ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Reblozyl 25 mg powder for solution for injection
Reblozyl 75 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Reblozyl 25 mg powder for solution for injection
Each vial contains 25 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

Reblozyl 75 mg powder for solution for injection
Each vial contains 75 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

Luspatercept is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy (see section 5.1).

Reblozyl is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent beta-thalassaemia (see section 5.1).

4.2 Posology and method of administration

Reblozyl treatment should be initiated by a physician experienced in treatment of haematological diseases.

Posology

Prior to each Reblozyl administration, the haemoglobin (Hb) level of patients should be assessed. In case of a red blood cell (RBC) transfusion occurring prior to dosing, the pre-transfusion Hb level must be considered for dosing purposes.

The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks.

- *Myelodysplastic syndromes*

In patients who are not RBC transfusion-free after at least 2 consecutive doses at the 1.0 mg/kg starting dose, the dose should be increased to 1.33 mg/kg. If patients are not RBC transfusion-free after at least 2 consecutive doses at the 1.33 mg/kg dose level, the dose should be increased to 1.75 mg/kg. The dose increase should not occur more frequently than every 6 weeks (2 administrations) and should not exceed the maximum dose of 1.75 mg/kg every 3 weeks. The dose should not be increased immediately after a dose delay.

For patients with a pre-dose Hb level of > 9 g/dL and who have not yet achieved transfusion independence, a dose increase may be required at the physician's discretion; the risk of Hb increasing above the target threshold with concomitant transfusion cannot be excluded.

If a patient loses response (i.e., transfusion independence), the dose should be increased by one dose level (see Table 1).

- *Transfusion-dependent β-thalassaemia*

In patients who do not achieve a response, defined as a reduction in RBC transfusion burden of at least a third after ≥ 2 consecutive doses (6 weeks), at the 1.0 mg/kg starting dose, the dose should be increased to 1.25 mg/kg. The dose should not be increased beyond the maximum dose of 1.25 mg/kg every 3 weeks.

If a patient loses response (if the RBC transfusion burden increases again after an initial response) the dose should be increased by one dose level (see Table 2).

- *Non-transfusion-dependent β-thalassaemia*

In patients who do not achieve or maintain a response, defined as an increase from baseline in pre-dose Hb of ≥1 g/dL, after ≥ 2 consecutive doses (6 weeks) at the same dose level (in absence of transfusions, i.e., at least 3 weeks after the last transfusion), the dose should be increased by one dose level (see Table 2). The dose should not exceed the maximum dose of 1.25 mg/kg every 3 weeks.

Increase to next dose level

Increase to next dose level based on current dose is provided below.

Table 1: Increase to next dose level for MDS

Current dose	Increased dose
0.8 mg/kg	1 mg/kg
1 mg/kg	1.33 mg/kg
1.33 mg/kg	1.75 mg/kg

Table 2: Increase to next dose level for β-thalassaemia

Current dose	Increased dose
0.6 mg/kg*	0.8 mg/kg
0.8 mg/kg	1 mg/kg
1 mg/kg	1.25 mg/kg

* Applicable only to non-transfusion-dependent β-thalassaemia.

Dose reduction and dose delay

In case of Hb increase > 2 g/dL within 3 weeks in absence of transfusion compared with the Hb value at previous dose, Reblozyl dose should be reduced by one dose level.

If the Hb is ≥ 11.5 g/dL in the absence of transfusion for at least 3 weeks, the dose should be delayed until the Hb is ≤ 11.0 g/dL. If there is also a concomitant rapid increase in Hb from the Hb value at previous dose (> 2 g/dL within 3 weeks in absence of transfusion), a dose reduction to one step down should be considered after the dose delay.

Dose should not be reduced below 0.8 mg/kg (for MDS or transfusion-dependent β-thalassaemia) and below 0.6 mg/kg (for non-transfusion-dependent β-thalassaemia).

Reduced dose during treatment with luspatercept are provided below.

Table 3: Reduced dose for MDS

Current dose	Reduced dose
1.75 mg/kg	1.33 mg/kg
1.33 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg

Table 4: Reduced dose for β-thalassaemia

Current dose	Reduced dose
1.25 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg
0.8 mg/kg	0.6 mg/kg*

* Applicable only to non-transfusion-dependent β-thalassaemia.

Dose modification due to adverse reactions

Instructions on dose interruptions or reductions for luspatercept treatment-related adverse reactions are outlined in Table 5.

Table 5: Dose modification instructions

Treatment-related adverse reactions*	Dose instructions
Grade 2 adverse reactions (see section 4.8), including Grade 2 hypertension (see sections 4.4 and 4.8)	• Interrupt treatment • Restart at previous dose when adverse reaction has improved or returned to baseline
Grade ≥ 3 hypertension (see sections 4.4 and 4.8)	• Interrupt treatment • Restart at reduced dose once the blood pressure is controlled as per dose reduction guidance
Other persistent Grade ≥ 3 adverse reactions (see section 4.8)	• Interrupt treatment • Restart at previous dose or at reduced dose when adverse reaction has improved or returned to baseline as per dose reduction guidance
Extramedullary haemopoiesis (EMH) masses causing serious complications (see sections 4.4 and 4.8)	• Discontinue treatment

***** Grade 1: mild; Grade 2: moderate; Grade 3: severe; and Grade 4: life-threatening.

Missed doses
In case of a missed or delayed scheduled treatment administration, the patient should be administered Reblozyl as soon as possible and dosing continued as prescribed with at least 3 weeks between doses.

Patients experiencing a loss of response
If patients experience a loss of response to Reblozyl, causative factors (e.g. a bleeding event) should be assessed. If typical causes for a loss of haematological response are excluded, dose increase should be considered as described above for the respective indication being treated (see Table 1 and Table 2).

Discontinuation
Reblozyl should be discontinued if patients do not experience a reduction in transfusion burden (for transfusion-dependent MDS or β-thalassaemia patients) or an increase from baseline Hb in the absence of transfusions (for non-transfusion-dependent β-thalassaemia patients) after 9 weeks of treatment (3 doses) at the maximum dose level, if no alternative explanations for response failure are found (e.g. bleeding, surgery, other concomitant illnesses) or if unacceptable toxicity occurs at any time.

Special populations

Elderly
No starting dose adjustment is required for Reblozyl (see section 5.2). Limited data are available in β-thalassaemia patients ≥ 60 years of age.

Hepatic impairment
No starting dose adjustment is required for patients with total bilirubin (BIL) > upper limit of normal (ULN) and/or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 3 x ULN (see section 5.2).
No specific dose recommendation can be made for patients with ALT or AST ≥ 3 x ULN or liver injury CTCAE Grade ≥ 3 due to lack of data (see section 5.2).

Renal impairment
No starting dose adjustment is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] < 90 and ≥ 30 mL/min/1.73 m^2). Only limited data are available for patients with moderate renal impairment.
No specific dose recommendation can be made for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) due to lack of clinical data (see section 5.2). Patients with renal impairment at baseline have been observed to have higher exposure (see section 5.2). Consequently, these patients should be closely monitored for adverse reactions and dose adjustment should be managed accordingly (see Table 5).

Paediatric population
There is no relevant use of Reblozyl in the paediatric population for the indication of myelodysplastic syndromes, or in paediatric patients less than 6 years of age in β-thalassaemia. The safety and efficacy of Reblozyl in the paediatric patients aged from 6 years to less than 18 years have not yet been established in β-thalassaemia. For non-clinical data, see section 5.3.

Method of administration
For subcutaneous use.

After reconstitution, Reblozyl solution should be injected subcutaneously into the upper arm, thigh or abdomen. The exact total dosing volume of the reconstituted solution required for the patient should be calculated and slowly withdrawn from the single-dose vial(s) into a syringe.

The recommended maximum volume of medicinal product per injection site is 1.2 mL. If more than 1.2 mL is required, the total volume should be divided into separate similar volume

injections and administered across separate sites using the same anatomical location but on opposite sides of the body.

If multiple injections are required, a new syringe and needle must be used for each subcutaneous injection. No more than one dose from a vial should be administered.

If the Reblozyl solution has been refrigerated after reconstitution, it should be removed from the refrigerator 15-30 minutes prior to injection to allow it to reach room temperature. This will allow for a more comfortable injection.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).
- Patients requiring treatment to control the growth of EMH masses (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Thromboembolic events
In β-thalassaemia patients, thromboembolic events (TEEs) were reported in 3.6% (8/223) of patients treated with luspatercept in the double-blind phase of the pivotal study in transfusion-dependent patients and in 0.7% (1/134) of patients during the open-label phase of the pivotal study in non-transfusion-dependent patients. Reported TEEs included deep vein thrombosis (DVT), portal vein thrombosis, pulmonary emboli, ischaemic stroke and superficial thrombophlebitis (see section 4.8). All patients with TEEs were splenectomised and had at least one other risk factor for developing TEE (e.g. history of thrombocytosis or concomitant use of hormone replacement therapy). The occurrence of TEE was not correlated with elevated Hb levels. The potential benefit of treatment with luspatercept should be weighed against the potential risk of TEEs in β-thalassaemia patients with a splenectomy and other risk factors for developing TEE. Thromboprophylaxis according to current clinical guidelines should be considered in patients with β-thalassaemia at higher risk.

Extramedullary haemopoiesis masses
In transfusion-dependent β-thalassaemia patients, extramedullary haemopoiesis (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. Spinal cord compression symptoms due to EMH masses occurred in 1.9% (6/315) of patients treated with luspatercept (see section 4.8).

In non-transfusion-dependent 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 (see section 4.8).

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.

Increased blood pressure
In MDS and β-thalassaemia pivotal studies, patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of 5 mmHg from baseline (see section 4.8). An increased incidence of hypertension was observed in the first 12 months of treatment in non-transfusion-dependent β-thalassaemia patients treated with luspatercept (see section 4.8).

The treatment must be started only if the blood pressure is adequately controlled. Blood pressure should be monitored prior to each luspatercept administration. Luspatercept dose may require adjustment or may be delayed and patients should be treated for hypertension as per current clinical guidelines (see Table 5 in section 4.2). The potential benefit of treatment with Reblozyl should be re-evaluated in case of persistent hypertension or exacerbations of preexisting hypertension.

Traumatic fracture
In non-transfusion-dependent β-thalassaemia patients, traumatic fractures were observed in 8.3% (8/96) of patients treated with luspatercept. Patients should be informed of the risk of traumatic fracture.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No formal clinical interaction studies have been performed. Concurrent use of iron-chelating agents had no effect on luspatercept pharmacokinetics.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females
Women of childbearing potential have to use effective contraception during treatment with Reblozyl and for at least 3 months after the last dose. Prior to starting treatment with Reblozyl, a pregnancy test has to be performed for women of childbearing potential.

Pregnancy
Treatment with Reblozyl should not be started if the woman is pregnant (see section 4.3). There are no data from the use of Reblozyl in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Reblozyl is contraindicated during pregnancy (see section 4.3). If a patient becomes pregnant, Reblozyl should be discontinued.

Breast-feeding
It is unknown whether luspatercept or its metabolites are excreted in human milk. Luspatercept was detected in the milk of lactating rats (see section 5.3). Because of the unknown adverse effects of luspatercept in newborns/infants, a decision must be made whether to discontinue breast-feeding during therapy with Reblozyl and for 3 months after the last dose or to discontinue Reblozyl therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
The effect of luspatercept on fertility in humans is unknown. Based on findings in animals, luspatercept may compromise female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Reblozyl may have a minor influence on the ability to drive and use machines. The ability to react when performing these tasks may be impaired due to risks of fatigue, vertigo, dizziness or

syncope (see section 4.8). Therefore, patients should be advised to exercise caution until they know of any impact on their ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Myelodysplastic syndromes
The most frequently reported adverse drug reactions in patients receiving Reblozyl (at least 15% of patients) were fatigue, diarrhoea, asthenia, nausea, dizziness, back pain and headache. The most commonly reported Grade ≥ 3 adverse drug reactions (at least 2% of patients) included syncope/presyncope, fatigue, hypertension and asthenia. The most commonly reported serious adverse drug reactions (at least 2% of patients) were urinary tract infection, back pain and syncope.

Asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment.

Treatment discontinuation due to an adverse reaction occurred in 2.0% of patients treated with luspatercept. The adverse reactions leading to treatment discontinuation in the luspatercept treatment arm were fatigue and headache.

Transfusion-dependent β-thalassaemia
The most frequently reported adverse drug reactions in patients receiving Reblozyl (at least 15% of patients) were headache, bone pain and arthralgia. The most commonly reported Grade ≥ 3 adverse drug reaction was hyperuricaemia. The most serious adverse reactions reported included thromboembolic events of deep vein thrombosis, ischaemic stroke portal vein thrombosis and pulmonary embolism (see section 4.4).

Bone pain, asthenia, fatigue, dizziness and headache occurred more frequently during the first 3 months of treatment.

Treatment discontinuation due to an adverse reaction occurred in 2.6% of patients treated with luspatercept. The adverse reactions leading to treatment discontinuation in the luspatercept treatment arm were arthralgia, back pain, bone pain and headache.

Non-transfusion-dependent β-thalassaemia
The most frequently reported adverse drug reactions in patients receiving Reblozyl (at least 15% of patients) were bone pain, headache, arthralgia, back pain, prehypertension and hypertension. The most commonly reported Grade ≥ 3 and most serious adverse reaction (at least 2% of patients) reported was traumatic fracture. Spinal cord compression due to EMH masses occurred in 1% of patients.

Bone pain, back pain, upper respiratory tract infection, arthralgia, headache and prehypertension occurred more frequently during the first 3 months of treatment.

The majority of adverse drug reactions were non-serious and did not require discontinuation. Treatment discontinuation due to an adverse reaction occurred in 3.1% of patients treated with luspatercept. Adverse reactions leading to treatment discontinuation were spinal cord compression, extramedullary haemopoiesis and arthralgia.

Tabulated list of adverse reactions
The highest frequency for each adverse reaction that was observed and reported in patients in the pivotal studies in MDS, β-thalassaemia and the long-term follow-up study is shown in Table 6 below. The adverse reactions are listed below by body system organ class and preferred

term. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

Table 6. Adverse drug reactions (ADRs) in patients treated with Reblozyl for MDS and / or β-thalassaemia in the three pivotal studies

System organ class	Preferred term	Frequency (all grades) for MDS	Frequency (all grades) for β-thalassaemia
Infections and infestations	bronchitis	Very common	Common[a]
	urinary tract infection	Very common	Common[a]
	upper respiratory tract infection	Common	Very common[a]
	influenza	Common	Very common
Blood and lymphatic system disorders	extramedullary haemopoiesis [VI]	Not known [VII]	Common
Immune system disorders	hypersensitivity [I, VI]	Common	Common
Metabolism and nutrition disorders	hyperuricaemia	Common	Common
Psychiatric disorders	insomnia	Common	Very common[b]
	anxiety		Common
	irritability		Common
Nervous system disorders	dizziness	Very common	Very common
	headache	Very common	Very common
	migraine		Common[b]
	spinal cord compression[VI]		Common
	syncope/presyncope	Common	Common[a]
Ear and labyrinth disorders	vertigo/vertigo positional	Common	Common[a]
Vascular disorders	prehypertension		Very common[b]
	hypertension[II, VI]	Common	Very common
	thromboembolic events[IV, VI]	Common	Common
Respiratory, thoracic and mediastinal disorders	cough	Very common	
	epistaxis	Common	Common[b]
	dyspnoea	Very common	Common
Gastrointestinal disorders	abdominal pain	Common	Very common[b]
	diarrhoea	Very common	Very common[a]
	nausea	Very common	Very common
Hepatobiliary disorders	alanine aminotransferase increased		Common[V]
	aspartate aminotransferase increased		Very common[V]
	blood bilirubin increased		Very common[V]

System organ class	Preferred term	Frequency (all grades) for MDS	Frequency (all grades) for β-thalassaemia
Musculoskeletal and connective tissue disorders	back pain	Very common	Very common
	arthralgia[VI]	Common	Very common
	bone pain[VI]	Common	Very common
Renal and urinary disorders	proteinuria		Common[b]
	albuminuria		Common[b]
General disorders and administration site conditions	influenza-like illness	Common	
	fatigue	Very common	Very common[a]
	asthenia	Very common	Very common
	injection site reactions [III, VI]	Common	Common
Injury, poisoning and procedural complications	traumatic fracture[VI]		Common[b]

The three pivotal studies are ACE-536-MDS-001(MDS), ACE-536-B-THAL-001 (transfusion-dependent β-thalassaemia) and ACE-536-B-THAL-002 (non-transfusion-dependent β-thalassaemia).
[I] Hypersensitivity includes eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption.
[II] Hypertension includes essential hypertension, hypertension and hypertensive crisis.
[III] Injection site reactions include injection site erythema, injection site pruritus, injection site swelling and injection site rash.
[IV] Thromboembolic events include deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism.
[V] Frequency is based on laboratory values of any grade.
[VI] See section 4.8 Description of selected adverse reactions.
[VII] Reported only in post-marketing.

[a] ADRs observed in transfusion-dependent β-thalassaemia study ACE-536-B-THAL-001.
[b] ADRs observed in non-transfusion-dependent β-thalassaemia study ACE-536-B-THAL-002.

Description of selected adverse reactions

Bone pain
Bone pain was reported in 36.5% of non-transfusion-dependent β-thalassaemia patients treated with luspatercept (placebo 6.1%), in 19.7% of transfusion-dependent β-thalassaemia patients treated with luspatercept (placebo 8.3%) and in 2.6% of MDS patients treated with luspatercept (placebo 3.9%). In non-transfusion-dependent β-thalassaemia patients treated with luspatercept, most events (32/35) were Grade 1-2, with 3 events Grade 3. No patient discontinued due to bone pain. In transfusion-dependent β-thalassaemia patients treated with luspatercept, bone pain was most common in the first 3 months (16.6%) compared to months 4-6 (3.7%). Most events (41/44 events) were Grade 1-2, with 3 events Grade 3. One of the 44 events was serious, and 1 event led to treatment discontinuation.

Arthralgia
Arthralgia was reported in 29.2% of non-transfusion-dependent β-thalassaemia patients treated with luspatercept (placebo 14.3%), in 19.3% of transfusion-dependent β-thalassaemia patients treated with luspatercept (placebo 11.9%) and in 5.2% of MDS patients treated with luspatercept (placebo 11.8%). In non-transfusion-dependent β-thalassaemia patients treated with luspatercept, most events (26/28) were Grade 1-2, with 2 events Grade 3. In the transfusion-dependent and non-transfusion-dependent β-thalassaemia patients treated with luspatercept, arthralgia led to treatment discontinuation in 2 patients (0.9%) and 1 patient (1.0%), respectively.

Hypertension
Patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of 5 mmHg from baseline not observed in patients receiving placebo. Hypertension was reported in 8.5% of MDS patients treated with luspatercept (placebo 9.2%), in 19.8% of non-transfusion-dependent β-thalassaemia patients treated with luspatercept (placebo 2.0%), and in 8.1% of transfusion-dependent β-thalassaemia patients treated with luspatercept (placebo 2.8%). See section 4.4.

An increased incidence of hypertension was observed over time in the first 8-12 months in non-transfusion-dependent β-thalassaemia patients treated with luspatercept. See section 4.4.

Grade 3 hypertension events were reported in MDS patients, for 5 patients (3.3%) treated with luspatercept and in 3 patients (3.9%) receiving placebo. In non-transfusion-dependent β-thalassaemia patients, most events (16/19) were Grade 1-2 with 3 events Grade 3 (3.1%) in patients treated with luspatercept (0.0% placebo). In transfusion-dependent β-thalassaemia patients, Grade 3 events were reported in 4 patients (1.8%) treated with luspatercept (0.0% placebo). See section 4.4.

Hypersensitivity
Hypersensitivity-type reactions (including eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption) were reported in 4.6% of MDS patients (placebo 2.6%) and in 4.5% of transfusion-dependent β-thalassaemia patients treated with luspatercept (placebo 1.8%). In clinical studies, all events were Grade 1-2. In transfusion-dependent β-thalassaemia patients treated with luspatercept, hypersensitivity led to treatment discontinuation in 1 patient (0.4%). Face oedema occurred in 3.1% (placebo 0.0%) of non-transfusion-dependent β-thalassaemia patients.

Injection site reactions
Injection site reactions (including injection site erythema, injection site pruritus, injection site swelling and injection site rash) were reported in 5.2% of non-transfusion-dependent β-thalassaemia patients (placebo 0.0%), in 3.9% of MDS patients (placebo 0.0%) and in 2.2% of transfusion-dependent β-thalassaemia patients (placebo 1.8%). In clinical studies, all events were Grade 1 and none led to discontinuation.

Thromboembolic events
Thromboembolic events (including deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism) occurred in 3.6% of transfusion-dependent β-thalassaemia patients receiving luspatercept (placebo 0.9%). In the open-label phase of the pivotal study in non-transfusion-dependent β-thalassaemia, thromboembolic event (superficial thrombophlebitis) occurred in 0.7% of patients. All events were reported in patients who had undergone splenectomy and had at least one other risk factor. No difference in TEEs was observed between luspatercept and placebo arms in MDS patients. See section 4.4.

Extramedullary haemopoiesis masses
EMH masses occurred in 10/315 (3.2%) transfusion-dependent β-thalassaemia patients receiving luspatercept (placebo 0.0%). Five events were Grade 1-2, 4 events were Grade 3, and 1 event was Grade 4. Three patients discontinued due to EMH masses. See section 4.4.

EMH masses occurred in 6/96 (6.3%) non-transfusion-dependent β-thalassaemia patients receiving luspatercept (placebo 2%). Most (5/6) were Grade 2 and 1 was Grade 1. One patient discontinued due to EMH masses. 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. Most (7/8) were Grade 1-2 and manageable with standard clinical practice. In 6/8 patients, luspatercept was continued after onset of event. See section 4.4.

EMH masses may also occur after extended treatment with luspatercept (i.e. after 96 weeks).

Spinal cord compression
Spinal cord compression or symptoms due to EMH masses occurred in 6/315 (1.9%) transfusion-dependent β-thalassaemia patients receiving luspatercept (placebo 0.0%). Four patients discontinued treatment due to Grade ≥ 3 symptoms of spinal cord compression.

Spinal cord compression due to EMH masses occurred in 1/96 (1.0%) non-transfusion-dependent β-thalassaemia patient with a history of EMH masses receiving luspatercept (placebo 0.0%). This patient discontinued treatment due to Grade 4 spinal cord compression. See section 4.4.

Traumatic fracture
Traumatic fracture occurred in 8 (8.3%) non-transfusion-dependent β-thalassaemia patients receiving luspatercept (placebo 2.0%), and in 1 (0.4%) transfusion-dependent β-thalassaemia patient receiving luspatercept (placebo 0.0%). In non-transfusion-dependent β-thalassaemia patients, Grade ≥ 3 events were reported for 4 patients (4.2%) treated with luspatercept and in 1 patient (2.0%) receiving placebo.

Immunogenicity
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 transfusion-dependent and non-transfusion-dependent β-thalassaemia, an analysis of 380 β-thalassaemia patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 7 (1.84%) β-thalassaemia patients tested positive for treatment-emergent anti-luspatercept antibodies, including 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 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 anti-luspatercept antibodies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose with luspatercept may cause an increase of Hb values above the desired level. In the event of an overdose, treatment with luspatercept should be delayed until Hb is ≤ 11 g/dL.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic preparations, other antianaemic preparations, ATC code: B03XA06.

Mechanism of action
Luspatercept, an erythroid maturation agent, is a recombinant fusion protein that binds selected transforming growth factor-β (TGF-β) superfamily ligands. By binding to specific endogenous ligands (e.g. GDF-11, activin B) luspatercept inhibits Smad2/3 signalling, resulting in erythroid

maturation through differentiation of late-stage erythroid precursors (normoblasts) in the bone marrow. Smad2/3 signalling is abnormally high in disease models characterised by ineffective erythropoiesis, i.e. MDS and β-thalassaemia, and in the bone marrow of MDS patients.

Clinical efficacy and safety

Myelodysplastic syndromes
The efficacy and safety of luspatercept were evaluated in a Phase 3 multicentre, randomised, double-blind, placebo-controlled study MEDALIST (ACE-536-MDS-001) in adult patients with anaemia requiring RBC transfusions (≥ 2 units/8 weeks) due to International Prognostic Scoring System-Revised (IPSS-R) very low-, low- or intermediate-risk MDS who have ring sideroblasts (≥ 15%). Patients were required to have either received prior treatment with an erythropoiesis-stimulating agent (ESA) with inadequate response, to be ineligible for ESAs (determined to be unlikely to respond to ESA treatment with serum erythropoietin (EPO) > 200 U/L), or intolerant to ESA treatment. Patients with deletion 5q (del5q) MDS were excluded from the study.

Patients in both arms were treated for 24 weeks, then continued treatment if they had demonstrated clinical benefit and absence of disease progression. The study was unblinded for analyses when all patients had at least received 48 weeks of treatment or discontinued treatment.

A total of 229 patients were randomised to receive luspatercept 1.0 mg/kg (n=153) or placebo (n=76) subcutaneously every 3 weeks. A total of 128 (83.7%) and 68 (89.5%) patients receiving luspatercept and placebo respectively completed 24 weeks of treatment. A total of 78 (51%) and 12 (15.8%) patients receiving luspatercept and placebo respectively completed 48 weeks of treatment. Dose titration up to 1.75 mg/kg was allowed. Dose could be delayed or reduced depending upon Hb level. All patients were eligible to receive best supportive care (BSC), which included RBC transfusions, iron-chelating agents, use of antibiotic, antiviral and antifungal therapy, and nutritional support, as needed. The key baseline disease characteristics in patients with MDS in study ACE-536-MDS-001 are shown in Table 7.

Table 7. Baseline characteristics in MDS patients with <5% marrow blasts in study ACE-536-MDS-001

	Luspatercept (N=153)	**Placebo (N=76)**
Demographics		
Age[a] (years) Median (min, max)	71 (40, 95)	72 (26, 91)
Age categories, n (%) <64 years 65-74 years ≥75	 29 (19.0) 72 (47.1) 52 (34.0)	 16 (21.1) 29 (38.2) 31 (40.8)
Sex, n (%) Male Female	 94 (61.4) 59 (38.6)	 50 (65.8) 26 (34.2)
Race, n (%) Black White Not collected or reported Other	 1 (0.7) 107 (69.9) 44 (28.8) 1 (0.7)	 0 (0.0) 51 (67.1) 24 (31.6) 1 (1.3)
Disease characteristics		
Serum EPO (U/L) categories[b], n (%) < 200 200 to 500 > 500 Missing	 88 (57.5) 43 (28.1) 21 (13.7) 1 (0.7)	 50 (65.8) 15 (19.7) 11 (14.5) 0

	Luspatercept (N=153)	Placebo (N=76)
Serum ferritin (µg/L) Median (min, max)	1089.2 (64, 5968)	1122.1 (165, 5849)
IPSS-R classification risk category, n (%)		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75.0)
Intermediate	25 (16.3)	13 (17.1)
Other	1 (0.7)	0
Baseline RBC Transfusion burden/ 8 weeks[c], n (%)		
≥ 6 units	66 (43.1)	33 (43.4)
≥ 6 and < 8 units	35 (22.9)	15 (20.2)
≥ 8 and < 12 units	24 (15.7)	17 (22.4)
≥ 12 units	7 (4.6)	1 (1.3)
< 6 units	87 (56.9)	43 (56.6)
≥ 4 and < 6 units	41 (26.8)	23 (30.3)
< 4 units	46 (30.1)	20 (26.3)
Hb[d] (g/dL) Median (min, max)	7.6 (6, 10)	7.6 (5, 9)
SF3B1, n (%)		
Mutated	149 (92.2)	65 (85.5)
Unmutated	12 (7.8)	10 (13.2)
Missing	0	1 (1.3)

EPO=erythropoietin; Hb=haemoglobin; IPSS-R=International Prognostic Scoring System-Revised
[a] Age was calculated based on the informed consent signing date.
[b] Baseline EPO was defined as the highest EPO value within 35 days of the first dose of study drug.
[c] Collected over 16 weeks prior to randomisation.
[d] Baseline Hb was defined as the last value measured on or before the date of the first dose of investigational product (IP). After applying the 14/3 day rule, baseline Hb was defined as the lowest Hb value that was within 35 days on or prior to the first dose of IP.

The efficacy results are summarised below.

Table 8. Efficacy results in patients with MDS in study ACE-536-MDS-001

Endpoint	Luspatercept (N=153)	Placebo (N=76)
Primary endpoint		
• **RBC-TI ≥ 8 weeks (Week 1-24)** Number of responders (response rate %)	58 (37.9)	10 (13.2)
• Common risk difference on response rate (95% CI)	24.56 (14.48, 34.64)	
Odds ratio (95% CI)[a]	5.065 (2.278, 11.259)	
p-value[a]	< 0.0001	
Secondary endpoints		
• **RBC-TI ≥ 12 weeks (Weeks 1-24)** Number of responders (response rate %)	43 (28.1)	6 (7.9)
• Common risk difference on response rate (95% CI)	20.00 (10.92, 29.08)	
Odds ratio (95% CI)[a]	5.071 (2.002, 12.844)	
p-value[a]	0.0002	
• **RBC-TI ≥ 12 weeks (Weeks 1-48)** Number of responders (response rate %)[b]	51 (33.3)	9 (11.8)
• Common risk difference on response rate (95% CI)	21.37 (11.23, 31.51)	
Odds ratio (95% CI)[a]	4.045 (1.827, 8.956)	
p-value[a]	0.0003	

Endpoint	Luspatercept (N=153)	Placebo (N=76)
Transfusion event frequency[c]		
• **Weeks 1-24**		
Interval transfusion rate (95% CI)	6.26 (5.56, 7.05)	9.20 (7.98, 10.60)
Relative risk *vs.* placebo	0.68 (0.58, 0.80)	
• **Weeks 25-48**		
Interval transfusion rate (95% CI)	6.27 (5.47, 7.19)	8.72 (7.40, 10.28)
Relative risk *vs.* placebo	0.72 (0.60, 0.86)	
RBC Transfusion units[c]		
• **Weeks 1-24**		
Baseline transfusion burden <6 units/8 weeks		
LS Mean (SE)	7.2 (0.58)	12.8 (0.82)
95% CI for LS mean	6.0, 8.3	11.1, 14.4
LS mean difference (SE) (luspatercept *vs.* placebo)	-5.6 (1.01)	
95% CI for LS mean difference	-7.6, -3.6	
Baseline transfusion burden ≥6 units/8 weeks		
LS Mean (SE)	18.9(0.93)	23.7(1.32)
95% CI for LS mean	17.1, 20.8	21.1, 26.4
LS mean difference (SE) (luspatercept *vs.* placebo)	-4.8 (1.62)	
95% CI for LS mean difference	-8.0, -1.6	
• **Weeks 25-48**		
Baseline transfusion burden <6 units/8 weeks		
LS Mean (SE)	7.5 (0.57)	11.8(0.82)
95% CI for LS mean	6.3, 8.6	10.1, 13.4
LS mean difference (SE) (luspatercept *vs.* placebo)	-4.3 (1.00)	
95% CI for LS mean difference	-6.3, -2.3	
Baseline transfusion burden ≥6 units/8 weeks		
LS Mean (SE)	19.6(1.13)	22.9(1.60)
95% CI for LS mean	17.4, 21.9	19.7, 26.0
LS mean difference (SE) (luspatercept *vs.* placebo)	-3.3(1.96)	
95% CI for LS mean difference	-7.1, 0.6	

RBC-TI: RBC Transfusion Independent; CI: confidence interval; CMH = Cochran-Mantel-Haenszel;
[a] CMH test stratified for average baseline transfusion burden (≥ 6 units *vs.* < 6 units per 8 weeks), and baseline IPSS-R score (very low or low *vs.* intermediate).
[b] After the Week 25 disease assessment visit, patients who were no longer deriving benefit discontinued therapy; few placebo patients contributed data for evaluation at the later timepoint compared with luspatercept (n=12 *vs.* n=78 respectively).
[c] Post-hoc analysis using baseline imputation.

A treatment effect in favour of luspatercept over placebo was observed in most subgroups analysed using transfusion independence ≥ 12 weeks (during week 1 to week 24), including patients with high baseline endogenous EPO level (200-500 U/L) (23.3% *vs.* 0%, explorative analysis).

Only limited data are available for the group with transfusion burden of ≥ 8 units/8 weeks. Safety and efficacy have not been established in patients with a transfusion burden of > 12 units/8 weeks.

Exploratory findings

Table 9. Exploratory efficacy results in patients with MDS in study ACE-536-MDS-001

Endpoint	Luspatercept (N=153)	Placebo (N=76)
mHI-E[a]		
• **Weeks 1-24**		
Number of responders (response rate %)	81 (52.9)	9 (11.8)
(95% CI)	(44.72, 61.05)	(5.56, 21.29)
RBC transfusion reduction of 4 units/8 weeks, n (%)	52/107 (48.6)	8/56 (14.3)
Mean Hb increase of ≥ 1.5 g/dL for 8 weeks, n (%)	29/46 (63.0)	1/20 (5.0)
• **Weeks 1-48**		
Number of responders (response rate %)	90 (58.8)	13 (17.1)
(95% CI)	(50.59, 66.71)	(9.43, 27.47)
RBC transfusion reduction of 4 units/8 weeks, n (%)	58/107 (54.2)	12/56 (21.4)
Mean Hb increase of ≥ 1.5 g/dL for 8 weeks, n (%)	32/46 (69.6)	1/20 (5.0)
Mean change from baseline in mean serum ferritin with imputation by baseline (ITT population)		
Mean change from baseline in mean serum ferritin averaged over Weeks 9 through 24 (µg/L)[b]		
LS Mean (SE)	9.9 (47.09)	190.0 (60.30)
95% CI for LS Mean	-82.9, 102.7	71.2, 308.8
Treatment comparison (luspatercept *vs.* placebo)[c]		
LS mean difference (SE)	-180.1 (65.81)	
95% CI for LS mean difference	-309.8, -50.4	

Hb=haemoglobin

[a] mHI-E = modified haematological improvement – erythroid. The proportion of patients meeting the HI-E criteria as per International Working Group (IWG) 2006 criteria sustained over a consecutive 56-day period during the indicated treatment period. For patients with baseline RBC transfusion burden of ≥ 4 units/8 weeks, mHI-E was defined as a reduction in RBC transfusion of at least 4 units/8 weeks. For patients with baseline RBC transfusion burden of < 4 units/8 weeks, mHI-E was defined as a mean increase in Hb of ≥ 1.5 g/dL for 8 weeks in the absence of RBC transfusions.

[b] If a patient did not have a serum ferritin value within the designated postbaseline interval, the serum ferritin is imputed from the baseline value.

[c] Analysis of covariance was used to compare the treatment difference between groups (including nominal p-value), with the change in serum ferritin as the dependent variable, treatment group (2 levels) as a factor, and baseline serum ferritin value as covariates, stratified by average baseline RBC transfusion requirement (≥ 6 units *vs.* < 6 units of RBC per 8 weeks), and baseline IPSS-R (very low or low *vs.* intermediate).

The median duration of the longest RBC Transfusion Independent (RBC-TI) period among responders in the luspatercept treatment arm was 30.6 weeks.

A total of 62.1% (36/58) of the luspatercept responders who achieved RBC-TI ≥ 8 weeks from Week 1-24 had 2 or more episodes of RBC-TI at the time of analysis.

Transfusion-dependent β-thalassaemia

The efficacy and safety of luspatercept were evaluated in a Phase 3 multicentre, randomised, double-blind, placebo-controlled study BELIEVE (ACE-536-B-THAL-001) in adult patients with transfusion-dependent β-thalassaemia–associated anaemia who require RBC transfusions (6-20 RBC units/24 weeks) with no transfusion-free period > 35 days during that period.

Patients in both the luspatercept and placebo arms were treated for at least 48 and up to 96 weeks. After unblinding, placebo patients were able to cross-over to luspatercept.

A total of 336 adult patients were randomised to receive luspatercept 1.0 mg/kg (n=224) or placebo (n=112) subcutaneously every 3 weeks. Dose titration to 1.25 mg/kg was allowed. Dose could be delayed or reduced depending upon Hb level. All patients were eligible to receive BSC, which included RBC transfusions, iron-chelating agents, use of antibiotic, antiviral and

antifungal therapy, and nutritional support, as needed. The study excluded patients with Hb S/β-thalassaemia or alpha (α)-thalassaemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent DVT or stroke or recent use of ESA, immunosuppressant or hydroxyurea therapy were also excluded. The key baseline disease characteristics in patients with β-thalassaemia in study ACE-536-B-THAL-001 are shown in Table 10.

Table 10. Baseline characteristics in patients with transfusion-dependent β-thalassaemia in study ACE-536-B-THAL-001

	Luspatercept (N=224)	**Placebo (N=112)**
Demographics		
Age (years) Median (min, max)	30.0 (18, 66)	30.0 (18, 59)
Age categories, n (%) ≤ 32 > 32 to ≤ 50 > 50	129 (57.6) 78 (34.8) 17 (7.6)	63 (56.3) 44 (39.3) 5 (4.5)
Sex, n (%) Male Female	92 (41.1) 132 (58.9)	49 (43.8) 63 (56.3)
Race, n (%) Asian Black White Not collected or reported Other	81 (36.2) 1 (0.4) 122 (54.5) 5 (2.2) 15 (6.7)	36 (32.1) 0 60 (53.6) 5 (4.5) 11 (9.8)
Disease characteristics		
Pretransfusion Hb threshold[a], 12 week run-in (g/dL) Median (min, max)	9.30 (4.6, 11.4)	9.16 (6.2, 11.5)
Baseline transfusion burden 12 weeks Median (min, max) (units/12 weeks) (Week -12 to Day 1)	6.12 (3.0, 14.0)	6.27 (3.0, 12.0)
β-thalassaemia gene mutation grouping, n (%) β0/β0 Non-β0/β0 Missing[b]	68 (30.4) 155 (69.2) 1 (0.4)	35 (31.3) 77 (68.8) 0

[a]The 12-week pretransfusion threshold was defined as the mean of all documented pretransfusions Hb values for a patient during the 12 weeks prior to Cycle 1 Day 1.
[b] "Missing" category includes patients in the population who had no result for the parameter listed.

The study was unblinded for analyses when all patients had at least received 48 weeks of treatment or discontinued treatment.

The efficacy results are summarised below.

Table 11. Efficacy results in patients with transfusion-dependent β-thalassaemia in study ACE-536-B-THAL-001

Endpoint	Luspatercept (N=224)	Placebo (N=112)
Primary endpoint		
≥ 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks compared to the 12-week interval prior to treatment		
Weeks 13-24	48 (21.4)	5 (4.5)
Difference in proportions (95% CI)[a]	17.0 (10.4, 23.6)	
p-value[b]	< 0.0001	
Secondary endpoints		
Weeks 37-48	44 (19.6)	4 (3.6)
Difference in proportions (95% CI)[a]	16.1 (9.8, 22.3)	
p-value[b]	< 0.0001	
≥ 50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks compared to the 12-week interval prior to treatment		
Weeks 13-24	17 (7.6)	2 (1.8)
Difference in proportions (95% CI)[a]	5.8 (1.6, 10.1)	
p-value[b]	0.0303	
Weeks 37-48	23 (10.3)	1 (0.9)
Difference in proportions (95% CI)[a]	9.4 (5.0, 13.7)	
p-value[b]	0.0017	

CI: confidence interval.
[a] Difference in proportions (luspatercept + BSC – placebo + BSC) and 95% CIs estimated from the unconditional exact test.
[b] P-value from the Cochran Mantel-Haenszel test stratified by the geographical region.

Exploratory findings

Table 12. Exploratory efficacy results in patients with transfusion-dependent β-thalassaemia in study ACE-536-B-THAL-001

Endpoint	Luspatercept (N=224)	Placebo (N=112)
≥ 33% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks compared to the 12-week interval prior to treatment		
Any consecutive 12 weeks*	158 (70.5)	33 (29.5)
Difference in proportions (95% CI)[a]	41.1 (30.7, 51.4)	
Any consecutive 24 weeks*	92 (41.1)	3 (2.7)
Difference in proportions (95% CI)[a]	38.4 (31.3, 45.5)	
≥ 50% reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks compared to the 12-week interval prior to treatment		
Any consecutive 12 weeks*	90 (40.2)	7 (6.3)
Difference in proportions (95% CI)[a]	33.9 (26.1, 41.8)	
Any consecutive 24 weeks*	37 (16.5)	1 (0.9)
Difference in proportions (95% CI)[a]	15.6 (10.5, 20.8)	
Least square (LS) mean change from baseline in transfusion burden (RBC units/48 weeks)		
Weeks 1 to Week 48 LS mean	-4.67	+1.16
LS mean of difference (luspatercept-placebo) (95% CI)[b]	-5.83 (-7.01, -4.6)	
Weeks 49 to Week 96 LS mean	-5.66	+2.19

Endpoint	Luspatercept (N=224)	Placebo (N=112)
LS mean of difference (luspatercept-placebo) (95% CI)[b]	-7.84 (-14.44, -1.25)	

ANCOVA = analysis of covariance; CI: confidence interval.
[a] Difference in proportions (luspatercept + BSC – placebo + BSC) and 95% CIs estimated from the unconditional exact test.
[b] Estimates are based on ANCOVA model with geographical regions and baseline transfusion burden as covariates.

A reduction in mean serum ferritin levels was observed from baseline in the luspatercept arm compared to an increase in the placebo arm at Week 48 (-233.51 µg/L *vs.* +114.28 µg/L which resulted in a least square mean treatment difference of -347.8 µg/L (95% CI: -516.95, -178.65).

A total of 80.4% (127/158) of luspatercept responders who achieved at least a 33% reduction in transfusion burden during any consecutive 12-week interval achieved 2 or more episodes of response at the time of analysis.

Non-transfusion-dependent β-thalassaemia
The efficacy and safety of luspatercept were evaluated in a Phase 2 multicentre, randomised, double-blind, placebo-controlled study BEYOND (ACE-536-B-THAL-002) in adult patients with non-transfusion-dependent β-thalassaemia-associated anaemia (Hb concentration ≤ 10 g/dL).

A total of 145 adult patients receiving RBC transfusions (0-5 RBC units in the 24-week period prior to randomization), with a baseline Hb level ≤ 10.0 g/dL (defined as average of at least 2 Hb measurments ≥ 1 week apart within 4 weeks prior to randomization) were randomized to receive luspatercept (n=96) or placebo (n=49) subcutaneously every 3 weeks. Patients were stratified at randomization based on their baseline Hb level and their non-transfusion-dependent β-thalassaemia (NTDT) patient-reported outcome (PRO; NTDT-PRO) Tiredness/Weakness (T/W) weekly domain score. Dose titration to 1.25 mg/kg was allowed. Dose could be delayed or reduced depending upon Hb level. Overall, 53% of luspatercept patients (n=51) and 92% of patients on placebo (n=45) had their dose increased to 1.25 mg/kg within the 48-week treatment period. Among patients receiving luspatercept, 96% were exposed for 6 months or longer and 86% were exposed for 12 months or longer. A total of 89 (92.7%) patients receiving luspatercept and 35 (71.4%) patients receiving placebo completed 48 weeks of treatment.

All patients were eligible to receive BSC, which included RBC transfusions, iron-chelating agents, use of antibiotic, antiviral, and antifungal therapy, and nutritional support, as needed. Concurrent treatment for anemia with blood transfusions was allowed, at the discretion of the physician, for low haemoglobin levels, symptoms associated with anemia (eg, haemodynamic or pulmonary compromise requiring treatment) or comorbidities. The study excluded patients with Hb S/β-thalassaemia or alpha (α)-thalassaemia or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency), active hepatitis C or B, or HIV. Patients with recent DVT or stroke or recent use of ESA, immunosuppressant or hydroxyurea therapy, or on chronic anticoagulant or uncontrolled hypertension were also excluded. Only a limited number of patients with comorbidities associated with underlying anemia such as pulmonary hypertension, liver and kidney disease and diabetes were included in the study.

The key baseline disease characteristics in the Intention-To-Treat (ITT) population with non-transfusion-dependent β-thalassaemia in study ACE-536-B-THAL-002 are shown in Table 13.

Table 13. Baseline characteristics in patients with non-transfusion-dependent β-thalassaemia in study ACE-536-B-THAL-002

	ITT population	
	Luspatercept (N=96)	**Placebo (N=49)**
Demographics		
Age (years) Median (min, max)	 39.5 (18, 71)	 41 (19, 66)
Sex, n (%) Male Female	 40 (41.7) 56 (58.3)	 23 (46.9) 26 (53.1)
Race, n (%) Asian White Other	 31 (32.3) 59 (61.5) 6 (6.3)	 13 (26.5) 28 (57.1) 8 (16.3)
Disease characteristics		
β-thalassaemia diagnosis, n (%) β-thalassaemia HbE/β-thalassaemia β-thalassaemia combined with α-thalassaemia	 63 (65.6) 28 (29.2) 5 (5.2)	 34 (69.4) 11 (22.4) 4 (8.2)
Baseline Hb level[a] (g/dL) Median (min, max)	 8.2 (5.3, 10.1)	 8.1 (5.7, 10.1)
Patients with mean baseline Hb level[a] category (g/dL), n (%) < 8.5	 55 (57.3)	 29 (59.2)
Baseline NTDT-PRO T/W domain score[b], n (%) Median (min, max)	 4.3 (0, 9.5)	 4.1 (0.4, 9.5)
Baseline NTDT-PRO T/W domain score[b] category, n (%) ≥ 3	 66 (68.8)	 35 (71.4)
Baseline transfusion burden (units/24 weeks) Median (min, max)	 0 (0, 4)	 0 (0, 4)
Splenectomy, n (%) Yes	 34 (35.4)	 26 (53.1)
MRI LIC (mg/g dw)[c], n Median (min, max)	 95 3.9 (0.8, 39.9)	 47 4.1 (0.7, 28.7)
MRI spleen volume (cm^3), n Median (min, max)	 60 879.9 (276.1, 2419.0)	 22 1077.0 (276.5, 2243.0)
Baseline use of ICT, n (%)	28 (29.2)	16 (32.7)

	ITT population	
	Luspatercept (N=96)	**Placebo (N=49)**
Baseline serum ferritin (µg/L)[d] Median (min, max)	456.5 (30.0, 3528.0)	360.0 (40.0, 2265.0)

Hb = haemoglobin; HbE = haemoglobin E; ICT = Iron Chelation Therapy; LIC = liver iron concentration; max = maximum; min = minimum; MRI = magnetic resonance imaging; NTDT-PRO T/W = non-transfusion-dependent β-thalassaemia patient-reported outcome tiredness and weakness domain score;
[a] Mean of at least 2 Hb values by the central laboratory during the 28-day screening period.
[b] Baseline defined as the average of non-missing NTDT-PRO T/W domain score over 7 days before Dose 1 Day 1.
[c] The value of LIC was either the value collected from the electronic Case Report Form (eCRF) or the value derived from T2*, R2*, or R2 parameter depending on which techniques and software were used for MRI LIC acquisition.
[d] Baseline mean serum ferritin was calculated during the 24 weeks on or prior to Dose 1 Day 1. Baseline ICT was calculated during the 24 weeks on or prior to Dose 1 Day 1.

The efficacy results are summarised below.

Table 14. Efficacy results in patients with non-transfusion-dependent β-thalassaemia in study ACE-536-B-THAL-002

	ITT population	
Endpoint	**Luspatercept (N=96)**	**Placebo (N=49)**
Primary endpoint **Increase from baseline ≥1.0 g/dL in mean Hb over continuous 12-week interval (in absence of transfusions)**		
• **Week 13-24** Response rate[a], n [(%) (95% CI)][b]	74 [(77.1) (67.4, 85.0)]	0.0 [(0.0) (0.0, 7.3)]
p-value[c]	< 0.0001	

CI = confidence interval; Hb = haemoglobin
[a] Defined as number of patients with ≥ 1.0 g/dL Hb increase in the absence of RBC transfusion compared to baseline (i.e. the average of ≥2 Hb measurements at ≥ 1 week apart within 4 weeks before Dose 1 Day 1).
[b] The 95% CI for response rate (%) was estimated from the Clopper-Pearson exact test.
[c] The odds ratio (luspatercept *vs.* placebo) with 95% CI and p-value were estimated from the CMH test stratified by baseline Hb category (<8.5 *vs.* ≥ 8.5 g/dL) and baseline NTDT-PRO T/W domain score category (≥ 3 *vs.* < 3) defined at randomization as covariates.
Note: Patients with missing Hb at Week 13-24 were classified as non-responders in the analysis.

A total of 77.1% of luspatercept treated patients achieved an increase from baseline ≥ 1.0 g/dL in mean Hb over continuous 12-week interval (in absence of transfusions) (Week 13-24). This effect was maintained in the 57.3% of patients who reached Week 144 of treatment.

Paediatric population

Myelodysplastic syndromes
The European Medicines Agency has waived the obligation to submit the results of studies with Reblozyl in all subsets of the paediatric population in myelodysplastic syndromes (see section 4.2 for information on paediatric use).

β-thalassaemia
The European Medicines Agency has deferred the obligation to submit the results of studies with Reblozyl in one or more subsets of paediatric population older than 6 years of age in β-thalassaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
In healthy volunteers and patients, luspatercept is slowly absorbed following subcutaneous administration, with the C_{max} in serum often observed approximately 7 days post-dose across all dose levels. Population pharmacokinetic (PK) analysis suggests that the absorption of luspatercept into the circulation is linear over the range of studied doses, and the absorption is not significantly affected by the subcutaneous injection location (upper arm, thigh or abdomen). Interindividual variability in AUC was approximately 38% in MDS patients and 36% in β-thalassaemia patients.

Distribution
At the recommended doses, the mean apparent volume of distribution was 9.68 L for MDS patients and 7.26 L for β-thalassaemia patients. The small volume of distribution indicates that luspatercept is confined primarily in extracellular fluids, consistent with its large molecular mass.

Biotransformation
Luspatercept is expected to be catabolised into amino acids by general protein degradation process.

Elimination
Luspatercept is not expected to be excreted into urine due to its large molecular mass that is above the glomerular filtration size exclusion threshold. At the recommended doses, the mean apparent total clearance was 0.516 L/day for MDS patients and 0.441 L/day for β-thalassaemia. The mean half-life in serum was approximately 13 days for MDS patients and 11 days for β-thalassaemia patients.

Linearity/non-linearity
The increase of luspatercept C_{max} and AUC in serum is approximately proportional to increases in dose from 0.125 to 1.75 mg/kg. Luspatercept clearance was independent of dose or time.

When administered every three weeks, luspatercept serum concentration reaches the steady state after 3 doses, with an accumulation ratio of approximately 1.5.

Hb response
In patients who received < 4 units of RBC transfusion within 8 weeks prior to the study, Hb increased within 7 days of treatment initiation and the increase correlated with the time to reach luspatercept C_{max}. The greatest mean Hb increase was observed after the first dose, with additional smaller increases observed after subsequent doses. Hb levels returned to baseline value approximately 6 to 8 weeks from the last dose (0.6 to 1.75 mg/kg). Increasing luspatercept serum exposure (AUC) was associated with a greater Hb increase in patients with MDS or β-thalassaemia.

In non-transfusion-dependent β-thalassaemia patients who had a baseline transfusion burden of 0 to 5 units within 24 weeks, increasing luspatercept serum exposure (time-averaged AUC) was associated with a greater probability of achieving a Hb increase (≥ 1 g/dL or ≥ 1.5 g/dL) and a longer duration of such Hb increases. The luspatercept serum concentration achieving 50% of the maximum stimulatory effect on Hb production was estimated to be 7.6 μg/mL.

Special populations

Elderly
Population PK analysis for luspatercept included patients with ages ranging from 18 to 95 years old, with a median age of 72 years for MDS patients and of 33 years for β-thalassaemia patients. No clinically significant difference in AUC or clearance was found across age groups in MDS patients (< 65, 65-74, and ≥ 75 years) or in β-thalassaemia patients (18 to 71 years).

Hepatic impairment
Population PK analysis for luspatercept included patients with normal hepatic function (BIL, ALT, and AST ≤ ULN; N = 207), mild hepatic impairment (BIL > 1 – 1.5 x ULN, and ALT or AST > ULN; N = 160), moderate hepatic impairment (BIL > 1.5 – 3 x ULN, any ALT or AST; N = 138), or severe hepatic impairment (BIL > 3 x ULN, any ALT or AST; N = 40) as defined by the National Cancer Institute criteria of hepatic dysfunction. Effects of hepatic function categories, elevated liver enzymes (ALT or AST, up to 3 x ULN) and elevated total BIL (4 – 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. PK data are insufficient for patients with liver enzymes (ALT or AST) ≥ 3 x ULN. No PK data are available for patients with liver cirrhosis (Child-Pugh Classes A, B and C) as no dedicated study was performed.

Renal impairment
Population PK analysis for luspatercept included patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2; N = 315), mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2; N = 171), or moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2; N = 59). Luspatercept serum exposure (AUC) was 27% to 41% higher in patients with mild to moderate renal impairment than in patients with normal renal function. PK data are not available for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or end-stage kidney disease.

Other intrinsic factors
The following population characteristics have no clinically significant effect on luspatercept AUC or clearance: sex and race (Asian *vs.* White).

The following baseline disease characteristics had no clinically significant effect on luspatercept clearance: serum erythropoietin level, RBC transfusion burden, MDS ring sideroblasts, β-thalassaemia genotype (β0/β0 *vs.* non-β0/β0) and splenectomy.

The volume of distribution and clearance of luspatercept increased with increase of body weight, supporting the body weight-based dosing regimen.

5.3 Preclinical safety data

Single and repeat-dose toxicity
Following repeated administration of luspatercept in rats, toxicities included: membranoproliferative glomerulonephritis; congestion, necrosis and/or mineralisation of the adrenal glands; hepatocellular vacuolation and necrosis; mineralisation of the glandular stomach; and decreased heart and lung weights with no associated histology findings. A clinical observation of swollen hindlimbs/feet was noted in several studies in rats and rabbits (including juvenile and reproductive toxicity studies). In one juvenile rat, this correlated histopathologically with new bone formation, fibrosis, and inflammation. Membranoproliferative glomerulonephritis was also seen in monkeys. Additional toxicities in monkeys included: vascular degeneration and inflammatory infiltrates in the choroid plexus.

For the 6-month toxicity study, the longest duration study in monkeys, the no-observed-adverse-effect level (NOAEL) was 0.3 mg/kg (0.3-fold of clinical exposure at 1.75 mg/kg every 3 weeks). A NOAEL was not identified in rats and the lowest-observed-adverse-effect-level (LOAEL) in the rat 3-month study was 1 mg/kg (0.9-fold of clinical exposure at 1.75 mg/kg every 3 weeks).

Carcinogenesis and mutagenesis
Neither carcinogenicity nor mutagenicity studies with luspatercept have been conducted. Haematological malignancies were observed in 3 out of 44 rats examined in the highest dose group (10 mg/kg) in the definitive juvenile toxicity study. The occurrence of these tumours in

young animals is unusual and the relationship to luspatercept therapy cannot be ruled out. At the 10 mg/kg dose, at which tumours were observed, the exposure represents an exposure multiple of approximately 4 times the estimated exposure at a clinical dose of 1.75 mg/kg every three weeks.

No other proliferative or pre-neoplastic lesions, attributable to luspatercept, have been observed in any species in other non-clinical safety studies conducted with luspatercept, including the 6-month study in monkeys.

Fertility
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 corpora lutea, implantations and viable embryos. No such effects were observed when exposure in animals was at 1.5 times the clinical exposure. Effects on fertility in female rats were reversible after a 14-week recovery period.

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.

Embryo-foetal development (EFD)
Embryo-foetal developmental toxicology studies (range-finding and definitive studies) were conducted in pregnant rats and rabbits. In the definitive studies, doses of up to 30 mg/kg or 40 mg/kg every week were administered twice during the period of organogenesis. 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. Embryofoetal 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 both species, effects of luspatercept were observed in the EFD studies 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.

Pre- and post-natal development
In a pre- and post-natal development study, with dose levels of 3, 10, or 30 mg/kg administered once every 2 weeks from gestational day (GD) 6 through post-natal day (PND) 20, adverse findings at all doses consisted of lower F_1 pup body weights in both sexes at birth, throughout lactation, and post weaning (PND 28); lower body weights during the early premating period (Week 1 and 2) in the F_1 females (adverse only at the 30 mg/kg/dose) and lower body weights in F_1 males during the premating, pairing and post-mating periods; and microscopic kidney findings in F_1 pups. Additionally, non-adverse findings included delayed male sexual maturation at the 10 and 30 mg/kg/dose. The delay in growth and the adverse kidney findings, in the F_1 generation, precluded the determination of a NOAEL for F_1 general and developmental toxicity. However, there was no effect on behavioural indices, fertility or reproductive parameters at any dose level in either sex, therefore the NOAEL for behavioural assessments, fertility and reproductive function in the F_1 animals was considered to be the 30 mg/kg/dose. Luspatercept is transferred through the placenta of pregnant rats and rabbits and is excreted into the milk of lactating rats.

Juvenile toxicity
In a study in juvenile rats, luspatercept was administered from postnatal day (PND) 7 to PND 91 at 0, 1, 3, or 10 mg/kg. Many of the findings seen in repeat-dose toxicity studies in adult rats were repeated in the juvenile rats. These findings included glomerulonephritis in the kidney, haemorrhage/congestion, necrosis and mineralization of the adrenal gland, mucosal mineralization in the stomach, lower heart weights, and swollen hindlimbs/feet. 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 non-adverse 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, an 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (E330)
Sodium citrate (E331)
Polysorbate 80
Sucrose
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
4 years.

After reconstitution
When stored in the original container, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated for up to 8 hours at room temperature (≤ 25°C) or for up to 24 hours at 2°C - 8°C.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C - 8°C.

Do not freeze the reconstituted solution.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Reblozyl 25 mg powder for solution for injection
3 mL Type I glass vial with a hydrophobic inner coating closed with a bromobutyl rubber stopper and aluminium seal with yellow polypropylene flip-off cap.

Reblozyl 75 mg powder for solution for injection
3 mL Type I glass vial with a hydrophobic inner coating closed with a bromobutyl rubber stopper and aluminium seal with orange polypropylene flip-off cap.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Reblozyl must be reconstituted gently prior to administration. Aggressive shaking should be avoided.

Reconstitution of the product
Reblozyl is supplied as a lyophilised powder for reconstitution before use. Only water for injections (WFI) should be used when reconstituting Reblozyl.

The appropriate number of Reblozyl vials should be reconstituted to achieve the desired dose. A syringe with appropriate graduations must be used for reconstitution to ensure accurate dosage.

The following steps should be followed for reconstitution:

1. Remove the coloured cap from the vial and wipe the top with an alcohol wipe.

2. Reblozyl 25 mg powder for solution for injection
   Add 0.68 mL WFI into the vial by means of a syringe with appropriate graduations with a needle directing the flow onto the lyophilised powder. Allow to stand for one minute. Each 25 mg single-dose vial will deliver at least 0.5 mL of 50 mg/mL luspatercept.

   Reblozyl 75 mg powder for solution for injection
   Add 1.6 mL WFI into the vial by means of a syringe with appropriate graduations with a needle directing the flow onto the lyophilised powder. Allow to stand for one minute. Each 75 mg single-dose vial will deliver at least 1.5 mL of 50 mg/mL luspatercept.

3. Discard the needle and syringe used for reconstitution. Do not use them for subcutaneous injection.
4. Gently swirl the vial in a circular motion for 30 seconds. Stop swirling and let the vial sit in an upright position for 30 seconds.
5. Inspect the vial for undissolved powder in the solution. If undissolved powder is observed, repeat step 4 until the powder is completely dissolved.
6. Invert the vial and gently swirl in an inverted position for 30 seconds. Bring the vial back to the upright position and let it sit for 30 seconds.
7. Repeat step 6 seven more times to ensure complete reconstitution of material on the sides of the vial.
8. Visually inspect the reconstituted solution prior to administration. When properly mixed, Reblozyl reconstituted solution is a colourless to slightly yellow, clear to slightly opalescent solution which is free of visible foreign particulate matter. Do not use if undissolved product or foreign particulate matter is observed.
9. If the reconstituted solution is not used immediately, see section 6.3 for storage conditions.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/20/1452/001
EU/1/20/1452/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 June 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Lonza Biologics Tuas Pte Ltd.
35 Tuas South Ave. 6,
Singapore, Singapore 637377
Singapore

Biogen MA Inc.
5000 Davis Dr
Research Triangle Park, NC
27709
USA

Name and address of the manufacturer responsible for batch release

Celgene Distribution B.V.
Orteliuslaan 1000
3528 BD Utrecht
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile

or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

An updated RMP shall be submitted by CHMP agreed deadline.

Additional risk minimisation measures

Prior to launch of Reblozyl 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 National Competent Authority.

The MAH shall ensure that in each member state where Reblozyl is marketed, all HCPs who intend to prescribe Reblozyl 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 BMS 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:

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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Reblozyl 25 mg powder for solution for injection
luspatercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 25 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate (E330), sodium citrate (E331), polysorbate 80, sucrose, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with the local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1452/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

REBLOZYL 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Reblozyl 25 mg powder for injection
luspatercept
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Reblozyl 75 mg powder for solution for injection
luspatercept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 75 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate (E330), sodium citrate (E331), polysorbate 80, sucrose, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with the local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1452/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

REBLOZYL 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Reblozyl 75 mg powder for injection
luspatercept
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Reblozyl 25 mg powder for solution for injection
Reblozyl 75 mg powder for solution for injection
luspatercept

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Reblozyl is and what it is used for

Reblozyl contains the active substance luspatercept. It is used for:

Myelodysplastic syndromes
Myelodysplastic syndromes (MDS) are a collection of many different blood and bone marrow disorders.
- Red blood cells become abnormal and do not develop properly.
- Patients can get a number of signs and symptoms including a low red blood cell count (anaemia) and may need red blood cell transfusions.

Reblozyl is used in adults with anaemia caused by MDS, who need red blood cell transfusions. It is used in adults who have already had or are not able to have erythropoietin therapies.

Beta-thalassaemia
β-thalassaemia is a blood problem that is passed down through genes.
- It affects the production of haemoglobin.
- Patients can get a number of signs and symptoms including a low red blood cell count (anaemia) and may need red blood cell transfusions.

Reblozyl is used to treat anaemia in adults with β-thalassaemia who may or may not need regular red blood cell transfusions.

How Reblozyl works
Reblozyl improves your body's ability to make red blood cells. Red blood cells contain haemoglobin, which is a protein that carries oxygen throughout your body. As your body makes more red blood cells, your haemoglobin level increases.

For MDS and β-thalassaemia patients in need of regular blood transfusions
Having Reblozyl can avoid or reduce the need for red blood cell transfusions.
- Red blood cell transfusions can cause abnormally high levels of iron in the blood and in different organs of the body. This can be harmful over time.

For β-thalassaemia patients not in need of regular blood transfusions
Having Reblozyl can improve your aneamia by increasing your haemoglobin level.

2. What you need to know before you are given Reblozyl

Do not use Reblozyl
- if you are allergic to luspatercept or any of the other ingredients of this medicine (listed in section 6)
- if you are pregnant (see section on Pregnancy)
- if you require treatment for the control of mass producing blood cells outside the bone marrow (extramedullary haemopoiesis masses, EMH masses)

Warnings and precautions
Talk to your doctor before being given this medicine if:
- you are a β-thalassaemia patient and you have had your spleen removed. You may have a higher risk of getting a blood clot. Your doctor will talk to you about other possible risk factors that may increase your risk – these include:
  - hormone replacement therapy or
  - a previous blood clot

  Your doctor may use preventive measures or medicines to reduce the chances of you getting a blood clot.
- you have severe back pain that does not go away, numbness or weakness or loss of voluntary movement in legs, hands or arms, loss of bowel and bladder control (incontinence). They may be symptoms of EMH masses and compression of spinal cord.
- you have ever had high blood pressure – this is because Reblozyl may increase it. Your blood pressure will be checked before you are given Reblozyl and throughout treatment. You will be given Reblozyl only if your blood pressure is under control.
- you have a condition that affects the strength and health of your bones (osteopenia and osteoporosis). You may have a risk of breaking your bones more easily.

Routine tests
You will have a blood test before each dose of this medicine. This is because your doctor needs to make sure your haemoglobin level is suitable for you to be given treatment.

If you have kidney problems, your doctor may perform additional tests.

Children and adolescents
This medicine is not recommended for use in children and adolescents under 18 years.

Other medicines and Reblozyl
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy
- Do not use this medicine during pregnancy and for at least 3 months before getting pregnant. Reblozyl may cause harm to your unborn baby.
- Your doctor will arrange a pregnancy test before starting treatment.
- If you think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Breast-feeding
- Do not breast-feed when using this medicine and for 3 months after your last dose. It is not known if it passes into the mother's milk.

Contraception
- You should use an effective method of contraception during treatment with Reblozyl and for at least 3 months after your last dose.

Talk to your doctor about contraceptive methods that may be right for you while you are using this medicine.

Fertility
If you are a woman, this medicine may cause fertility problems. This could affect your ability to have a baby. Talk to your doctor for advice before using it.

Driving and using machines
You may feel tired, dizzy, or faint, while using Reblozyl. If this happens do not drive or use any tools or machines and contact your doctor straight away.

Reblozyl contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Reblozyl is given

Before you are given this medicine, your doctor will have carried out blood tests and decided if you need Reblozyl.

Reblozyl will be given by an injection under your skin (subcutaneously).

How much will you be given
The dose is based on how much you weigh – in kilograms. The injections will be given by a doctor, nurse or other healthcare professional.

- The recommended starting dose is 1.0 mg for each kilogram of body weight.
- This dose should be given once every three weeks.
- Your doctor will check your progress and may change your dose if needed.

Your doctor will monitor your blood pressure while you are using Reblozyl.

Myelodysplastic syndromes
The maximum single dose is 1.75 mg for each kilogram of body weight.

Beta-thalassaemia
The maximum single dose is 1.25 mg for each kilogram of body weight.

If you miss a dose
If you miss an injection of Reblozyl, or an appointment is delayed, you will receive a Reblozyl injection as soon as possible. Then, your dose will continue as prescribed – with at least 3 weeks between doses.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine may cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor straight away if you notice the following:

- difficulty in walking or speaking, dizziness, loss of balance and coordination, numbness or paralysis in the face, leg or arm (often on one side of your body), blurred vision. They may all be symptoms of a stroke.
- painful swelling and tightness in the leg or arm (blood clots)
- severe back pain that does not go away, numbness or weakness or loss of voluntary movement in legs, hands or arms, loss of bowel and bladder control (incontinence). They may be symptoms of extramedullary haemopoiesis masses (EMH masses) and compression of spinal cord.
- swelling of the area around the eyes, the face, lips, mouth, tongue or throat
- allergic reactions
- rashes

Other side effects include:

Very common side effects (may affect more than 1 in 10 people):

- chest infection
- cough
- difficulty in breathing or shortness of breath
- high blood pressure without symptoms or associated with headache
- urinary tract infection
- upper respiratory tract infection
- flu or flu like symptoms
- dizziness, headache
- diarrhoea, feeling sick (nausea)
- belly pain
- back, joint or bone pain
- feeling tired or weak
- difficulty to sleep or to stay asleep
- changes in blood test results (increase in liver enzymes, increase in blood creatinine). These may be signs of liver and kidney problems.

Common side effects (may affect up to 1 in 10 people):

- fainting, spinning feeling
- broken bones caused by trauma
- bleeding from the nose
- intense headache on one side of the head
- redness, burning and pain at the site of injection (injection site reactions) or swelling, itchy skin (injection site erythema)
- high level of uric acid in the blood (shown in tests)
- foamy urine. This may be a sign of too much protein in your urine (proteinuria and albuminuria).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Reblozyl

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after EXP. The expiry date refers to the last day of that month.

Unopened vials: Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original carton in order to protect from light.

After first opening and reconstitution, Reblozyl should be used immediately. If not used immediately, when held in the original carton the reconstituted medicinal product may be stored for up to 8 hours at room temperature (≤ 25°C) or for up to 24 hours at 2°C – 8°C.

Do not freeze the reconstituted solution.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Reblozyl contains
- The active substance is luspatercept. Each vial contains 25 mg or 75 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.
- The other excipients are citric acid monohydrate (E330), sodium citrate (E331), polysorbate 80, sucrose, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

What Reblozyl looks like and contents of the pack
Reblozyl is a white to off-white powder for solution for injection. Reblozyl is supplied in glass vials containing 25 mg or 75 mg of luspatercept.

Each pack contains 1 vial.

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Celgene Distribution B.V.
Orteliuslaan 1000
3528 BD Utrecht
Netherlands

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Traceability
In order to improve the traceability of biological medicinal products, the name and batch number of the administered medicinal product should be clearly recorded.

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.

Storage of the product
Unopened vial
Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original carton in order to protect from light.

Reconstituted solution
When stored in the original carton, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated for up to 8 hours at room temperature (≤ 25°C) or for up to 24 hours at 2°C – 8°C.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C – 8°C.

Do not freeze the reconstituted solution.

Dose calculation
The total dose, according to the patient's weight (kg) can be calculated as follow:

Total dose (mg) = Dose level (mg/kg) x patient's weight (kg) every three weeks.

Reconstitution instructions
Reblozyl is supplied as a lyophilised powder to be reconstituted with water for injections (WFI). A syringe with appropriate graduations must be used for reconstitution to ensure accurate dosage. See Table 1.

Table 1. Reblozyl reconstitution table

Strength	Amount of WFI required for reconstitution	Post-reconstitution concentration (nominal value)
25 mg vial	0.68 mL	50 mg/mL (0.5 mL)
75 mg vial	1.6 mL	50 mg/mL (1.5 mL)

1. Remove the coloured cap from the vial and wipe the top with an alcohol wipe.
2. Add WFI into the vial by means of a syringe with appropriate graduations with a needle directing the flow onto the lyophilised powder. Allow to stand for one minute.
3. Discard the needle and syringe used for reconstitution. Do not use them for subcutaneous injection.
4. Gently swirl the vial in a circular motion for 30 seconds. Stop swirling and let the vial sit in an upright position for 30 seconds.
5. Inspect the vial for undissolved powder in the solution. If undissolved powder is observed, repeat step 4 until the powder is completely dissolved.

6. Invert the vial and gently swirl in an inverted position for 30 seconds. Bring the vial back to the upright position and let it sit for 30 seconds.
7. Repeat step 6 seven more times to ensure complete reconstitution of material on the sides of the vial.
8. Visually inspect the reconstituted solution prior to administration. When properly mixed, Reblozyl reconstituted solution is a colourless to slightly yellow, clear to slightly opalescent solution which is free of visible foreign particulate matter. Do not use if undissolved product or foreign particulate matter is observed.
9. If the reconstituted solution is not used immediately, see *Storage of the product* section above.

Method of administration

If the Reblozyl reconstituted solution has been refrigerated, remove from the refrigerator 15-30 minutes prior to injection to allow it to reach room temperature. This will allow for a more comfortable injection.

The recommended maximum volume of medicinal product per injection site is 1.2 mL. If more than 1.2 mL is required, the total volume of Reblozyl should be divided into separate similar volume injections and administered across separate sites using the same anatomical location but on opposite sides of the body. Reconstitute the appropriate number of Reblozyl vials to achieve the desired dose.

Inject Reblozyl subcutaneously into the upper arm, thigh or abdomen.

If multiple injections are required, use a new syringe and needle for each subcutaneous injection. Discard any unused portion. Do not administer more than one dose from a vial.

Disposal

Dispose of any unused medicinal product or waste material in accordance with local requirements.