Summary Report of Benefit-Risk Assessment

REBLOZYL POWDER FOR SOLUTION FOR INJECTION 25 MG/VIAL AND 75 MG/VIAL

NEW DRUG APPLICATION

Active Ingredient(s)	Luspatercept
Product Registrant	Bristol-Myers Squibb (Singapore) Pte. Ltd.
Product Registration Number	SIN16470P, SIN16471P
Application Route	Abridged evaluation
Date of Approval	06 April 2022

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A INTRODUCTION

Reblozyl is indicated for:

- 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.
- treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia.

The active substance, luspatercept, is a recombinant fusion protein that binds to selected transforming growth factor-β superfamily ligands and inhibits Smad2/3 signalling, resulting in the maturation of erythroid in the bone marrow.

Reblozyl is available as powder for solution for injection containing 25 mg/vial or 75 mg/vial of luspatercept. Other ingredients contained in the vial are citric acid monohydrate, sodium citrate, polysorbate 80, sucrose, hydrochloric acid and sodium hydroxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, luspatercept, is manufactured at Biogen MA Inc, North Carolina, USA. The drug product, Reblozyl powder for solution for injection 25 mg/vial and 75 mg/vial are manufactured at Patheon Italia S.p.A., Monza, Italy.

Drug substance:
Adequate controls have been presented for the reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on five consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B, and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the storage at ≤ -65°C with a shelf life of 5 years. The packaging is a 2 litre polyethylene terephthalate glycol (PETG) bottle with high-density polyethylene (HDPE) closure.

Drug product:
The manufacturing process utilises aseptic processing.

The manufacturing site involved is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the

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manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the shelf-life of 36 months when stored between 2 – 8 °C and the in-use periods of 8 hours at ≤ 25°C or 24 hours at 2 - 8 °C after reconstitution. The container closure system is a type I TopLyo® film coated borosilicate clear glass vial with bromobutyl rubber stopper and a crimp seal with a flip-off cap.

C ASSESSMENT OF CLINICAL EFFICACY

Myelodysplastic syndromes (MDS)

The clinical efficacy of luspatercept for the treatment of transfusion-dependent anaemia due to MDS with ring sideroblasts was based on data from one pivotal study, MEDALIST (Study ACE-536-MDS-001) and two supporting studies (Study A536-03 and Study A536-05).

Study A536-03 was a Phase 2, open-label, dose-ascending study that investigated subcutaneous (SC) luspatercept doses ranging from 0.125 mg/kg to 1.75 mg/kg every 3 weeks (Q3W) for up to 5 cycles in 107 adult patients with transfusion-dependent anaemia due to International Prognostic Scoring System (IPSS-R) low- or intermediate-1 risk MDS, or non-proliferative chronic myelomonocytic leukemia (CMML) who were not receiving prior treatment with an erythropoietin stimulating agent (ESA) and had no alternative treatment options.

The results showed that 42 patients (70%) with low transfusion burden (LTB) (defined as requiring <4 units of red blood cell (RBC) transfusions within 8 weeks prior to Cycle 1 Day 1) treated with luspatercept at dose levels of ≥0.75 mg/kg achieved an erythroid response (defined as haemoglobin (Hgb) increase by ≥1.5 g/dL from baseline for ≥14 days without requiring RBC transfusions).

In the cohort of patients who had high transfusion burden (HTB) (defined as requiring ≥4 units of RBC transfusions within 8 weeks prior to Cycle 1 Day 1), 24 patients (51.1%) achieved an erythroid response (defined as a reduction of either ≥4 units or ≥50% of units of RBC transfused over a period of 8 weeks compared to pretreatment). Of these, 21 patients were treated with luspatercept dose of 0.75 mg/kg to 1.75 mg/kg, and 3 patients were treated with luspatercept dose of 0.125 mg/kg to 0.5 mg/kg. A larger mean decrease from baseline in RBC transfusion units was seen in patients treated with luspatercept doses of 0.75 mg/kg to 1.75 mg/kg compared to patients treated with luspatercept dose of 0.125 mg/kg to 0.5 mg/kg (decreased by 0.64 unit versus 0.01 unit over a consecutive 8-week interval).

The efficacy of luspatercept observed in Study A536-03 was maintained during the long-term extension Phase 2 **Study A536-05**, which involved 70 subjects. Erythroid response was achieved by 37 LTB patients (78.7%) and 19 HTB patients (82.6%) as of the data cutoff date. The maximum tolerated dose was not reached at luspatercept dose of 1.75 mg/kg Q3W for up to 5 treatment cycles in Study A536-03 and no new safety concern was identified during the longer treatment (≥17 treatment cycles) in Study A536-05.

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The **MEDALIST study** was a Phase 3, randomised, double-blind, placebo-controlled, multicentre study that compared luspatercept with placebo in adult patients with anaemia due to IPSS-R very low-, low-, or intermediate-risk MDS with ring sideroblasts who are refractory or intolerant to, or ineligible for ESA treatment. All patients were to have an average RBC transfusion requirement of ≥2 units per 8 weeks, Hgb ≤10 g/dL prior to RBC transfusion and no consecutive 56-day period that was RBC transfusion-free during the 16 weeks immediately preceding randomisation.

Patients were randomised in a 2:1 ratio to receive either SC injections of luspatercept at a starting dose of 1 mg/kg Q3W or SC placebo injections Q3W. The study protocol allowed dose delays, dose reductions and/or discontinuations due to increased Hgb or adverse events (AEs) in either treatment arm. At Cycle 3 Day 1, patients may increase their dose in a stepwise manner, first to 1.33 mg/kg and then to a maximum of 1.75 mg/kg if they had ≥1 RBC transfusion event during the two most recent prior treatment cycles at the same dose level and have not met the protocol dose delay and/or reduction criteria in the two most recent treatment cycles. Best supportive care may be used in combination with the study drug when clinically indicated as per the investigator, excluding the use of ESA, immunosuppressant, hypomethylating agents and chemotherapy.

At Week 25 visit, patients whose disease did not progress and had shown evidence of clinical benefit such as decreased in RBC transfusion requirement or Hgb increase compared with baseline will continue the double-blind treatment in the extension phase and were treated until they experienced unacceptable toxicities, disease progression, withdrawal of consent from study, died or lost to follow-up. Patients who did not meet the clinical benefit criteria were discontinued from treatment.

The primary efficacy endpoint was RBC-transfusion-independence over any consecutive 8-week period (RBC-TI-8) from Week 1 to Week 24. The key secondary efficacy endpoint was RBC-transfusion-independence over any consecutive 12-week period (RBC-TI-12) from Week 1 to Week 48 and Week 1 to Week 24. A sequential testing approach was used for the primary and key secondary endpoints.

A total of 229 patients were randomised into the study, comprising 153 patients in the luspatercept arm and 76 patients in the placebo arm. The median treatment duration was 50.9 weeks (range: 6 to 207 weeks) in the luspatercept arm and 24.0 weeks (range: 7 to 103 weeks) in the placebo arm. The demographic characteristics of subjects at baseline were generally well balanced across the treatment arms. The median age was 71.0 years (range: 26.0 to 95.0 years), 184 (80.3%) patients were ≥65 years of age and 83 (36.2%) patients were ≥75 years of age. The stratification for IPSS-R risk category was well-balanced between the treatment arms. Overall, 10.5% patients had IPSS-R very low risk MDS, 72.5% patients had low risk MDS, and 16.6% patients had intermediate risk MDS. The median RBC transfusion volume over 8 weeks prior to baseline was 6 units for each of the treatment arms, and the median baseline haemoglobin level was 7.6 g/dL for both treatment arms. The majority of patients (95.2%) had previously received ESAs. Of the patients who had received prior ESAs, 97.3% in luspatercept arm and 98.6% in the placebo arm were refractory to ESA treatment. The percentage of patients who were intolerant to ESA treatment was 2.7% in luspatercept arm and 1.4% in the placebo arm. Among the 11 patients who had no prior treatment with ESA, 5 (3.3%) in luspatercept arm and 6 (7.9%) in the placebo arm were ineligible for ESA therapy due to elevated serum EPO >200 U/L. The percentage of patients who had a baseline serum erythropoietin level of >200 to 500 U/L was higher in luspatercept arm as compared to the placebo arm (28.1% vs 19.7%).

Treatment with luspatercept resulted in a statistically significantly higher rate of RBC-TI-8 response during Weeks 1 through 24 compared to placebo (37.9% vs 13.2%; odds ratio [OR] 5.07; 95% CI: 2.28, 11.26; p<0.0001). Luspatercept demonstrated a statistically significant higher RBC-TI-12 response rate in the key secondary endpoint as compared to the placebo arm (28.1% vs 7.9%; OR 5.07; 95% CI: 2.00, 12.84; p=0.0002).

Luspatercept also resulted in a statistically significantly higher proportion of patients who had mean Hgb increase of ≥1 g/dL compared to placebo treatment from Weeks 1 through 24 (35.3% vs 7.9%, respectively; p<0.0001) and from Weeks 1 through 48 (41.2% vs 10.5%, respectively; p<0.0001). The median reduction in RBC transfusion volume over 16 weeks was higher in the luspatercept arm than the placebo arm from Weeks 1 through 24 (4 units vs 0 unit) and Weeks 1 through 48 (5 units vs 2.5 units).

Summary of Key Efficacy Endpoints (Study MEDALIST)

	Luspatercept (N=153)	**Placebo (N=76)**	**Odds ratio / Hazard ratio**	**p-value [a]**
Primary efficacy endpoint				
RBC-TI-8 response rate, n (%) (Week 1 through 24)	58 (37.9)	10 (13.2)	5.065 (2.278, 11.259) [a]	<0.0001
Key secondary efficacy endpoints				
RBC-TI-12 response rate, n (%) (Week 1 through 24)	43 (28.1)	6 (7.9)	5.071 (2.002, 12.844) [a]	0.0002
RBC-TI-12 response rate, n (%) (Week 1 through 48)	51 (33.3)	9 (11.8)	4.045 (1.827, 8.956) [a]	0.0003
Secondary efficacy endpoints				
RBC-TI-8 response rate, n (%) (Week 1 through 48)	69 (45.1)	12 (15.8)	5.306 (2.526, 11.146) [a]	<0.0001
Mean Hgb increase ≥1.0 g/dL, n (%) (Week 1 through 24)	54 (35.3)	6 (7.9)	-	<0.0001
Mean Hgb increase ≥1.0 g/dL, n (%) (Week 1 through 48)	63 (41.2)	8 (10.5)	-	<0.0001
Median change from baseline in RBC transfusion volume over 16 weeks (Week 9 through 24)	-4 units	0 unit	-	-
Median change from baseline in RBC transfusion volume over 16 weeks (Week 33 through 48)	-5 units	-2.5 units	-	-
≥50% reduction in RBC transfusion volume for any 16-week period, n (%)	84 (54.9)	15 (19.7)	-	-
mHI-E [b] response rate, n (%) (Week 1 through 24)	81 (52.9)	9 (11.8)	-	-
RBC transfusion reduction of 4 units per 8 weeks, n/N [c] (%)	52/107 (48.6)	8/56 (14.3)	-	-
Mean Hgb increase of ≥1.5 g/dL for 8 weeks, n/N [d] (%)	29/46 (63.0)	1/20 (5.0)	-	-
mHI-E [b] response rate, n (%) (Week 1 through 48)	90 (58.8)	13 (17.1)	-	-
RBC transfusion reduction of 4 units per 8 weeks, n/N [c] (%)	58/107 (54.2)	12/56 (21.4)	-	-

Mean Hgb increase of ≥1.5 g/dL for 8 weeks, n/N [d] (%)	32/46 (69.6)	1/20 (5.0)	-	-
Death event, n (%)	45 (29.4)	24 (31.6)	0.986 (0.595, 1.636) [f]	0.9580
Follow-up time (months), median Median survival (months) (95% CI) [e]	34.1 46.0 (42.0, NE)	34.3 NE (43.1, NE)	-	-

CI: confidence interval; Hgb: haemoglobin; NE: not evaluable; mHI-E: modified haematologic improvement for erythroid parameter; RBC: red blood cell; RBC-TI-8: absence of any RBC transfusion during any consecutive 8-week period; RBC-TI-12: absence of any RBC transfusion during any consecutive 12-week period

[a] The odds ratio was based on Cochran-Mantel-Haenszel test stratified for average baseline transfusion burden (≥6 units versus <6 units per 8 weeks), and baseline IPSS-R (very low or low versus intermediate).

[b] For subjects with baseline RBC transfusion burden ≥4 units/8week, mHI-E was defined as a reduction in RBC transfusion of at least 4 units/8 weeks; for subjects with baseline RBC transfusion burden <4 units/8 weeks, mHI-E was defined as a mean increase of Hgb of ≥1.5 g/dL for 8 weeks in the absence of RBC transfusions.

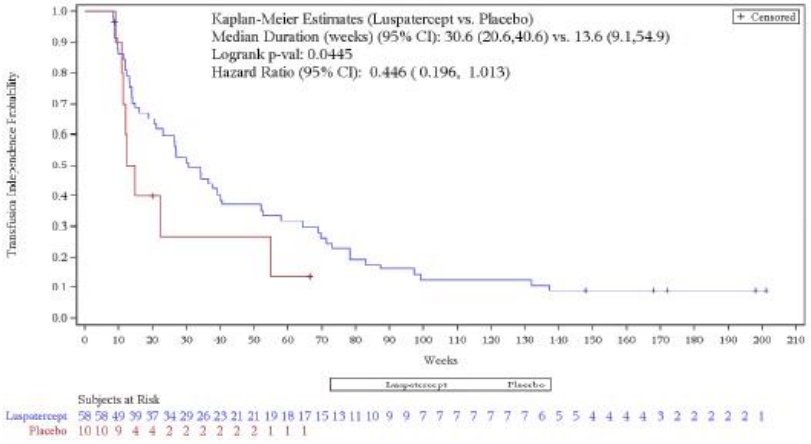
[c] Percentage based on number of subjects (N) with baseline RBC transfusion burden of ≥4 units/8 weeks.

[d] Percentage based on number of subjects (N) with baseline RBC transfusion burden of <4 units/8 weeks.

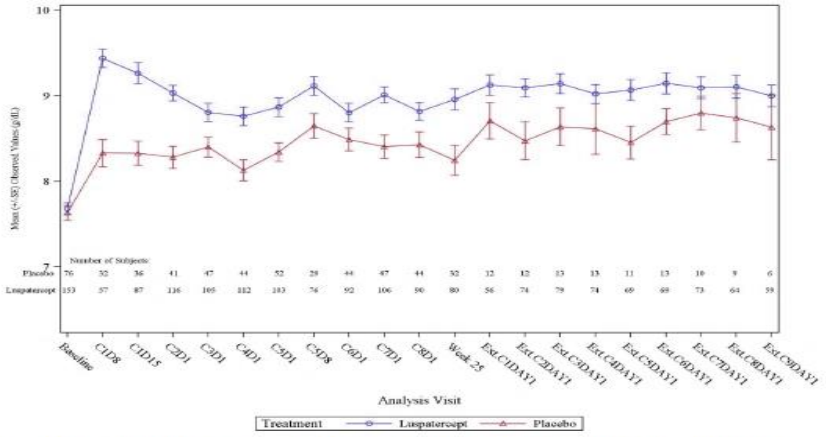
[e] Median was from the Kaplan-Meier method stratified by average baseline RBC transfusion requirement (≥6 units versus <6 units of RBC per 8 weeks) and baseline IPSS-R score (very low or low versus intermediate).

[f] The hazard ratio was from the Cox proportional hazards model with RBC transfusion requirement (≥6 units versus <6 units of RBC per 8 weeks) and baseline IPSS-R score (very low or low versus intermediate) as covariates.

Kaplan-Meier curves for Duration of RBC-TI-8 Response in Patients who Responded During Week 1 through 24 (ITT population) (Study MEDALIST)



Mean (SE) Observed Haemoglobin values by time point from Baseline through Week 48 (ITT population) (Study MEDALIST)



C = cycle; D = day; Ext = extension; IP = investigational product; ITT = intent-to-treat; RBC = red blood cell; SE = standard error of the mean.

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Pre-specified subgroup analyses demonstrated a consistent treatment effect for the primary endpoint across subgroups analysed, including age group (≤64 years, 65-74 years, ≥75 years), ECOG performance status (0 or 1, 2), average baseline RBC transfusion requirement (≥6 units/8 weeks, <6 units/8 weeks, 4 - <6 units/8 weeks, <4 units/8 weeks), baseline IPSS-R risk (intermediate, very low or low, very low, low), and baseline serum EPO (<100 U/L, 100 - <200 U/L, 200-500 U/L, >500 U/L).

Overall, the results in MEDALIST study supported the treatment benefit of luspatercept for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts and who had an unsatisfactory response to or are ineligible for EPO-based therapy.

Beta (β)-thalassaemia

The clinical efficacy of luspatercept for the treatment of transfusion-dependent anaemia associated with β-thalassaemia was based on data from one pivotal study, BELIEVE (Study ACE-536-B-THAL-001) and two supporting studies (Study A536-04 and Study A536-06).

Study A536-04 was a Phase 2, open-label, dose-ascending study that investigated SC luspatercept doses ranging from 0.2 mg/kg to 1.5 mg/kg Q3W for up to 5 cycles in 35 adult patients with anaemia associated with β-thalassaemia. The study demonstrated that erythroid response (defined as Hgb increase of ≥1.5 g/dL from baseline for ≥14 days in the absence of RBC transfusion) was achieved in 9 (27.3%) patients who were non-transfusion dependent (NTD) (defined as having received <4 units of RBC within 8 weeks prior to Cycle 1 Day 1) and treated with luspatercept at doses ≥0.8 mg/kg.

In the cohort of patients who were transfusion-dependent (TD) (defined as requiring ≥4 units of RBC transfusions within 8 weeks confirmed over 6 months prior to Cycle 1 Day 1), 25 (80.6%) patients treated with luspatercept at doses ranging from 0.6 mg/kg to 1.25 mg/kg achieved ≥20% reduction in RBC transfusion burden during any consecutive 12-week interval, and 26 (83.9%) of patients achieved ≥50% reduction in RBC transfusion burden during any consecutive 8-week interval.

The efficacy of luspatercept observed in Study A536-04 was maintained during the long-term extension Phase 2 **Study A536-06**, with 21 (77.8%) of NTD patients achieving Hgb increase of ≥1.0 g/dL over any consecutive 8- or 12-week interval in the absence of RBC transfusion and 23 (95.8%) of TD patients achieving ≥20% reduction in RBC transfusion burden from baseline during any consecutive 12-week interval. Luspatercept was generally well-tolerated up to the maximum tolerated dose of 1.25 mg/kg Q3W.

The **BELIEVE study** was a Phase 3, randomised, double-blind, placebo-controlled, multicentre study that compared luspatercept with placebo in adult patients with β-thalassaemia or β-thalassaemia with haemoglobin E (HbE) who require regular RBC transfusions (defined as 6 to 20 RBC units in the 24 weeks prior to randomisation and no transfusion-free period for >35 days during that period). Patients were randomised in a 2:1 ratio to receive either SC injections of luspatercept at a starting dose of 1 mg/kg Q3W or SC placebo injections Q3W. The study protocol allowed dose delays, dose reductions and/or discontinuations due to increased Hgb or AEs in either treatment arms. Patients may increase their dose to a maximum of 1.25 mg/kg if the RBC transfusion reduction over at least two dose cycles (approximately 6 weeks) was <33% compared with baseline, or ≥33% but ≤50% compared to baseline and at the discretion of the Investigator. Best supportive care including RBC transfusions, iron chelation therapy (ICT), antibiotic, antiviral, antifungal therapies, and/or

nutritional support may be used in combination with the treatment when clinically indicated per the Investigator.

Patients who completed 48-week double-blind treatment period could continue to receive the study drug to which they were initially randomised in the double-blind treatment period for up to 48 weeks or until the date of study unblinding, at the Investigator's discretion. Dose titration during the long-term, double-blind treatment period was allowed.

The primary efficacy endpoint was haematologic improvement by ≥33% from Week 13 to 24 (defined as ≥33% reduction in RBC transfusion burden from baseline with a reduction of at least 2 units compared with the 12-week interval prior to randomisation). The key secondary efficacy endpoints were haematologic improvement ≥33% from Week 37 to 48, haematologic improvement ≥50% from Week 13 to 24 and Week 37 to 48, and the change in transfusion burden from Week 13 to 24. A sequential testing approach was used for the primary and key secondary endpoints.

A total of 336 patients were randomised into the study, comprising 224 patients in the luspatercept arm and 112 patients in the placebo arm. The median treatment duration was 153.57 weeks (range: 1.7 to 215.0 weeks) in the luspatercept arm and 74.71 weeks (range: 8.9 to 104.0 weeks) in the placebo arm. The patient demographics were well-balanced between the treatment arms. The median age was 30.0 years (range: 18.0 to 66.0 years), 192 (57.1%) patients were ≤32 years of age and 22 (6.5%) patients were >50 years of age. The majority of patients were female (58.0%), White (54.2%) or Asian (34.8%). Overall, 76.5% patients had a diagnosis of β-thalassaemia, 15.5% patients had HbE/β-thalassaemia and 7.7% patients had β-thalassaemia combined with α-thalassaemia.

The baseline characteristics of patients were representative of a patient population who had high transfusion dependency due to β-thalassaemia and heavily iron overloaded despite chronic ICT. Overall, 43.5% of patients had received >15 RBC units per 24 weeks interval, and 42.6% of patients had received >10 to ≤15 RBC units per 24 weeks interval. The mean liver iron concentration (LIC) at baseline was 11.39 mg/g dry weight (dw), and 97.3% of patients had used at least one ICT prior to randomisation. A total of 57.7% of patients were splenectomised and 68.2% of patients had abnormal LIC values of >3 mg/g dw.

Treatment with luspatercept resulted in a statistically significantly higher response rate for haematologic improvement by ≥33% compared to placebo from Week 13 to 24 (21.4% vs 4.5%; odds ratio 5.79; 95% CI: 2.24, 14.97; p<0.0001) and from Week 37 to 48 (19.6% vs 3.6%; odds ratio 6.44; 95% CI: 2.27, 18.26; p<0.0001). Luspatercept demonstrated a statistically significantly higher response rate for the key secondary efficacy endpoint of haematologic improvement by ≥50% compared to the placebo arm from Week 13 to 24 (7.6% vs 1.8%; odds ratio 4.55; 95% CI: 1.03, 20.11; p=0.0303) and from Week 37 to 48 (10.3% vs 0.9%; odds ratio 11.92; 95% CI: 1.65, 86.29; p=0.0017). The mean change in RBC transfusion requirement from baseline at Week 13 to 24 was statistically significantly higher in luspatercept arm compared to the placebo arm (-0.67 RBC units vs +0.66 RBC units; p<0.0001).

The secondary efficacy endpoints results demonstrated that luspatercept resulted in a longer duration of haematologic improvement compared to placebo. At ≥33% and ≥50% reductions in RBC transfusion burden, the longest median duration of transfusion burden reduction was 104 days vs 90 days and 90 days vs 97.5 days, respectively. The proportion of patients who maintained RBC transfusion independence was higher in the luspatercept arm as compared to the placebo arm for any 6 weeks interval (17.0% vs 6.3%), any 8 weeks interval (10.7% vs

1.8%) and any 12 weeks interval (4.0% vs 0%). A greater change in mean serum ferritin level from baseline was seen in the luspatercept arm than the placebo arm (-248 µg/L vs +106 µg/L).

Treatment with luspatercept did not result in a reduction of LIC from baseline compared to placebo (+0.10 mg/g dw vs +0.08 mg/g dw) over the 48-week double-blind treatment period.

Summary of Key Efficacy Endpoints (Study BELIEVE)

	Luspatercept (N=224)	Placebo (N=112)	Odds ratio	p-value [a]
Primary efficacy endpoint				
≥33% reduction in RBC transfusion burden from baseline, n (%) (Week 13 to Week 24)	48 (21.4)	5 (4.5)	5.79 (2.24, 14.97)	<0.0001
Key secondary efficacy endpoints				
≥33% reduction from baseline in RBC transfusion burden, n (%) (Week 37 to Week 48)	44 (19.6)	4 (3.6)	6.44 (2.27, 18.26)	<0.0001
≥50% reduction from baseline in RBC transfusion burden, n (%) (Week 13 to Week 24)	17 (7.6)	2 (1.8)	4.55 (1.03, 20.11)	0.0303
≥50% reduction from baseline in RBC transfusion burden from baseline, n (%) (Week 37 to Week 48)	23 (10.3)	1 (0.9)	11.92 (1.65, 86.29)	0.0017
Mean change in transfusion burden from baseline to the fixed Week 13 to Week 24 interval (RBC units/12 weeks)	-0.67	0.66	-	<0.0001
LS mean of difference (95% CI) [b]	-1.35 (-1.77, -0.93)			
Other efficacy endpoints				
RBC transfusion independence [c] for any 6-week interval, n (%)	38 (17.0)	7 (6.3)	3.18 (1.36, 7.44)	0.0055
RBC transfusion independence [c] for any 8-week interval, n (%)	24 (10.7)	2 (1.8)	6.76 (1.56, 29.28)	0.0036
RBC transfusion independence [c] for any 12-week interval, n (%)	9 (4.0)	0	INF	0.0317
Time to first ≥33% reduction in RBC transfusion burden Mean (days) Median (days)	 56.1 12.0	 119.2 107	-	-
Time to first ≥50% reduction in RBC transfusion burden Mean (days) Median (days)	 80.5 24.5	 90.3 43.0	-	-
Mean change in serum ferritin from baseline (µg/L)	-248.02	106.62	-	<0.0001
LS mean of difference (95% CI) [b]	-347.80 (-516.95, -178.65)			
Mean change in LIC at Week 48 (mg/g dw)	0.10	0.08	-	0.8685
LS mean of difference (95% CI) [b]	0.11 (-1.16, 1.38)			

CI: confidence interval; CMH: Cochran-Mantel Haenszel; dw: dry weight; LS: least squares; RBC: red blood cell; INF: infinity; LIC: liver iron concentration

[a] Odds ratio (luspatercept minus placebo) and 95% CIs were estimated from the CMH method stratified by the geographical regions defined at randomisation.

[b] Difference in proportions (luspatercept minus placebo). Estimates were based on an ANCOVA model with geographical regions defined at randomisation and baseline transfusion burden as covariates.
[c] Transfusion independence was defined as the absence of any transfusion during any consecutive rolling 6-, 8-, or 12-week interval within the entire study period.

Pre-specified subgroup analyses demonstrated a consistent treatment effect for the primary endpoint across the subgroups analysed, including region (North America, Europe, Middle East, North Africa, Asia-Pacific), age group (≤32 years, >32 years), splenectomy (yes, no), sex (female, male), β-thalassaemia gene (β0/β0, non-β0/β0), baseline transfusion burden (≤6 RBC units/12 weeks, >6 RBC units/12 weeks), baseline haemoglobin level (<9 g/dL, ≥9 g/dL), and baseline LIC (≤3 mg/g dw, >3 to ≤7 mg/g dw, >7 to ≤15 mg/g dw, >15 mg/g dw).

Overall, the results in BELIEVE study supported the treatment benefit of luspatercept for adult patients with transfusion-dependent anaemia associated with β-thalassaemia.

D ASSESSMENT OF CLINICAL SAFETY

Myelodysplastic syndrome (MDS)

The safety data on the use of luspatercept in patients with transfusion-dependent anaemia due to MDS were mainly derived from Study MEDALIST, comprising a total of 229 patients (153 patients in the luspatercept arm and 76 patients in the placebo arm). The median treatment duration was longer in the luspatercept arm (50.9 weeks) compared to the placebo arm (24.0 weeks).

A total of 200 (87.3%) patients had their study drug dose increased from 1 mg/kg to 1.33 mg/kg at least once in the study (129 [84.3%] patients in the luspatercept arm and 71 [93.4%] patients in the placebo arm). The treatment dose was increased from 1.33 mg/kg to 1.75 mg/kg in 105 (68.6%) patients in the luspatercept arm and 64 (84.2%) patients in the placebo arm. A higher proportion of patients in the luspatercept arm than the placebo arm remained at 1 mg/kg dose level throughout the study (15.7% vs 6.6%). Treatment dose reduction from 1 mg/kg to 0.8 mg/kg had occurred in 9 (5.9%) of patients in the luspatercept arm (one of these patients had a further dose reduction to 0.6 mg/kg) and none in the placebo arm. The most common reason for dose reduction was Grade 3 or higher adverse event (AE) related to study drug in 5 (3.3%) patients and increase in Hgb ≥2.0 g/dL compared to predose Hgb of previous treatment cycle in 3 (2.0%) patients.

Overview of Safety Profile (Study MEDALIST, Safety Analysis Set)

Number (%) of patients with:	Luspatercept (N=153)	Placebo (N=76)
Any TEAE	151 (98.7)	70 (92.1)
Treatment-related TEAE	71 (46.4)	26 (34.2)
Serious TEAE	66 (43.1)	23 (30.3)
Grade 3 or 4 TEAE	86 (56.2)	34 (44.7)
Death	8 (5.2)	4 (5.3)
TEAE leading to study drug dose interruption	42 (27.5)	4 (5.3)
TEAE leading to study drug dose reduction	9 (5.9)	0
TEAE leading to study drug discontinuation	22 (14.4)	6 (7.9)

TEAE: treatment-emergent adverse event; SAE: serious adverse event

Treatment-emergent adverse events (TEAEs) with exposure-adjusted incidence rates of ≥ 5 events per 100 person-years that were reported more frequently in the luspatercept arm compared to the placebo arm included diarrhoea (25.8 events vs 18.4 events, respectively), dizziness (19.2 vs 8.9), nausea (20.1 vs 13.7), bronchitis (10.7 vs 2.2), vertigo (5.8 vs 0) and influenza (5.3 vs 0). TEAEs for which an imbalance in exposure-adjusted incidence rate between treatment arms was observed were mainly Grade 1 or 2 in severity. The incidence of overall TEAEs was consistent across the dose titration levels.

Grade 3 or 4 TEAEs with exposure-adjusted incidence rate of ≥ 1 event per 100 person-years that were reported more frequently in the luspatercept arm compared to the placebo arm were asthenia (2.7 events vs 0 events, respectively), fall (5.0 vs 4.3), hyperuricemia (4.1 vs 2.2), iron overload (3.2 vs 2.2), syncope (2.8 vs 2.2), femur fracture (2.3 vs 0), atrioventricular block (1.4 vs 0), cataract (1.4 vs 0), diabetes mellitus (1.4 vs 0), hyponatraemia (1.3 vs 0) and pyrexia (1.3 vs 0).

TEAEs that led to the permanent discontinuation of study drug were reported more frequently in the luspatercept arm than the placebo arm (14.4% vs 7.9%, respectively). The difference was driven by higher percentages of patients in luspatercept arm compared to the placebo arm who experienced refractory anaemia with an excess of blasts (2.0% vs 0%) and sepsis (2.0% vs 0%). In total, 8 (5.2%) patients in the luspatercept arm and 4 (5.3%) patients in the placebo arm died on-treatment during the study. The causes of deaths were generally consistent with the natural course of MDS in a predominantly older population, and none of the deaths were related to the study drug.

The adverse event of special interest for luspatercept was hypertension. Patients treated with luspatercept showed an average of 5 mmHg increase in the systolic and diastolic blood pressure from baseline. Blood pressure increase could be managed with dose interruptions and/or dose modifications and this has been described in the package insert.

Overall, the safety profile of luspatercept was considered acceptable for the intended population of transfusion-dependent patients with significant comorbidities of MDS, and the luspatercept-related AEs were manageable through dose interruptions and/or dose reductions.

<u>Beta (β)-thalassaemia</u>

The safety data on the use of luspatercept in patients with transfusion-dependent anaemia associated with β-thalassaemia were mainly derived from Study BELIEVE, comprising a total of 332 patients (223 patients in the luspatercept arm and 109 patients in the placebo arm). The median treatment duration was longer in the luspatercept arm (153.57 weeks) compared to placebo arm (74.71 weeks).

A total of 162 (51.4%) patients had their study drug dose increased from 1 mg/kg to 1.25 mg/kg at any time in the study (116 [52.0%] in the luspatercept arm and 72 [66.1%] patients in the placebo arm). Treatment dose reduction from 1 mg/kg to 0.8 mg/kg had occurred in 27 (12.1%) patients in the luspatercept arm and 3 (2.8%) patients in placebo arm. A second dose reduction from 0.8 mg/kg to 0.6 mg/kg had occurred in 7 (3.1%) patients in the luspatercept arm and 1 (0.9%) patient in the placebo arm.

Overall of Safety Profile (Study BELIEVE, Safety Analysis Set)

Number (%) of patients with:	Luspatercept (N=223)	Placebo (N=109)
Any TEAE	219 (98.2)	102 (93.6)
Treatment-related TEAE	135 (60.5)	31 (28.4)
Serious TEAE	53 (23.8)	8 (7.3)
Grade 3 or 4 TEAE	84 (37.7)	19 (17.4)
Treatment-related Grade 3 or 4 TEAE	27 (12.1)	1 (0.9)
TEAE leading to death	2 (0.9)	1 (0.9)
Treatment-related TEAE leading to death	0	0
TEAE leading to study drug dose delay	46 (20.6)	11 (10.1)
Treatment-related TEAE leading to study drug dose delay	15 (6.7)	3 (2.8)
TEAE leading to study drug dose reduction	10 (4.5)	3 (2.8)
Treatment-related TEAE leading to study drug dose reduction	9 (4.0)	2 (1.8)
TEAE leading to study drug discontinuation	25 (11.2)	2 (1.8)
Treatment-related TEAE leading to study drug discontinuation	20 (9.0)	1 (0.9)

TEAE: treatment-emergent adverse event; SAE: serious adverse event

TEAEs that were reported by ≥5% of luspatercept-treated patients and at a ≥5% higher incidence than the placebo arm included headache (35.0% vs 24.8%, respectively), arthralgia (22.9% vs 13.8%), bone pain (22.4% vs 8.3%), cough (22.4% vs 8.3%), abdominal pain (13.5% vs 6.4%), dizziness (13.5% vs 4.6%), vomiting (13.5% vs 7.3%), nausea (13.0% vs 5.5%), hypertension (10.3% vs 2.8%), nasal congestion (9.4% vs 2.8%), dyspepsia (8.5% vs 0.9%), hyperuricaemia (7.2% vs 0%), and tonsilitis (7.2% vs 1.8%).

Treatment-related TEAEs that were reported by ≥5% of patients and reported more frequently in luspatercept arm compared to the placebo arm included bone pain (19.3% vs 4.6%, respectively), back pain (19.3% vs 8.3%), arthralgia (13.0% vs 4.6%), pain in extremity (7.2% vs 0%), fatigue (6.3% vs 3.7%) and headache (10.8% vs 7.3%). Grade 3 or higher TEAEs that were reported more frequently in the luspatercept arm compared to the placebo arm included back pain (2.7% vs 0.9%), bone pain (1.8% vs 0%), hyperuricaemia (2.2% vs 0%), anaemia (4.0% vs 0%), and liver iron concentration increased (2.7% vs 0.9%)

TEAEs that led to the permanent discontinuation of study drug were reported more frequently in the luspatercept arm than the placebo arm (11.2% vs 1.8%). Most of such events were reported in 2 or less patients. The TEAEs that led to the permanent discontinuation of study drug in luspatercept arm compared to placebo arm were arthralgia, back pain, deep vein thrombosis, extramedullary haemopoiesis and sinus tachycardia (2 vs 0 patients for all).

The adverse events of special interest for luspatercept in this patient population were thromboembolic events and hypertension. The exposure-adjusted incidence rates of thromboembolic event was 3.5 per 100 patient-years in the luspatercept arm and 0.8 per 100 patient-years in the placebo arm. All the patients who experienced thromboembolic events were splenectomised and had additional baseline risk factors. The thromboembolic event rate in luspatercept arm was similar to that reported in regularly-transfused patients with β-thalassaemia who have undergone splenectomy. The exposure-adjusted incidence rates of hypertension event was 7.3 per 100 patient-years in the luspatercept arm and 3.3 per 100 patient-years in the placebo arm. Grade 3 hypertension events were reported in 4 patient (1.8%) treated with luspatercept and none in the placebo arm. Thromboembolic and hypertension events have been described in the warnings and precaution and adverse drug

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reaction sections in the package insert and will be monitored as part of routine pharmacovigilance.

Overall, luspatercept presented an acceptable safety profile for patients with transfusion-dependent anaemia associated with β-thalassaemia, which was similar to that in patients with transfusion-dependent MDS.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Myelodysplastic syndrome (MDS)

Anaemia is common in patients with low-risk MDS, and most patients become dependent on RBC transfusion. Long-term RBC transfusion is associated with iron overload and cardiovascular complications. The current pharmacological strategy for managing anaemia in low-risk MDS includes erythropoietin stimulating agent (ESA). Treatment with ESA is less effective for patients with high endogenous erythropoietin (EPO) level, and the majority of patients who had an initial response eventually may become unresponsive to ESA. There remains an unmet medical need for alternative treatment options for patients with transfusion-dependent anaemia due to low-risk MDS who had an unsatisfactory response to or are ineligible for EPO-based therapy.

The MEDALIST study demonstrated that luspatercept statistically significantly increased the RBC transfusion independence rate compared to placebo for at least 8 weeks (odds ratio 5.07; 95% CI: 2.28, 11.26; p<0.0001) and for at least 12 weeks (odds ratio 5.07; 95% CI: 2.00, 12.84; p=0.0002). The proportion of patients with Hgb increase by ≥1 g/dL was higher in luspatercept arm than placebo arm from Week 1 to 24 (35.3% vs 7.9%, respectively) and Week 1 to 48 (41.2% vs 10.5%, respectively). In addition, luspatercept-treated patients showed greater reduction in RBC transfusion volume compared to placebo from Week 9 to 24 (4 units vs 0 unit) and from Week 33 to 48 (5 units vs 2.5 units). A higher proportion of patients in luspatercept arm achieved ≥50% reduction in RBC transfusion volume for any 16-week period compared to placebo arm (54.9% vs 19.7%, respectively).

The safety profile of luspatercept for patients with transfusion-dependent anaemia due to low-risk MDS was considered acceptable relative to its benefits. The notable safety finding with luspatercept in this population is hypertension, which has been adequately addressed in the local package insert with relevant warnings and precautions, dose interruption, dose modification and/or treatment discontinuation.

Overall, the benefit-risk profile of luspatercept for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy was considered positive.

Beta (β)-thalassaemia

β-thalassemia is an inherited haemoglobinopathy. RBC transfusion is the mainstay of therapy for anaemia associated with β-thalassemia and most patients become transfusion dependent with iron overload and are reliant on long-term iron chelation treatment. There is an unmet medical need for therapies to ameliorate ineffective erythropoiesis in patients with anaemia associated with β-thalassemia.

The BELIEVE study showed that luspatercept significantly reduced the RBC transfusion burden by ≥33% compared to placebo from Week 13 to 24 (odds ratio 5.79; 95% CI: 2.24, 14.97; p<0.0001). The reduction in RBC transfusion burden by ≥50% was also statistically significantly higher with luspatercept treatment compared to placebo treatment (odds ratio 4.55; 95% CI: 1.03, 20.11; p=0.0303). In addition, luspatercept-treated patients showed greater mean change in RBC transfusion burden from baseline as compared to placebo (-0.67 RBC units per 12 weeks interval vs +0.66 RBC units per 12 weeks interval).

The safety profile of luspatercept for patients with anaemia due to β-thalassaemia was consistent with that for patients with anaemia associated with low-risk MDS. The notable safety findings with luspatercept in this population were thromboembolic events and hypertension events. These safety findings have been adequately addressed in the package insert via with relevant warnings and precautions, dose interruptions, dose modifications and/or treatment discontinuations.

Overall, the benefit-risk profile of luspatercept for treatment of adult patients with transfusion-dependent anaemia associated with β-thalassaemia was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of luspatercept was deemed favourable for the following indications:

- Treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS with ring sideroblasts who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy
- Treatment of adult patients with transfusion-dependent anaemia associated with β-thalassaemia

Approval of the product registration was granted on 06 April 2022.

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APPROVED PACKAGE INSERT AT REGISTRATION

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REBLOZYL (Luspatercept)

Powder for Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

Reblozyl Powder for Solution for Injection 25 mg/vial
Reblozyl Powder for Solution for Injection 75 mg/vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Reblozyl Powder for Solution for Injection 25 mg/vial
Each vial contains 25 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

Reblozyl Powder for Solution for Injection 75 mg/vial
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 for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia (see section 5.1).

Limitation of use
Reblozyl is not indicated for use as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anaemia.

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.

Myelodysplastic syndromes

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

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 Reblozyl is 1.0 mg/kg administered once every 3 weeks by subcutaneous injection.

In patients who do not achieve a response after ≥ 2 consecutive doses (6 weeks), at the 1.0 mg/kg starting dose, the dose should be increased to 1.25 mg/kg. Minimum response is defined as a reduction in RBC transfusion burden by at least a third after ≥ 2 consecutive doses (6 weeks), at the 1.0 mg/kg starting dose. 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 β-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 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 (> 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

Current dose	Dose reduction
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 β-thalassaemia

Current dose	Dose reduction
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.

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.

Discontinuation
Reblozyl 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 Reblozyl (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 ≥ 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). 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 should be closely monitored for renal function as per standard of care.

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 months of age in β-thalassaemia. For non-clinical data, see section 5.3.

The safety and efficacy of Reblozyl in the paediatric patients aged from 6 months 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.

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).

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 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 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.

Increased blood pressure
In controlled clinical studies in MDS and β-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 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 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.

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 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 two pivotal studies in MDS and β-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 (≥ 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 3. Adverse drug reactions (ADRs) in patients treated with Reblozyl for MDS and β-thalassaemia

System organ class	Preferred term	Frequency (all grades) for MDS	Frequency (all grades) for β-thalassaemia
Infections and infestations	bronchitis	Very common	Common
	urinary tract infection	Very common	Common
	upper respiratory tract infection	Common	Very common
	influenza	Common	Common
Immune system disorders	hypersensitivity*	Common	Common
Metabolism and nutrition disorders	hyperuricaemia	Common	Common
Nervous system disorders	dizziness	Very common	Very common
	headache	Very common	Very common
	syncope/presyncope	Common	Common
Ear and labyrinth disorders	vertigo/vertigo positional	Common	Common
Vascular disorders	hypertension~	Common	Common
	thromboembolic events§	Common	Common
Respiratory, thoracic and mediastinal disorders	dyspnoea	Very common	Common
Gastrointestinal disorders	diarrhoea	Very common	Very common
	nausea	Very common	Common
Musculoskeletal and connective tissue disorders	back pain	Very common	Very common
	arthralgia	Common	Very common
	bone pain	Common	Very common
General disorders and administration site conditions	fatigue	Very common	Very common
	asthenia	Very common	Common
	injection site reactions#	Common	Common

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

~ Hypertension reaction includes essential hypertension, hypertension and hypertensive crisis.

Injection site reactions include injection site erythema, injection site pruritus, injection site swelling and injection site rash.

§ Thromboembolic events include deep vein thrombosis, portal vein thrombosis, ischaemic stroke and pulmonary embolism.

Description of selected adverse reactions

Bone pain
Bone pain was reported in 19.7% of β-thalassaemia patients treated with luspatercept (placebo 8.3%) and in 2.6% of MDS patients treated with luspatercept (placebo 3.9%). In 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 19.3% of β-thalassaemia patients treated with luspatercept (placebo 11.9%) and in 5.2% of MDS patients treated with luspatercept (placebo 11.8%). In the β-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 β-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 β-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 β-thalassaemia patients treated with luspatercept (1.8% placebo). In clinical studies, all events were Grade 1/2. In β-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 β-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 β-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.

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 β-thalassaemia, an analysis of 284 β-thalassaemia patients who were treated with luspatercept and who were evaluable for the presence of anti-luspatercept antibodies showed that 4 (1.4%) β-thalassaemia patients tested positive for treatment-emergent anti-luspatercept antibodies, including 2 (0.7%) β-thalassaemia patients who had neutralising antibodies against luspatercept.

Luspatercept serum concentration tended to decrease in the presence of neutralising antibodies. There were no severe systemic hypersensitivity reactions reported for patients with anti-luspatercept antibodies. There was no association between hypersensitivity type reactions or injection site reactions and presence of anti-luspatercept antibodies.

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, white blood cell count >13 x 10^9/L, neutrophils < 0.5 x 10^9 /L, platelets <50 x 10^9/L or with prior use of a disease modifying agent for treatment of 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

	Luspatercept (N=153)	Placebo (N=76)
Demographics		
Age[a] (years)		
Median (min, max)	71 (40, 95)	72 (26, 91)
Age categories, n (%)		
<64 years	29 (19.0)	16 (21.1)
65-74 years	72 (47.1)	29 (38.2)
≥75	52 (34.0)	31 (40.8)
Sex, n (%)		
Male	94 (61.4)	50 (65.8)
Female	59 (38.6)	26 (34.2)
Race, n (%)		
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)
Disease characteristics		
Serum EPO (U/L) categories[b], n (%)		
< 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
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)
Haemoglobin[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; IPSS-R=International Prognostic Scoring System-Revised

[a] Time since original MDS diagnosis was defined as the number of years from the date of original diagnosis to the date of informed consent.

[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 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

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	
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 versus 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 versus placebo	0.72 (0.60, 0.86)	
RBC Transfusion units[c] • **Weeks 1-24** Baseline transfusion burden <6 units/8 weeks LS Mean (SE) 95% CI for LS mean	7.2 (0.58) 6.0, 8.3	12.8 (0.82) 11.1, 14.4
LS mean difference (SE) (luspatercept versus placebo) 95% CI for LS mean difference	-5.6 (1.01) -7.6, -3.6	
Baseline transfusion burden ≥6 units/8 weeks LS Mean (SE) 95% CI for LS mean	18.9(0.93) 17.1, 20.8	23.7(1.32) 21.1, 26.4
LS mean difference (SE) (luspatercept versus placebo) 95% CI for LS mean difference	-4.8 (1.62) -8.0, -1.6	
• **Weeks 25-48** Baseline transfusion burden <6 units/8 weeks LS Mean (SE) 95% CI for LS mean	7.5 (0.57) 6.3, 8.6	11.8(0.82) 10.1, 13.4
LS mean difference (SE) (luspatercept versus placebo) 95% CI for LS mean difference	-4.3 (1.00) -6.3, -2.3	
Baseline transfusion burden ≥6 units/8 weeks LS Mean (SE) 95% CI for LS mean	19.6(1.13) 17.4, 21.9	22.9(1.60) 19.7, 26.0
LS mean difference (SE) (luspatercept versus placebo) 95% CI for LS mean difference	-3.3(1.96) -7.1, 0.6	

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

[a] 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).

[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% *versus* 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 6. Exploratory efficacy results in patients with MDS in 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 haemoglobin 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 haemoglobin 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	

[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 subject 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 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 ≥ 8 weeks from Week 1-24 had 2 or more episodes of RBC-TI at the time of analysis.

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 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 haemoglobin 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 ACE-536-B-THAL-001 are shown in Table 7.

Table 7. Baseline characteristics in patients with β-thalassaemia in 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 subject 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 8. Efficacy results in patients with β-thalassaemia in 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		
Primary endpoint – **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	
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 9. Exploratory efficacy results in patients with β-thalassaemia in 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
LS mean of difference (luspatercept-placebo) (95% CI)[b]	-7.84 (-14.44, -1.25)	

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 *versus* +114.28 µg/L which resulted in a least square mean treatment difference of -347.8 µg/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.

Paediatric population

The safety and efficacy of luspatercept in pediatric or adolescent patients (under 18 years of age) has not been established.

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 7.08 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 0.437 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.

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

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.

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). 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^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 *versus* 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 *versus* 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
3 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 Powder for Solution for Injection 25 mg/vial
2R, 13mm Type I clear glass TopLyo vial with 13 mm Flurotec® coated, gray bromobutyl rubber stopper and sealed with 13 mm aluminum flip-off seal with yellow polypropylene button

Reblozyl Powder for Solution for Injection 75 mg/vial
2R, 13mm Type I clear glass TopLyo vial with 13 mm Flurotec® coated, gray bromobutyl rubber stopper and sealed with 13 mm aluminum flip-off seal with orange polypropylene button

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 Powder for Solution for Injection 25 mg/vial
   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 Powder for Solution for Injection 75 mg/vial
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

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8. DATE OF REVISION OF THE TEXT

March 2022