LUSPATERCEPT

SUMMARY OF THE RISK MANAGEMENT PLAN FOR REBLOZYL®

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of REBLOZYL® (Luspatercept) is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of REBLOZYL® (Luspatercept) in Switzerland is the "Arzneimittelinformation/Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bristol-Myers Squibb SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of REBLOZYL® (Luspatercept).

SUMMARY OF THE RISK MANAGEMENT PLAN

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 Nov 2018. 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 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 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.