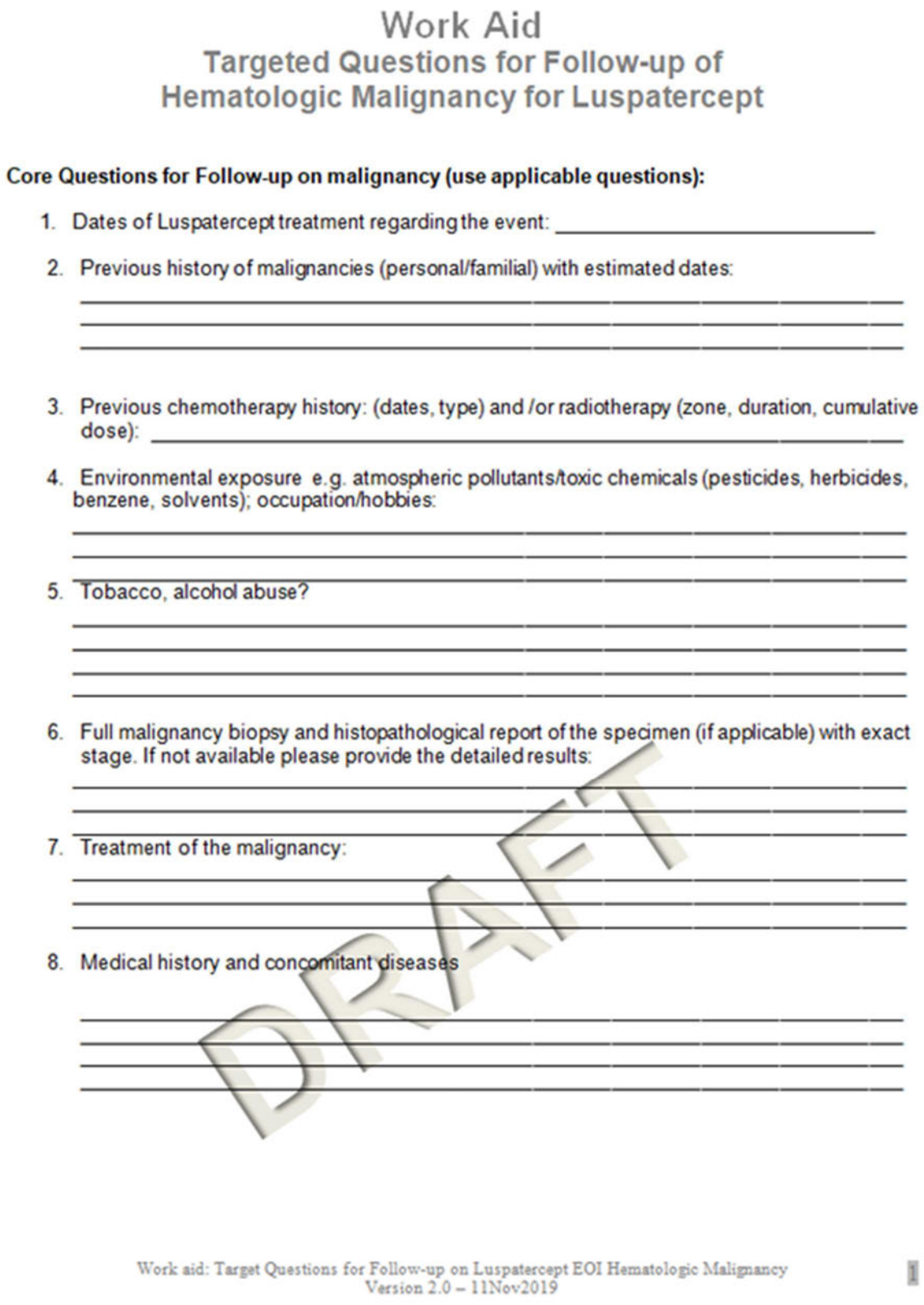
8) Specify AML type if not included in the bone marrow or cytogenetics documents.

9) Please provide information regarding environmental exposure, if any.

10) Relevant medical history including familial history of malignancies and previous antineoplastic treatments the patient may have received including radiotherapy with radiation zone and cumulative dose if any.

11) Other concomitant medications (administered prior to the event) including indications, therapy dates and dosing information.

Figure 4: **Targeted Questions for Follow-up of Haematologic Malignancy for Luspatercept**



Work Aid
Targeted Questions for Follow-up of
Hematologic Malignancy for Luspatercept

Core Questions for Follow-up on malignancy (use applicable questions):

1. Dates of Luspatercept treatment regarding the event: _____
2. Previous history of malignancies (personal/familial) with estimated dates:
   _____
   _____
   _____
3. Previous chemotherapy history: (dates, type) and /or radiotherapy (zone, duration, cumulative dose): _____
4. Environmental exposure e.g. atmospheric pollutants/toxic chemicals (pesticides, herbicides, benzene, solvents); occupation/hobbies:
   _____
   _____
   _____
5. Tobacco, alcohol abuse?
   _____
   _____
   _____
   _____
6. Full malignancy biopsy and histopathological report of the specimen (if applicable) with exact stage. If not available please provide the detailed results:
   _____
   _____
   _____
7. Treatment of the malignancy:
   _____
   _____
   _____
8. Medical history and concomitant diseases
   _____
   _____
   _____
   _____

DRAFT

Work aid: Target Questions for Follow-up on Luspatercept EOI Hematologic Malignancy
Version 2.0 – 11Nov2019 1

Work Aid
Targeted Questions for Follow-up of Hematologic Malignancy for Luspatercept

In addition to the Core Questions specific information should be requested based on the risk factors for individual types of hematologic Cancer:

AML Specific Questions:

1) Specify AML type if not included in the bone marrow or cytogenetics documents.

2) Relevant medical history including familial history of malignancies and previous antineoplastic treatments the patient may have received including radiotherapy with radiation zone and cumulative dose if any.

3) Other concomitant medications (administered prior to the event) including indications, therapy dates and dosing information.

Lymphoma:

Medical conditions that compromise the immune system:

☐ Autoimmune diseases

☐ Diseases requiring immune suppressive therapy-organ transplant

☐ Infection with HIV, Epstein-Barr virus+++, Helicobacter pylori, hepatitis B or C, human T-lymphotrophic virus type I,

☐ Burkitt's lymphoma

Figure 5: **Event-Specific Questionnaire for Healthcare Professionals – Pregnancy Follow-up**

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for HCP – Pregnancy Follow-up
(Patient or Partner of Patient)
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date:		Period Covered: [Date] to [Date]	
Reporter Information			
REPORTER NAME:			
ADDRESS:		CITY, STATE, ZIP, COUNTRY:	
PHONE NO.:		FAX NO.:	
Name of Patient or Pregnant Partner of Male Patient			
Current Pregnancy			
Prenatal Tests			
	Date	*Result*	
Ultrasound			
Ultrasound			
Ultrasound			
Amniocentesis			
Maternal Serum AFP			
Other tests, specify			

Medications/Treatments (including herbal, alternative and over the counter medicines and dietary supplements) During Pregnancy

DRUG	*START DATE*	*STOP DATE/ CONTINUING*	*INDICATION*

Adverse Event(s) During Pregnancy

Event(s)	SERIOUS NO	SERIOUS YES	SERIOUS CRITERIA[1]	START DATE	STOP DATE	CAUSAL RELATIONSHIP TO CELGENE PRODUCT YES	NO	If No, what medications, disease states etc played a role in the event.

[1] Serious Criteria: 1) death, 2) life-threatening, 3) required inpatient hospitalization or prolongation of existing hospitalization, 4) a persistent or significant disability/incapacity, 5) a congenital anomaly/birth defect, 6) medically significant

SIGNATURE OF PERSON COMPLETING THIS FORM _____ DATE _____

MCN:

Figure 6: **Event-Specific Questionnaire for Primary Care Physician or Paediatrician –Infant Follow-up**

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up
Telephone: 1-800-721-5072
Fax: 609-818-3804
Email: Worldwide.Safety@BMS.com

Date: _____

Name of Patient or Name of Male Patient of Partner (Mother)_____

Name of Infant (if known) _____

Please provide information for the period from **[Date]** to **[Date]**.

Anomalies Diagnosed Since Initial Report:

_____

☐ None

Developmental Assessment:

☐ Normal

☐ Abnormal, specify _____

Infant Illnesses, Hospitalizations, Drug Therapies:

Infant Illnesses	Hospitalized?	Drug Therapies
	☐Yes ☐ No	
	☐Yes ☐ No	
	☐Yes ☐ No	
	☐Yes ☐ No	
	☐Yes ☐ No	

SIGNATURE OF PERSON COMPLETING THIS FORM _____ DATE _____

MCN:

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Prior to the launch of luspatercept in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the NCA.

The MAH shall ensure that in each member state where luspatercept is marketed, all HCPs who intend to prescribe luspatercept are provided with an HCP Information Pack, containing the following:

1. Information on where to find latest SmPC;
2. HCP Checklist;
3. Patient Card (for WCBP only).

Healthcare Professional Checklist

The HCP Checklist is to be used before initiating treatment, at each administration, and then at regular intervals when performing follow-up.

The HCP Checklist shall contain the following key messages:

- Information on studies in animals showing luspatercept reproductive and embryo-foetal toxicity and is therefore contraindicated during pregnancy.
- Reminder that luspatercept is contraindicated during pregnancy and in WCBP not using effective contraception.
- Need to provide counselling before treatment initiation and regularly thereafter regarding the potential teratogenic risk of luspatercept and required actions to minimise this risk.
- A pregnancy test must be carried out and negative results verified by the prescriber before starting treatment. It must be repeated at suitable intervals.
- Patients must use highly effective contraception during the treatment with luspatercept.
- While on treatment, women must not become pregnant. If a woman becomes pregnant or wants to become pregnant, luspatercept should be discontinued. Women of childbearing potential must use highly effective contraception during treatment with luspatercept and for at least 3 months following discontinuation of treatment with luspatercept.
- Need to provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy.
- Should a pregnancy occur during treatment or within 3 months following discontinuation of treatment with luspatercept, remind the patient that it should be reported to the HCP, NCA, and/or to Celgene by contacting the local e-mail address or visiting the URL provided in the material, irrespective of adverse outcomes observed.

Patient Card (for WCBP only)

The Patient Card is to be handed to WCBP by the HCP at the time of treatment initiation. The HCP is to request that the WCBP confirm whether they have the Patient Card prior to each subsequent administration and provide them with additional cards as needed.

The Patient Card shall contain the following key messages:

- Instructions to the WCBP on:
  - The need for a negative pregnancy test result prior to starting treatment with luspatercept in WCBP.
  - The need for WCBP to use at least one highly effective method of contraception during treatment with luspatercept and for at least 3 months following discontinuation.
  - The need to report to the doctor any suspected or confirmed pregnancy occurring during and for 3 months following discontinuation of treatment.