

To be sold by retail on the prescription of a 'Registered Oncologist/Haematologist' only.



# Luspatercept

## [ROJUZDA<sup>®</sup>]

### 1. GENERIC NAME

Luspatercept 25 mg powder for solution for injection

Luspatercept 75 mg powder for solution for injection

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Luspatercept 25 mg powder for solution for injection

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

Luspatercept 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 7.

### 3. DOSAGE FORM AND STRENGTH

Powder for solution for injection (powder for injection): 25 mg and 75 mg in vial

White to off-white lyophilized powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### *Myelodysplastic syndromes (MDS)*

Luspatercept 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.

#### *β-thalassaemia*

Luspatercept is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia.

### 4.2 Posology and method of administration

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

#### Posology

Prior to each Luspatercept 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.

#### *Myelodysplastic syndromes (MDS)*

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

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.

#### *β-thalassaemia*

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

In patients who do not achieve a response, defined as a reduction in RBC transfusion burden of at least a third after  $\geq 2$  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.

### *MDS and $\beta$ -thalassaemia*

#### Dose reduction and dose delay

In case of Hb increase  $> 2$  g/dL within 3 weeks of luspatercept treatment in absence of transfusion, the Luspatercept dose should be reduced by one dose level.

If the Hb is  $\geq 11.5$  g/dL in the absence of transfusion for at least 3 weeks, the dose should be delayed until the Hb is  $\leq 11.0$  g/dL. If there is also a concomitant rapid increase in Hb ( $> 2$  g/dL within 3 weeks in absence of transfusion), a dose reduction to one step down (minimum 0.8 mg/kg) should be considered after the dose delay.

Dose should not be reduced below 0.8 mg/kg.

Dose reductions during treatment with luspatercept are provided below.

**Table 1: Dose reductions for MDS**

<b>Current dose</b>	<b>Dose reduction</b>
1.75 mg/kg	1.33 mg/kg
1.33 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg

**Table 2: Dose reductions for  $\beta$ -thalassaemia**

<b>Current dose</b>	<b>Dose reduction</b>
1.25 mg/kg	1 mg/kg
1 mg/kg	0.8 mg/kg

If patients experience persistent treatment-related Grade 3 or higher adverse reactions (see section 4.8), the treatment should be delayed until toxicity has improved or returned to baseline.

After a dose delay, patients should be re-started at their previous dose or at reduced dose as per dose reduction guidance.

### $\beta$ -thalassaemia

In case of extramedullary haemopoiesis (EMH) masses causing serious complications (see sections 4.4 and 4.8), the treatment must be discontinued.

## MDS and $\beta$ -thalassaemia

### Missed doses

In case of a missed or delayed scheduled treatment administration, the patient should be administered Luspatercept 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 luspatercept, 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.

### Discontinuation

Luspatercept should be discontinued if patients do not experience a reduction in transfusion burden 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 luspatercept (see section 5.2).

### *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  $\geq$  3 x ULN or liver injury CTCAE Grade  $\geq$  3 due to lack of data (see section 5.3).

### *Renal impairment*

No starting dose adjustment is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] < 90 and  $\geq$  30 mL/min/1.73 m<sup>2</sup>). No specific dose recommendation can be made for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m<sup>2</sup>) due to lack of clinical data (see section 5.3). Patients with renal impairment at baseline should be closely monitored for renal function as per standard of care.

### *Paediatric population*

There is no relevant use of luspatercept in the paediatric population for the indication of myelodysplastic syndromes, or in paediatric patients less than 6 years of age in  $\beta$ -thalassaemia. For non-clinical data, see section 6.

The safety and efficacy of luspatercept in the paediatric patients aged from 6 years to less than 18 years have not yet been established in  $\beta$ -thalassaemia. For non-clinical data, see section 6.

## Method of administration

For subcutaneous use.

After reconstitution, luspatercept 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.

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 luspatercept 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 8.4.

### **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 7.
- Pregnancy (see section 4.6).
- Patients requiring treatment to control the growth of EMH masses (see section 4.4).
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### **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  $\beta$ -thalassaemia patients, thromboembolic events (TEEs) were reported in 3.6% (8/223) of patients treated with luspatercept in a controlled clinical study. Reported TEEs included deep vein thrombosis (DVT), portal vein thrombosis, pulmonary emboli and ischaemic stroke (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  $\beta$ -thalassaemia patients with a splenectomy and other risk factors for developing TEE. Thromboprophylaxis according to current clinical guidelines should be considered in patients with  $\beta$ -thalassaemia at higher risk.

#### Extramedullary haemopoiesis masses

In transfusion-dependent  $\beta$ -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).

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 controlled clinical studies in MDS and  $\beta$ -thalassaemia, patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of 5 mmHg from baseline (see section 4.8). Blood pressure should be monitored prior to each luspatercept administration. In case of persistent hypertension or exacerbations of pre-existing hypertension, patients should be treated for hypertension as per current clinical guidelines.

#### Sodium content

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

### **4.5 Drug interactions**

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

### **4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)**

#### Women of childbearing potential / Contraception in females

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

#### Pregnancy

Treatment with luspatercept should not be started if the woman is pregnant (see section 4.3). There are no data from the use of luspatercept in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Luspatercept is contraindicated during pregnancy (see section 4.3). If a patient becomes pregnant, luspatercept 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 luspatercept and for 3 months after the last dose or to discontinue luspatercept therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## Fertility

The effect of luspatercept on fertility in humans is unknown. Based on findings in animals, luspatercept may compromise female fertility (see section 6).

### **4.7 Effects on ability to drive and use machines**

Luspatercept 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 luspatercept (at least 15% of patients) were fatigue, diarrhoea, asthenia, nausea, dizziness, back pain and headache. The most commonly reported Grade 3 or higher 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.

##### *$\beta$ -thalassaemia*

The most frequently reported adverse drug reactions in patients receiving luspatercept (at least 15% of patients) were headache, bone pain and arthralgia. The most commonly reported Grade 3 or higher 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.

Tabulated list of adverse reactions

The highest frequency for each adverse reaction that was observed and reported in the pivotal studies in MDS,  $\beta$ -thalassaemia is shown in Table 3 below. The adverse reactions are listed below by body system organ class and preferred term. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ).



**Table 3. Adverse drug reactions (ADRs) in patients treated with Luspatercept for MDS and  $\beta$ -thalassaemia**

<b>System organ class</b>	<b>Preferred term</b>	<b>Frequency (all grades) for MDS</b>	<b>Frequency (all grades) for <math>\beta</math>-thalassaemia</b>
<b>Infections and infestations</b>	bronchitis	Very common	Common
	urinary tract infection	Very common	Common
	upper respiratory tract infection	Common	Very common
	influenza	Common	Common
Blood and lymphatic system disorders	extramedullary haemopoiesis	Not known **	Common
<b>Immune system disorders</b>	hypersensitivity*	Common	Common
<b>Metabolism and nutrition disorders</b>	hyperuricaemia	Common	Common
<b>Nervous system disorders</b>	dizziness	Very common	Very common
	headache	Very common	Very common
	syncope/presyncope	Common	Common
	spinal cord compression <sup>§</sup>		Common
<b>Ear and labyrinth disorders</b>	vertigo/vertigo positional	Common	Common
<b>Vascular disorders</b>	hypertension <sup>~</sup>	Common	Common
	thromboembolic events <sup>§</sup>	Common	Common
<b>Respiratory, thoracic and mediastinal disorders</b>	dyspnoea	Very common	Common
<b>Gastrointestinal disorders</b>	diarrhoea	Very common	Very common
	nausea	Very common	Common
<b>Musculoskeletal and connective tissue disorders</b>	back pain	Very common	Very common
	arthralgia	Common	Very common
	bone pain	Common	Very common
<b>General disorders and administration site conditions</b>	fatigue	Very common	Very common
	asthenia	Very common	Common
	injection site reactions <sup>#</sup>	Common	Common

\* Hypersensitivity includes eyelid oedema, drug hypersensitivity, swelling face, periorbital oedema, face oedema, angioedema, lip swelling, drug eruption.

<sup>~</sup> Hypertension reaction includes essential hypertension, hypertension and hypertensive crisis.

<sup>#</sup> Injection site reactions include injection site erythema, injection site pruritus, injection site swelling and injection site rash.

<sup>§</sup> Thromboembolic events include deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism.

<sup>§</sup> See section 4.8 Description of selected adverse reactions.

\*\*Reported only in post-marketing.

## Description of selected adverse reactions

### *Bone pain*

Bone pain was reported in 19.7% of  $\beta$ -thalassaemia patients treated with luspatercept (placebo 8.3%) and in 2.6% of MDS patients treated with luspatercept (placebo 3.9%). In  $\beta$ -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 19.3% of  $\beta$ -thalassaemia patients treated with luspatercept (placebo 11.9%) and in 5.2% of MDS patients treated with luspatercept (placebo 11.8%). In the  $\beta$ -thalassaemia patients treated with luspatercept, arthralgia led to treatment discontinuation in 2 patients (0.9%).

### *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%) and in 8.1% of  $\beta$ -thalassaemia patients treated with luspatercept (placebo 2.8%). See section 4.4.

In MDS patients, Grade 3 events were reported for 5 patients (3.3%) treated with luspatercept and in 3 patients (3.9%) receiving placebo. No patient discontinued due to hypertension.

In  $\beta$ -thalassaemia patients, Grade 3 events were reported in 4 patients (1.8%) treated with luspatercept (0.0% placebo). No patient discontinued due to hypertension. 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 (2.6% placebo) and 4.5% of  $\beta$ -thalassaemia patients treated with luspatercept (1.8% placebo). In clinical studies, all events were Grade 1/2. In  $\beta$ -thalassaemia patients treated with luspatercept, hypersensitivity led to treatment discontinuation in 1 patient (0.4%).

### *Injection site reactions*

Injection site reactions (including injection site erythema, injection site pruritus, injection site swelling and injection site rash) were reported in 3.9% of MDS (placebo 0.0%) and in 2.2% of  $\beta$ -thalassaemia patients receiving luspatercept (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  $\beta$ -thalassaemia patients receiving luspatercept (placebo 0.9%). 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  $\beta$ -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 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  $\beta$ -thalassaemia patients receiving luspatercept (placebo 0.0%). Four patients discontinued treatment due to Grade  $\geq 3$  symptoms of spinal cord compression.

#### *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  $\beta$ -thalassaemia, an analysis of 284  $\beta$ -thalassaemia patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 4 (1.4%)  $\beta$ -thalassaemia patients tested positive for treatment-emergent anti-luspatercept antibodies, including 2 (0.7%)  $\beta$ -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

## **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  $\leq 11$  g/dL.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Mechanism of action

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- $\beta$  (TGF- $\beta$ ) 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  $\beta$ -thalassaemia, and in the bone marrow of MDS patients.

### 5.2 Pharmacodynamic properties

#### 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 ( $\geq 2$  units/8 weeks) due to International Prognostic Scoring System-Revised (IPSS-R) very low-, low- or intermediate-risk MDS who have ring sideroblasts ( $\geq 15\%$ ). 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 ACE-536-MDS-001 are shown in Table 4.

**Table 4. Baseline characteristics in MDS patients with <5% marrow blasts in ACE-536-MDS-001**

	<b>Luspatercept (N=153)</b>	<b>Placebo (N=76)</b>
<b>Demographics</b>		
<b>Age<sup>a</sup> (years)</b> Median (min, max)	71 (40, 95)	72 (26, 91)
<b>Age categories, n (%)</b>		
<64 years	29 (19.0)	16 (21.1)
65-74 years	72 (47.1)	29 (38.2)
≥75	52 (34.0)	31 (40.8)
<b>Sex, n (%)</b>		
Male	94 (61.4)	50 (65.8)
Female	59 (38.6)	26 (34.2)
<b>Race, n (%)</b>		
Black	1 (0.7)	0 (0.0)
White	107 (69.9)	51 (67.1)
Not collected or reported	44 (28.8)	24 (31.6)
Other	1 (0.7)	1 (1.3)
<b>Disease characteristics</b>		
<b>Serum EPO (U/L) categories<sup>b</sup>, n (%)</b>		
< 200	88 (57.5)	50 (65.8)
200 to 500	43 (28.1)	15 (19.7)
> 500	21 (13.7)	11 (14.5)
Missing	1 (0.7)	0
<b>Serum ferritin (µg/L)</b> Median (min,max)	1089.2 (64, 5968)	1122.1 (165, 5849)
<b>IPSS-R classification risk category, n (%)</b>		
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
<b>Baseline RBC Transfusion burden/ 8 weeks<sup>c</sup>, n (%)</b>		
≥ 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)

	<b>Luspatercept (N=153)</b>	<b>Placebo (N=76)</b>
<b>Haemoglobin<sup>d</sup> (g/dL)</b>		
Median (min, max)	7.6 (6, 10)	7.6 (5, 9)
<b>SF3B1, n (%)</b>		
Mutated	149 (92.2)	65 (85.5)
Unmutated	12 (7.8)	10 (13.2)
Missing	0	1 (1.3)

EPO=erythropoietin; IPSS-R=International Prognostic Scoring System-Revised

<sup>a</sup> Time since original MDS diagnosis was defined as the number of years from the date of original diagnosis to the date of informed consent.

<sup>b</sup> Baseline EPO was defined as the highest EPO value within 35 days of the first dose of study drug.

<sup>c</sup> Collected over 16 weeks prior to randomisation.

<sup>d</sup> Baseline haemoglobin 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 5. Efficacy results in patients with MDS in ACE-536-MDS-001**

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

<b>Endpoint</b>	<b>Luspatercept (N=153)</b>	<b>Placebo (N=76)</b>
<b>Transfusion event frequency<sup>c</sup></b>		
• <b>Weeks 1-24</b>		
Interval transfusion rate (95% CI)	6.26 (5.56, 7.05)	9.20 (7.98, 10.60)
Relative risk versus placebo	0.68 (0.58, 0.80)	
• <b>Weeks 25-48</b>		
Interval transfusion rate (95% CI)	6.27 (5.47, 7.19)	8.72 (7.40, 10.28)
Relative risk versus placebo	0.72 (0.60, 0.86)	
<b>RBC Transfusion units<sup>c</sup></b>		
• <b>Weeks 1-24</b>		
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 versus 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 versus placebo)	-4.8 (1.62)	
95% CI for LS mean difference	-8.0, -1.6	
• <b>Weeks 25-48</b>		
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 versus 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 versus placebo)	-3.3(1.96)	
95% CI for LS mean difference	-7.1, 0.6	

RBC-TI: RBC Transfusion Independent; CI: confidence interval

<sup>a</sup> Cochran-Mantel-Haenszel test stratified for average baseline transfusion burden (≥ 6 units *versus* < 6 units per 8 weeks), and baseline IPSS-R score (very low or low *versus* intermediate).

<sup>b</sup> 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).

<sup>c</sup> Post-hoc analysis using baseline imputation.

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

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

### Exploratory findings

**Table 6. Exploratory efficacy results in patients with MDS in ACE-536-MDS-001**

Endpoint	Luspatercept (N=153)	Placebo (N=76)
<b>mHI-E<sup>a</sup></b>		
• <b>Weeks 1-24</b>		
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 haemoglobin increase of $\geq 1.5$ g/dL for 8 weeks, n (%)	29/46 (63.0)	1/20 (5.0)
• <b>Weeks 1-48</b>		
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 haemoglobin increase of $\geq 1.5$ g/dL for 8 weeks, n (%)	32/46 (69.6)	1/20 (5.0)
<b>Mean change from baseline in mean serum ferritin with imputation by baseline (ITT population)</b>		
Mean change from baseline in mean serum ferritin averaged over Weeks 9 through 24 ( $\mu\text{g/L}$ ) <sup>b</sup>		
LS Mean (SE)	9.9 (47.09)	190.0 (60.30)
95% CI for LS Mean	-82.9, 102.7	71.2, 308.8
<b>Treatment Comparison (Luspatercept vs Placebo)<sup>c</sup></b>		
LS Mean Difference (SE)	-180.1 (65.81)	
95% CI for LS Mean Difference	-309.8, -50.4	

<sup>a</sup> 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  $\geq 4$  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  $\geq 1.5$  g/dL for 8 weeks in the absence of RBC transfusions.

<sup>b</sup> If a subject did not have a serum ferritin value within the designated postbaseline interval, the serum ferritin is imputed from the baseline value.

<sup>c</sup> 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 ( $\geq 6$  units versus  $< 6$  units of RBC per 8 weeks), and baseline IPSS-R (very low or low versus intermediate).



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

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

### *$\beta$ -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  $\beta$ -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 haemoglobin S/ $\beta$ -thalassaemia or alpha ( $\alpha$ )-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  $\beta$ -thalassaemia in ACE-536-B-THAL-001 are shown in Table 7.

**Table 7. Baseline characteristics in patients with  $\beta$ -thalassaemia in ACE-536-B-THAL-001**

	<b>Luspatercept (N=224)</b>	<b>Placebo (N=112)</b>
<b>Demographics</b>		
<b>Age (years)</b>		
Median (min, max)	30.0 (18, 66)	30.0 (18, 59)
<b>Age categories, n (%)</b>		
$\leq$ 32	129 (57.6)	63 (56.3)
> 32 to $\leq$ 50	78 (34.8)	44 (39.3)
> 50	17 (7.6)	5 (4.5)
<b>Sex, n (%)</b>		
Male	92 (41.1)	49 (43.8)
Female	132 (58.9)	63 (56.3)
<b>Race, n (%)</b>		
Asian	81 (36.2)	36 (32.1)
Black	1 (0.4)	0
White	122 (54.5)	60 (53.6)
Not collected or reported	5 (2.2)	5 (4.5)
Other	15 (6.7)	11 (9.8)

	<b>Luspatercept (N=224)</b>	<b>Placebo (N=112)</b>
<b>Disease characteristics</b>		
<b>Pretransfusion Hb threshold<sup>a</sup>, 12 week run-in (g/dL)</b> Median (min, max)	9.30 (4.6, 11.4)	9.16 (6.2, 11.5)
<b>Baseline transfusion burden 12 weeks</b> Median (min, max) (units/12 weeks) (Week -12 to Day 1)	6.12 (3.0, 14.0)	6.27 (3.0, 12.0)
<b>β-thalassaemia gene mutation grouping, n (%)</b>		
β0/β0	68 (30.4)	35 (31.3)
Non-β0/β0	155 (69.2)	77 (68.8)
Missing <sup>b</sup>	1 (0.4)	0

<sup>a</sup>The 12-week pretransfusion threshold was defined as the mean of all documented pretransfusions hb values for a subject during the 12 weeks prior to Cycle 1 Day 1.

<sup>b</sup> "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 8. Efficacy results in patients with β-thalassaemia in ACE-536-B-THAL-001**

<b>Endpoint</b>	<b>Luspatercept (N=224)</b>	<b>Placebo (N=112)</b>
<b>≥ 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</b>		
Primary endpoint – <b>Weeks 13-24</b>	48 (21.4)	5 (4.5)
Difference in proportions (95% CI) <sup>a</sup>	17.0 (10.4, 23.6)	
p-value <sup>b</sup>	< 0.0001	
<b>Weeks 37-48</b>	44 (19.6)	4 (3.6)
Difference in proportions (95% CI) <sup>a</sup>	16.1 (9.8, 22.3)	
p-value <sup>b</sup>	< 0.0001	
<b>≥ 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</b>		
<b>Weeks 13-24</b>	17 (7.6)	2 (1.8)
Difference in proportions (95% CI) <sup>a</sup>	5.8 (1.6, 10.1)	
p-value <sup>b</sup>	0.0303	
<b>Weeks 37-48</b>	23 (10.3)	1 (0.9)
Difference in proportions (95% CI) <sup>a</sup>	9.4 (5.0, 13.7)	
p-value <sup>b</sup>	0.0017	

CI: confidence interval.

<sup>a</sup> Difference in proportions (luspatercept + BSC – placebo + BSC) and 95% CIs estimated from the unconditional exact test.

<sup>b</sup> P-value from the Cochran Mantel-Haenszel test stratified by the geographical region.

Exploratory findings

**Table 9. Exploratory efficacy results in patients with  $\beta$ -thalassaemia in ACE-536-B-THAL-001**

Endpoint	Luspatercept (N=224)	Placebo (N=112)
<b><math>\geq 33\%</math> 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</b>		
<b>Any consecutive 12 weeks*</b>	158 (70.5)	33 (29.5)
Difference in proportions (95% CI) <sup>a</sup>	41.1 (30.7, 51.4)	
<b>Any consecutive 24 weeks*</b>	92 (41.1)	3 (2.7)
Difference in proportions (95% CI) <sup>a</sup>	38.4 (31.3, 45.5)	
<b><math>\geq 50\%</math> 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</b>		
<b>Any consecutive 12 weeks*</b>	90 (40.2)	7 (6.3)
Difference in proportions (95% CI) <sup>a</sup>	33.9 (26.1, 41.8)	
<b>Any consecutive 24 weeks*</b>	37 (16.5)	1 (0.9)
Difference in proportions (95% CI) <sup>a</sup>	15.6 (10.5, 20.8)	
<b>Least square (LS) mean change from baseline in transfusion burden (RBC units/48 weeks)</b>		
<b>Weeks 1 to Week 48</b>		
LS mean	-4.67	+1.16
LS mean of difference (luspatercept-placebo) (95% CI) <sup>b</sup>	-5.83 (-7.01, -4.6)	
<b>Weeks 49 to Week 96</b>		
LS mean	-5.66	+2.19
LS mean of difference (luspatercept-placebo) (95% CI) <sup>b</sup>	-7.84 (-14.44, -1.25)	

CI: confidence interval.

<sup>a</sup> Difference in proportions (luspatercept + BSC – placebo + BSC) and 95% CIs estimated from the unconditional exact test.

<sup>b</sup> 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  $\mu\text{g/L}$  versus +114.28  $\mu\text{g/L}$  which resulted in a least square mean treatment difference of -347.8  $\mu\text{g/L}$  (95% CI: -516.95, -178.65).

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.

### **5.3 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  $\beta$ -thalassaemia patients.

#### Distribution

At the recommended doses, the mean apparent volume of distribution was 9.68 L for MDS patients and 7.08 L for  $\beta$ -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 0.437 L/day for  $\beta$ -thalassaemia. The mean half-life in serum was approximately 13 days for MDS patients and 11 days for  $\beta$ -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.

#### Haemoglobin 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  $\beta$ -thalassaemia.

## 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 32 years for  $\beta$ -thalassaemia patients. No clinically significant difference in AUC or clearance was found across age groups (< 65, 65-74, and  $\geq$  75 years for MDS patients; 18-23, 24-31, 32-41, and 42-66 years for  $\beta$ -thalassaemia patients).

### *Hepatic impairment*

Population PK analysis for luspatercept included patients with normal hepatic function (BIL, ALT, and AST  $\leq$  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  $\mu$ mol/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)  $\geq$  3 x ULN.

### *Renal impairment*

Population PK analysis for luspatercept included patients with normal renal function (eGFR  $\geq$  90 mL/min/1.73 m<sup>2</sup>; N = 315), mild renal impairment (eGFR 60 to 89 mL/min/1.73 m<sup>2</sup>; N = 171), or moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m<sup>2</sup>; N = 59). No clinically significant difference in mean steady state  $C_{\max}$  and AUC was found across renal function groups. PK data are not available for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m<sup>2</sup>) 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 *versus* White).

The following baseline disease characteristics had no clinically significant effect on luspatercept clearance: serum erythropoietin level, RBC transfusion burden, MDS ring sideroblasts,  $\beta$ -thalassaemia genotype ( $\beta^0/\beta^0$  *versus* non- $\beta^0/\beta^0$ ) and splenectomy.

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

## 6. NON CLINICAL PROPERTIES

### 6.1 Animal toxicology or Pharmacology

#### 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 (dam 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<sub>1</sub> pup body weights in both sexes at birth, throughout lactation, and post weaning (PND 28); lower body weights during the early pre-mating period (Week 1 and 2) in the F<sub>1</sub> females (adverse only at the 30 mg/kg/dose) and lower body weights in F<sub>1</sub> males during the pre-mating, pairing and post-mating periods; and microscopic kidney findings in F<sub>1</sub> 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<sub>1</sub> generation, precluded the determination of a NOAEL for F<sub>1</sub> 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<sub>1</sub> 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.

## 7. DESCRIPTION

Please refer section 2- Qualitative and Quantitative information for drug product description information.

### List of excipients

Citric acid monohydrate  
Tri-sodium citrate Dihydrate  
Polysorbate 80  
Sucrose  
Hydrochloric acid (for pH adjustment)  
Sodium hydroxide (for pH adjustment)  
Water for Injection

## 8. PHARMACEUTICAL PARTICULARS

### 8.1 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 8.4.

### 8.2 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 ( $\leq 25^{\circ}\text{C}$ ) or for up to 24 hours at  $2^{\circ}\text{C} - 8^{\circ}\text{C}$ .

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  $2^{\circ}\text{C} - 8^{\circ}\text{C}$ .

Do not freeze the reconstituted solution.

### 8.3 Packaging information

#### Luspatercept 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.



Luspatercept 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

**8.4 Storage and handling instructions**

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 8.2.

**Special precautions for disposal and other handling**

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

Reconstitution of the product

Luspatercept is supplied as a lyophilised powder for reconstitution before use. Only water for injections (WFI) should be used when reconstituting Luspatercept.

The appropriate number of luspatercept 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. Luspatercept 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.

Luspatercept 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, Luspatercept 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 8.2 or storage conditions.

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

## **9. PATIENT COUNSELLING INFORMATION**

Please refer to section 4.4 Special warnings and precautions for use and section 4.6 Fertility, pregnancy and lactation for patient counselling information.

## **10. DETAILS OF MANUFACTURER**

Manufactured by: Patheon Italia S.p.A., Viale G.B., Stucchi 110, Monza, 20900, Italy.

Batch Release by:  
Bristol-Myers Squibb Company of Princeton, New Jersey, USA  
having premises at Celgene Distribution B.V., Orteliuslaan 1000, 3528BD Utrecht, Netherlands

Imported and marketed by:

Bristol-Myers Squibb India Private Limited,

Bldg.B-4, Gala No. 3B & 4B, Citylink Warehousing Complex, Mumbai Nashik Highway,  
Vadape Village, Taluka: Bhiwandi – 16, District: Thane Z5, Pin- 421302, India

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## **11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE**

Permission no. IMP/BIO/22/000002 dated 12-Jan-2022

## **12. DATE OF REVISION**

Date of Revision – 06 Mar 2024

Document Version Number 2.1

Source – EU Summary of Product Characteristics (SmPC) version 6.0 dated 27 Feb 2023

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