BLA 761136/S-009

SUPPLEMENT APPROVAL

Celgene Corporation, a Bristol-Myers Squibb Company
Attention: Amandeep Riar, PharmD
Associate Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Dr. Riar:

Please refer to your supplemental biologics license application (sBLA), dated and received February 28, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Reblozyl (luspatercept-aamt) for injection.

This Prior Approval supplemental biologics license application provides for a new indication for "anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions".

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of secondary malignancies, transformation from myelodysplastic syndromes (MDS) to acute myeloid leukemia (AML), thromboembolic events, and decrement in survival. These risks, which may take as long as 5 years or more to develop, may not have been detected during the short duration of the pivotal trial.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4486-1 Complete Study ACE-536-MDS-002: A phase 3, open-label, randomized study to compare the efficacy and safety of Luspatercept (ACE-536) versus Epoetin Alfa for the treatment of anemia due to IPSS-R very low, low or intermediate risk myelodysplastic syndromes (MDS) in ESA naive subjects who require red blood cell transfusions. Provide at least 5 years of follow-up from the first dose or 3 years after the last dose of study drug (or until death) for enrolled subjects. Long-term safety outcomes of interest include thromboembolic events reported as related to study medication by the investigator, transformation to acute myeloid leukemia, secondary malignancies, and survival. Include an updated safety analysis and submit datasets with the final clinical study report submission.

The timetable you submitted on August 2, 2023, states that you will conduct this study according to the following schedule:

Interim (Full Analysis Report):	12/2023
Study Completion:	12/2030
Final Report Submission:	09/2031

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 112562 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call May Zuwannin, Regulatory Project Manager, at 301-796-7775.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Deputy Division Director (Acting)
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REBLOZYL safely and effectively. See full prescribing information for REBLOZYL.

REBLOZYL® (luspatercept-aamt) for injection, for subcutaneous use
Initial U.S. Approval: 2019

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	8/2023
Dosage and Administration (2.2)	8/2023
Warnings and Precautions, Hypertension (5.2)	8/2023

----------INDICATIONS AND USAGE----------

REBLOZYL is an erythroid maturation agent indicated for the treatment of:

- Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions (1.1).
- Anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions (1.2).
- Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) (1.3).
- Limitations of Use: REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia (1.4).

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection (2.1, 2.2).
- Review hemoglobin (Hgb) results prior to each administration (2.1, 2.2).
- See full prescribing information for preparation and administration instructions (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

- For injection: 25 mg lyophilized powder in a single-dose vial for reconstitution (3)
- For injection: 75 mg lyophilized powder in a single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------

None (4).

----------WARNINGS AND PRECAUTIONS----------

- Thrombosis/Thromboembolism: Increased risk in patients with beta thalassemia. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly (5.1).
- Hypertension: Monitor blood pressure (BP) during treatment. Initiate anti-hypertensive treatment if necessary (5.2).
- Extramedullary Hematopoietic (EMH) Masses: Increased risk in patients with beta thalassemia. Monitor patients for symptoms and signs or complications resulting from the EMH masses. Treat according to clinical guidelines and discontinue treatment in case of serious complications due to EMH masses (5.3).
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.4, 8.1, 8.3).

----------ADVERSE REACTIONS----------

The most common (>10%) adverse reactions were fatigue, headache, musculoskeletal pain, arthralgia, dizziness/vertigo, nausea, diarrhea, cough, abdominal pain, dyspnea, COVID-19, edema peripheral, hypertension, and hypersensitivity (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.

Revised: 8/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Beta Thalassemia

REBLOZYL is indicated for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.

1.2 Myelodysplastic Syndromes Associated Anemia

REBLOZYL is indicated for the treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions.

1.3 Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/ Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia

REBLOZYL is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

1.4 Limitations of Use

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Beta Thalassemia

The recommended starting dose of REBLOZYL is 1 mg/kg once every 3 weeks by subcutaneous injection for patients with beta thalassemia. Prior to each REBLOZYL dose, review the patient's hemoglobin and transfusion record. Titrate the dose based on responses according to Table 1. Interrupt treatment for adverse reactions as described in Table 2. Discontinue REBLOZYL if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time.

If a planned administration of REBLOZYL is delayed or missed, administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses.

Dose Modifications for Response

Assess and review hemoglobin results prior to each administration of REBLOZYL. If an RBC transfusion occurred prior to dosing, use the pretransfusion hemoglobin for dose evaluation.

If a patient does not achieve a reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the REBLOZYL dose to 1.25 mg/kg. Do not increase the dose beyond the maximum dose of 1.25 mg/kg. In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or the predose hemoglobin is greater

than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL as described in Table 1.

Dose level modifications for response are provided in Table 1.

Table 1: Beta Thalassemia - REBLOZYL Dose Titration for Response

	REBLOZYL Dosing Recommendation*
Starting Dose	• 1 mg/kg every 3 weeks
Dose Increases for Insufficient Response at Initiation of Treatment	
No reduction in RBC transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose	• Increase the dose to 1.25 mg/kg every 3 weeks
No reduction in RBC transfusion burden after 3 consecutive doses (9 weeks) at 1.25 mg/kg	• Discontinue treatment
Dose Modifications for Predose Hemoglobin Levels or Rapid Hemoglobin Rise	
Predose hemoglobin is greater than or equal to 11.5 g/dL in the absence of transfusions	• Interrupt treatment • Restart when the hemoglobin is no more than 11 g/dL
Increase in hemoglobin greater than 2 g/dL within 3 weeks in the absence of transfusions and	
• current dose is 1.25 mg/kg	• Reduce dose to 1 mg/kg
• current dose is 1 mg/kg	• Reduce dose to 0.8 mg/kg
• current dose is 0.8 mg/kg	• Reduce dose to 0.6 mg/kg
• current dose is 0.6 mg/kg	• Discontinue treatment

* Do not increase the dose if the patient is experiencing an adverse reaction as described in Table 2.

Dose Modifications for Toxicity

For patients experiencing Grade 3 or higher adverse reactions, modify treatment as described in Table 2.

Table 2: Beta Thalassemia - REBLOZYL Dosing Modifications for Adverse Reactions

	REBLOZYL Dosing Recommendation*
Grade 3 or 4 hypersensitivity reactions	• Discontinue treatment
Other Grade 3 or 4 adverse reactions	• Interrupt treatment • Restart when the adverse reaction resolves to no more than Grade 1
Extramedullary hematopoietic (EMH) masses causing serious complications	• Discontinue treatment

* Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.

2.2 Recommended Dosage for Myelodysplastic Syndromes Associated Anemia

The recommended starting dosage of REBLOZYL is 1 mg/kg once every 3 weeks by subcutaneous injection for the treatment of anemia of MDS. Prior to each REBLOZYL dose, review the patient's hemoglobin and transfusion record. Titrate the dose based on responses according to Table 3. Interrupt treatment for adverse reactions as described in Table 4. Discontinue REBLOZYL if a patient does not experience a decrease in transfusion burden including no increase from baseline hemoglobin after 9 weeks of treatment (administration of 3 doses) at the maximum dose level (1.75 mg/kg), or if unacceptable toxicity occurs at any time.

If a planned administration of REBLOZYL is delayed or missed, administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses.

Dose Modifications for Response

Assess and review hemoglobin results prior to each administration of REBLOZYL. If an RBC transfusion occurred prior to dosing, use the pretransfusion hemoglobin for dose evaluation.

If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the REBLOZYL dose to 1.33 mg/kg (Table 3). If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg /kg dose level, increase the REBLOZYL dose to 1.75 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 1.75 mg/kg.

In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks in the absence of transfusion, increase the dose by one dose level. Wait a minimum of 6 weeks between dose increases.

Dose modifications for response are provided in Table 3.

Table 3: MDS Associated Anemia - REBLOZYL Dose Titration for Response

	REBLOZYL Dosing Recommendation*
Starting Dose	• 1 mg/kg every 3 weeks
Dose Increases for Insufficient Response at Initiation of Treatment	
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose	• Increase the dose to 1.33 mg/kg every 3 weeks
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at 1.33 mg/kg	• Increase the dose to 1.75 mg/kg every 3 weeks
No reduction in RBC transfusion burden including no increase from baseline hemoglobin after at least 3 consecutive doses (9 weeks) at 1.75 mg/kg	• Discontinue treatment

Dose Modifications for Predose Hemoglobin Levels or Rapid Hemoglobin Rise	
Predose hemoglobin is greater than or equal to 11.5 g/dL in the absence of transfusions	• Interrupt treatment • Restart when the hemoglobin is no more than 11 g/dL
Increase in hemoglobin greater than 2 g/dL within 3 weeks in the absence of transfusions and	
• current dose is 1.75 mg/kg	• Reduce dose to 1.33 mg/kg
• current dose is 1.33 mg/kg	• Reduce dose to 1 mg/kg
• current dose is 1 mg/kg	• Reduce dose to 0.8 mg/kg
• current dose is 0.8 mg/kg	• Reduce dose to 0.6 mg/kg
• current dose is 0.6 mg/kg	• Discontinue treatment

* Do not increase the dose if the patient is experiencing an adverse reaction as described in Table 4.

Dose Modifications for Toxicity

For patients experiencing Grade 3 or higher adverse reactions, modify treatment as described in Table 4.

Table 4: MDS Associated Anemia - REBLOZYL Dosing Modifications for Adverse Reactions

	REBLOZYL Dosing Recommendation*
Grade 3 or 4 hypersensitivity reactions	• Discontinue treatment
Other Grade 3 or 4 adverse reactions	• Interrupt treatment • When the adverse reaction resolves to no more than Grade 1, restart treatment at the next lower dose level** • If the dose delay is > 12 consecutive weeks, discontinue treatment

* Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.

**Per Table 3 dose reductions above.

2.3 Preparation and Administration

REBLOZYL should be reconstituted and administered by a healthcare professional.

Reconstitute REBLOZYL with Sterile Water for Injection, USP only.

Table 5: Reconstitution Volumes

Vial Size	Amount of Sterile Water for Injection, USP required for reconstitution	Final Concentration	Deliverable Volume
25 mg vial	0.68 mL	25 mg/0.5 mL (50 mg/mL)	0.5 mL
75 mg vial	1.6 mL	75 mg/1.5 mL (50 mg/mL)	1.5 mL

Reconstitute the number of REBLOZYL vials to achieve the appropriate dose based on the patient's weight. Use a syringe with suitable graduations for reconstitution to ensure accurate dosage.

Reconstitution Instructions

1. Reconstitute with Sterile Water for Injection, USP using volumes described in Table 5 (Reconstitution Volumes) with the stream directed onto the lyophilized powder. Allow to stand for one minute.

2. Discard the needle and syringe used for reconstitution. The needle and syringe used for reconstitution should not be used for subcutaneous injections.

3. 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.

4. Inspect the vial for undissolved particles in the solution. If undissolved powder is observed, repeat step 3 until the powder is completely dissolved.

5. 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.

6. Repeat step 5 seven more times to ensure complete reconstitution of material on the sides of the vial.

7. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. REBLOZYL is a colorless to slightly yellow, clear to slightly opalescent solution which is free of foreign particulate matter. Do not use if undissolved product or foreign particulate matter are observed.

8. If the reconstituted solution is not used immediately:

- Store at room temperature at 20°C to 25°C (68°F to 77°F) in the original vial for up to 8 hours. Discard if not used within 8 hours of reconstitution.
- Alternatively, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours in the original vial. Remove from refrigerated condition 15-30 minutes prior to injection to allow solution to reach room temperature for a more comfortable injection. Discard if not used within 24 hours of reconstitution.
- Do not freeze the reconstituted solution.

Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than 1 dose from a vial. Do not mix with other medications.

Instructions for Subcutaneous Administration

Calculate the exact total dosing volume of 50 mg/mL solution required for the patient.

Slowly withdraw the dosing volume of the reconstituted REBLOZYL solution from the single-dose vial(s) into a syringe. Divide doses requiring larger reconstituted volumes (i.e., greater than 1.2 mL) into separate similar volume injections and inject into separate sites. If multiple injections are required, use a new syringe and needle for each subcutaneous injection.

Administer the injection subcutaneously into the upper arm, thigh, and/or abdomen.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 25 mg white to off-white lyophilized powder in a single-dose vial for reconstitution.
- For injection: 75 mg white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombosis/Thromboembolism

In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. Reported TEEs included deep vein thromboses, pulmonary embolus, portal vein thrombosis, and ischemic strokes. Patients with known risk factors for thromboembolism, e.g. splenectomy or concomitant use of hormone replacement therapy, may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients with beta thalassemia at increased risk of TEE.

Monitor patients receiving REBLOZYL for signs and symptoms of thromboembolic events and institute treatment promptly.

5.2 Hypertension

Hypertension was reported in 63/554 (11.4%) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3-4 hypertension ranged from 2% to 9.6%.

In adult patients with beta thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) ≥130 mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP) ≥80 mm Hg.

In ESA-refractory or -intolerant adult patients with MDS with normal baseline blood pressure, 26 (30%) patients developed SBP ≥130 mm Hg and 23 (16%) patients developed DBP ≥80 mm Hg. In ESA-naïve adult patients with MDS with normal baseline blood pressure, 23 (36%) patients developed SBP ≥140 mm Hg and 11 (6%) patients developed DBP ≥80 mm Hg.

Monitor blood pressure prior to each administration. Manage new-onset hypertension or exacerbations of preexisting hypertension using anti-hypertensive agents.

5.3 Extramedullary Hematopoietic Masses

In adult patients with transfusion dependent beta thalassemia, EMH masses were observed in 3.2% of REBLOZYL-treated patients, with spinal cord compression symptoms due to EMH masses occurring in 1.9% of patients (BELIEVE and REBLOZYL long-term follow-up study).

In a study of adult patients with non-transfusion dependent beta thalassemia, a higher incidence of EMH masses was observed in 6.3% of REBLOZYL-treated patients *vs.* 2% of placebo-treated patients in the double-blind phase of the study, with spinal cord compression due to EMH masses occurring in 1 patient with a prior history of EMH. REBLOZYL is not indicated for use in patients with non-transfusion dependent beta-thalassemia.

Possible risk factors for the development of EMH masses in patients with beta thalassemia include history of EMH masses, splenectomy, splenomegaly, hepatomegaly, or low baseline hemoglobin (<8.5 g/dL). Signs and symptoms may vary depending on the anatomical location. Monitor patients with beta thalassemia at initiation and during treatment for symptoms and signs or complications resulting from the EMH masses and treat according to clinical guidelines. Discontinue treatment

with REBLOZYL in case of serious complications due to EMH masses. Avoid use of REBLOZYL in patients requiring treatment to control the growth of EMH masses.

5.4 Embryo-Fetal Toxicity

Based on findings from animal reproductive studies, REBLOZYL may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) of 1.75 mg/kg.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with REBLOZYL and for at least 3 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Thrombosis/Thromboembolism *[see Warnings and Precautions (5.1)]*
- Hypertension *[see Warnings and Precautions (5.2)]*
- Extramedullary Hematopoietic Masses *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to REBLOZYL as a single agent administered across a range of doses (0.125 mg/kg to 1.75 mg/kg) in 571 patients in 4 trials.

Beta Thalassemia

The safety of REBLOZYL in patients with beta thalassemia was evaluated in the BELIEVE trial *[see Clinical Studies (14.1)]*. Key eligibility criteria included adult patients with beta thalassemia (with the exception of patients with hemoglobin S or alpha-thalassemia disease) without major organ damage or recent DVT stroke and platelet counts less than or equal to 1000 x 10^9/L.

Patients received a starting dose of REBLOZYL 1 mg/kg subcutaneous injection every 3 weeks. Overall, 53% of patients had their dose increased to 1.25 mg/kg (46% REBLOZYL, n = 223) or placebo (66%, n = 109). The median duration of treatment was similar between the REBLOZYL and placebo arms (63.3 weeks vs. 62.1 weeks, respectively). Per protocol, patients in the REBLOZYL and placebo arms were to remain on therapy for at least 48 weeks in the double-blind phase of the trial.

Among patients receiving REBLOZYL, 94% were exposed for 6 months or longer and 72% were exposed for greater than one year.

The median age of patients who received REBLOZYL was 30 years (range: 18, 66); 59% female; 54% White and 36% Asian.

Serious adverse reactions occurred in 3.6% of patients on REBLOZYL. Serious adverse reactions reported in 1% of patients were cerebrovascular accident and deep vein thrombosis. A fatal adverse reaction occurred in one patient treated with REBLOZYL who died due to an unconfirmed case of AML (M6).

Permanent discontinuation due to an adverse reaction (Grades 1-4) occurred in 5.4% of patients who received REBLOZYL. Most frequent adverse reactions requiring permanent discontinuation in patients who received REBLOZYL included arthralgia (1%), back pain (1%), bone pain (<1%), and headache (<1%).

Dosage reductions due to an adverse reaction occurred in 2.7% of patients who received REBLOZYL. Most frequent adverse reactions requiring dosage reduction in >0.5% of patients who received REBLOZYL included hypertension and headache.

Dosage interruptions due to an adverse reaction occurred in 15.2% of patients who received REBLOZYL. Most frequent adverse reactions requiring dosage interruption in >1% of patients who received REBLOZYL included upper respiratory tract infection, ALT increase, and cough.

The most common adverse reactions (at least 10% for REBLOZYL and 1% more than placebo) were headache (26%), bone pain (20%), arthralgia (19%), fatigue (14%), cough (14%), abdominal pain (14%), diarrhea (12%), and dizziness (11%).

Table 6 summarizes the adverse reactions in BELIEVE.

Table 6: Adverse Drug Reactions (>5%) in Patients with Beta Thalassemia Receiving REBLOZYL with a Difference Between Arms of 1% in BELIEVE Trial

Body System Adverse Reaction	REBLOZYL (N=223)		Placebo (N=109)	
	All Grades n (%)	Grades ≥3[a] n (%)	All Grades n (%)	Grades ≥3 n (%)
Musculoskeletal and connective tissue disorders				
Bone Pain	44 (20)	3 (1)	9 (8)	0 (0)
Arthralgia	43 (19)	0 (0)	13 (12)	0 (0)
Infections and infestation				
Influenza	19 (9)	0 (0)	6 (6)	0 (0)
Viral Upper Respiratory Infection	14 (6)	1 (0.4)	2 (2)	0 (0)
Nervous system disorders				
Headache	58 (26)	1 (<1)	26 (24)	1 (1)
Dizziness	25 (11)	0 (0)	5 (5)	0 (0)
General disorders and administration site conditions				
Fatigue	30 (14)	0 (0)	14 (13)	0 (0)
Gastrointestinal disorders				
Abdominal Pain [b]	31 (14)	0 (0)	13 (12)	0 (0)
Diarrhea	27 (12)	1 (<1)	11 (10)	0 (0)

Body System Adverse Reaction	REBLOZYL (N=223)		Placebo (N=109)	
	All Grades n (%)	Grades ≥3[a] n (%)	All Grades n (%)	Grades ≥3 n (%)
Nausea	20 (9)	0 (0)	6 (6)	0 (0)
Vascular disorders				
Hypertension [c]	18 (8)	4 (2)	3 (3)	0 (0)
Metabolism and nutrition disorders				
Hyperuricemia	16 (7)	6 (3)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders				
Cough	32 (14)	0 (0)	12 (11)	0 (0)

[a] Limited to Grade 3 reactions with the exception of 4 events of Grade 4 hyperuricemia.
[b] Grouped term includes abdominal pain and abdominal pain upper.
[c] Grouped term includes essential hypertension, hypertension, and hypertensive crisis.

Clinically relevant adverse reactions in <5% of patients include vertigo/vertigo positional, syncope/presyncope, injection site reactions, hypersensitivity, extramedullary hematopoietic masses, and spinal cord compression.

Liver function abnormalities in the BELIEVE trial are shown in Table 7.

Table 7: Liver Function Laboratory Abnormalities in Patients with Beta Thalassemia in the BELIEVE Trial

	REBLOZYL N = 223 n (%)	Placebo N = 109 n (%)
ALT ≥ 3 × ULN	26 (12)	13 (12)
AST ≥ 3 × ULN	25 (11)	5 (5)
ALP ≥ 2 × ULN	17 (8)	1 (<1)
Total bilirubin ≥ 2 × ULN	143 (64)	51 (47)
Direct bilirubin ≥ 2 × ULN	13 (6)	4 (4)

ALP = alkaline phosphatase; ALT = alanine aminotransferase;
AST = aspartate aminotransferase; ULN = upper limit of normal.

Treatment of Myelodysplastic Syndromes Associated Anemia in ESA-naïve Patients

The safety of REBLOZYL in patients with very low- to intermediate-risk myelodysplastic syndromes was evaluated in the COMMANDS trial in 356 randomized patients *[see Clinical Studies (14.2)]*. Key eligibility criteria included adult patients who were ESA-naïve with endogenous sEPO levels of < 500 U/L and who required regular RBC transfusions.

The median time on treatment with REBLOZYL was 41.6 weeks (range, 0 – 165 weeks); 71.3% of patients were exposed for 24 weeks and 45.5% completed 48 weeks of treatment.

Among the 178 patients treated with REBLOZYL, 17 (9.6%) discontinued due to an adverse reaction, 48 (27%) had a dose interruption due to an adverse reaction, and 5 (2.8%) had a dose

reduction due to an adverse reaction. The most common (>10%) all-grade adverse reactions included diarrhea, fatigue, hypertension, edema peripheral, nausea, and dyspnea. The most common (>2%) Grade > 3 adverse reactions included hypertension and dyspnea. Selected laboratory abnormalities that changed from Grade 0-2 at baseline to Grade > 2 at any time during the studies in at least 10% of patients were glomerular filtration rate and total bilirubin increased.

Table 8 shows the most common adverse reactions for patients treated with REBLOZYL or epoetin alfa in the COMMANDS trial *[see Clinical Studies (14.2)]*.

Table 8: Adverse Reactions (≥5%) in Patients Receiving REBLOZYL in COMMANDS Trial

Body System /Adverse Reaction	REBLOZYL (N=178)		Epoetin Alfa (N=176)	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
General disorders and administration site conditions				
Fatigue [a, b]	38 (22)	0 (0)	12 (7)	0 (0)
Edema peripheral	23 (13)	0 (0)	12 (7)	0 (0)
Non-cardiac chest pain	9 (5)	1 (1)	6 (3)	0 (0)
Pyrexia	9 (5)	1 (1)	12 (7)	1 (1)
Gastrointestinal disorders				
Diarrhea	26 (15)	0 (0)	20 (11)	0 (0)
Nausea	21 (12)	0 (0)	13 (7)	0 (0)
Vascular disorders				
Hypertension [a]	25 (14)	17 (10)	13 (7)	9 (5)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	21 (12)	7 (4)	13 (7)	2 (1)
Dyspnea exertional	9 (5)	0 (0)	1 (1)	0 (0)
Nervous system disorders				
Dizziness	16 (9)	1 (1)	15 (9)	0 (0)
Headache	15 (8)	0 (0)	12 (7)	1 (1)
Musculoskeletal and connective tissue disorders				
Back Pain	16 (9)	2 (1)	13 (7)	3 (2)
Arthralgia	10 (6)	0 (0)	14 (8)	0 (0)
Myalgia	9 (5)	0 (0)	5 (3)	0 (0)
Osteoarthritis	9 (5)	1 (1)	4 (2)	0 (0)
Infections and infestations				
COVID-19	19 (11)	6 (3)	17 (10)	2 (1)
Urinary tract infection	13 (7)	0 (0)	7 (4)	0 (0)
Pneumonia	8 (5)	7 (4)	15 (9)	11 (6)

Metabolism and nutrition disorders				
Hyperuricemia	12 (7)	1 (1)	10 (6)	1 (1)
Decreased appetite	8 (5)	0 (0)	11 (6)	0 (0)
Blood and lymphatic system disorders				
Thrombocytopenia	11 (6)	7 (4)	3 (2)	1 (1)
Neutropenia	9 (5)	7 (4)	13 (7)	10 (6)
Psychiatric disorders				
Insomnia	9 (5)	0 (0)	6 (3)	0 (0)

[a] Reaction includes similar/grouped terms.

[b] Includes asthenic conditions.

Other clinically relevant adverse reactions reported in <5% of patients are injection site reactions, including erythema, pruritus, and rash.

Shifts from Grades 0-2 at baseline to Grades 2-3 abnormalities for selected laboratory tests in the COMMANDS trial are shown in Table 9.

Table 9: Selected Treatment -Emergent Laboratory Abnormalities in COMMANDS Trial that Shift to Grades 2-3

Parameter	REBLOZYL		Epoetin Alfa	
	N [a]	n (%)	N [a]	n (%)
Total bilirubin	171	38 (22)	165	19 (12)
GFR [b]	171	60 (35)	167	36 (22)

[a] Number of patients at Grades 0-1 at baseline.

[b] GFR= glomerular filtration rate (mL/min)

Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic / Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia in ESA-refractory or -intolerant patients

The safety of REBLOZYL at the recommended dose and schedule was evaluated in 242 patients with MDS with ring sideroblasts (n=192) or other myeloid neoplasms (n=50) in the MEDALIST trial. The safety population included 63% males and 37% females of median age 72 years (range, 30 – 95 years); of these patients, 81% were White, 0.4% Black, 0.4% Other, and race was not reported in 18.2% of patients. The median time on treatment with REBLOZYL was 50.4 weeks (range, 3 – 221 weeks); 67% of patients were exposed for 6 months or longer and 49% were exposed for greater than one year.

Among the 242 patients treated with REBLOZYL, 5 (2.1%) had a fatal adverse reaction, 11 (4.5%) discontinued due to an adverse reaction, and 7 (2.9%) had a dose reduction due to an adverse reaction. The most common (≥10%) all-grade adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection. The most common (≥2%) Grade ≥ 3 adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. Selected

laboratory abnormalities that changed from Grade 0-1 at baseline to Grade ≥ 2 at any time during the studies in at least 10% of patients included creatinine clearance decreased, total bilirubin increased, and alanine aminotransferase increased.

Table 10 shows the most common adverse reactions for patients treated with REBLOZYL or placebo through the first 8 cycles in the MEDALIST trial *[see Clinical Studies (14.3)]*.

Table 10: Adverse Reactions (≥5%) in Patients Receiving REBLOZYL with a Difference Between Arms of >2% in MEDALIST Trial Through Cycle 8

Body System /Adverse Reaction	REBLOZYL (N=153)		Placebo (N=76)	
	All Grades n (%)	Grade 3 n (%)	All Grades n (%)	Grade 3 n (%)
General disorders and administration site conditions				
Fatigue [a, b]	63 (41)	11 (7)	17 (22)	2 (3)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [b]	30 (20)	3 (2)	11 (14)	0 (0)
Nervous system disorders				
Dizziness/vertigo	28 (18)	1 (<1)	5 (7)	1 (1)
Headache [b]	21 (14)	0 (0)	5 (7)	0 (0)
Syncope / presyncope	8 (5)	5 (3)	0 (0)	0 (0)
Gastrointestinal disorders				
Nausea [b]	25 (16)	1 (<1)	8 (11)	0 (0)
Diarrhea [b]	25 (16)	0 (0)	7 (9)	0 (0)
Respiratory, thoracic and mediastinal disorder				
Dyspnea [b]	20 (13)	2 (1)	4 (5)	1 (1)
Immune system disorders				
Hypersensitivity reactions [b]	15 (10)	1 (<1)	5 (7)	0 (0)
Renal and urinary disorders				
Renal impairment [b]	12 (8)	3 (2)	3 (4)	0 (0)
Cardiac disorders				
Tachycardia [b]	12 (8)	0 (0)	1 (1)	0 (0)
Injury poisoning and procedural complications				
Injection site reactions	10 (7)	0 (0)	3 (4)	0 (0)
Infections and infestations				
Upper respiratory tract infection	10 (7)	1 (<1)	2 (3)	0 (0)
Influenza / influenza like illness	9 (6)	0 (0)	2 (3)	0 (0)

[a] Includes asthenic conditions.

[b] Reaction includes similar/grouped terms.

Other clinically relevant adverse reactions reported in <5% of patients include bronchitis, urinary tract infection, and hypertension *[see Warnings and Precautions (5.2)]*.

Shifts from Grades 0-1 to Grades 2-4 abnormalities for selected laboratory tests during the first 8 cycles in the MEDALIST trial are shown in Table 11.

Table 11: Selected Grades 2-4 Treatment-Emergent Laboratory Abnormalities Through Cycle 8 in the MEDALIST Trial

Parameter	REBLOZYL		Placebo	
	N[a]	n (%)	N[a]	n (%)
ALT elevated	151	13 (9)	74	5 (7)
AST elevated	152	6 (4)	76	0 (0)
Total bilirubin elevated	140	17 (12)	66	3 (5)
Creatinine clearance reduced	113	30 (27)	62	13 (21)

[a] Number of patients at Grades 0-1 at baseline.

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies, REBLOZYL may cause fetal harm when administered to a pregnant woman. There are no available data on REBLOZYL use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes including embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In embryo-fetal development studies, luspatercept-aamt was administered subcutaneously at 5, 15, or 30 mg/kg on gestation days 3 and 10 (rats) or 5, 20, or 40 mg/kg on gestation days 4 and 11 (rabbits). Effects in both species included reductions in numbers of live fetuses and fetal body weights, and increases in resorptions, post-implantation losses, and skeletal variations (such as asymmetric sternal centra in rats and angulated hyoid in rabbits). Effects were observed at exposures (based on AUC) approximately 7-times (rats) and 16-times (rabbits) the MRHD of 1.75 mg/kg.

In a pre- and postnatal development study, pregnant rats were administered luspatercept-aamt subcutaneously at 3, 10, or 30 mg/kg once every 2 weeks during organogenesis and through weaning, gestation day 6 through postnatal day 20. At all dose levels lower F_1 pup body weights and adverse kidney findings (such as membranoproliferative glomerulonephritis, tubular atrophy/hypoplasia, and vessel ectasia occasionally associated with hemorrhage) were observed. These effects were observed at exposures (based on AUC) approximately 1.6-times the MRHD of 1.75 mg/kg.

8.2 Lactation

Risk Summary

Luspatercept-aamt was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There are no data on the presence of REBLOZYL in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with REBLOZYL, and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting REBLOZYL treatment.

Contraception

Females

REBLOZYL may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with REBLOZYL and for at least 3 months after the last dose.

Infertility

Females

Based on findings in animals, REBLOZYL may impair female fertility *[see Nonclinical Toxicology (13.1)]*. Adverse effects on fertility in female rats were reversible after a 14-week recovery period.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Based on findings in juvenile animals, REBLOZYL is not recommended for use in pediatric patients *[see Non-Clinical Toxicology (13.1)]*.

8.5 Geriatric Use

Clinical studies of REBLOZYL in beta thalassemia did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients.

Clinical studies of REBLOZYL for treatment of anemia in ESA-naïve and ESA-refractory or -intolerant MDS included 347 (82%) patients ≥ 65 years of age and 167 (39%) patients ≥ 75

years of age. No differences in safety or effectiveness were observed between older (≥ 65 years) and younger patients.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

REBLOZYL contains luspatercept-aamt, which is not a controlled substance.

9.2 Abuse

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Abuse of REBLOZYL may be seen in athletes for the effects on erythropoiesis to enhance athletic performance. Abuse of drugs that increase erythropoiesis, such as REBLOZYL, by healthy persons may lead to polycythemia, which may be associated with life-threatening cardiovascular complications (e.g., stroke, myocardial infarction, and thromboembolism).

Luspatercept-aamt and its metabolites neither selectively penetrate the central nervous system, nor produce behavioral effects in animals that are consistent with central nervous system activity.

11 DESCRIPTION

Luspatercept-aamt is an erythroid maturation agent. Luspatercept-aamt is a receptor fusion protein consisting of a modified extracellular domain of the human activin receptor type IIB linked to a human IgG1 Fc domain with a calculated molecular mass of approximately 76 kD. Luspatercept is produced in Chinese hamster ovary cells by recombinant DNA technology.

REBLOZYL (luspatercept-aamt) for injection is a sterile, preservative-free, white to off-white, lyophilized powder in single-dose vials for subcutaneous use after reconstitution.

Each 25 mg single-dose vial provides nominal 25 mg of luspatercept-aamt and citric acid monohydrate (0.085 mg), polysorbate 80 (0.10 mg), sucrose (45.0 mg), and tri-sodium citrate dihydrate (1.35 mg) at pH 6.5. After reconstitution with 0.68 mL Sterile Water for Injection USP, the resulting concentration is 25 mg/0.5 mL of luspatercept-aamt and the nominal deliverable volume is 0.5 mL.

Each 75 mg single-dose vial provides nominal 75 mg of luspatercept-aamt and citric acid monohydrate (0.254 mg), polysorbate 80 (0.30 mg), sucrose (135 mg), and tri-sodium citrate dihydrate (4.06 mg) at pH 6.5. After reconstitution with 1.6 mL Sterile Water for Injection USP, the resulting concentration is 75 mg/1.5 mL (50 mg/mL) of luspatercept-aamt and the nominal deliverable volume is 1.5 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Luspatercept-aamt is a recombinant fusion protein that binds several endogenous TGF-β superfamily ligands, thereby diminishing Smad2/3 signaling. In models of β-thalassemia and MDS, luspatercept-aamt decreased abnormally elevated Smad2/3 signaling and improved hematology parameters associated with ineffective erythropoiesis in mice. Luspatercept-aamt promoted erythroid maturation through differentiation and increasing the percentage of late-stage erythroid

precursors (normoblasts) in the bone marrow of mice and increased erythroid precursors in humans, thereby increasing erythropoiesis.

12.2 Pharmacodynamics

Increases in Hemoglobin in Patients with Low RBC Transfusion Burden

In patients having received < 4 units of RBC transfusion within 8 weeks prior to study, hemoglobin increased within 7 days of initiating REBLOZYL and correlated with the time to luspatercept-aamt maximum serum concentration (C_{max}). The greatest hemoglobin (Hgb) increase occurred after the first dose; approximately 0.75 g/dL at a dose of 0.6 to 1.25 times the recommended starting dose for beta thalassemia, or approximately 1 g/dL at a dose of 0.75 to 1.75 times the recommended starting dose for MDS. Additional smaller increases were observed after subsequent doses. Hemoglobin levels returned to baseline approximately 6 to 8 weeks from the last dose following administration of luspatercept-aamt (0.6 to 1.75 mg/kg).

Increasing luspatercept-aamt serum exposure (AUC) was associated with greater Hgb increase in patients with beta thalassemia or MDS who had a baseline transfusion burden < 4 units/8 weeks. Increasing luspatercept-aamt serum exposure (time-averaged AUC) was associated with greater probability of achieving transfusion independence for at least 8 consecutive weeks in ESA-refractory or -intolerant patients with MDS requiring transfusions (≥ 2 units of RBC transfusion within 8 weeks).

12.3 Pharmacokinetics

Luspatercept-aamt exhibited linear pharmacokinetics (PK) over the dose range of 0.2 to 1.25 mg/kg (0.2 to 1.25 times the recommended starting dosage) in patients with beta thalassemia, and from 0.125 mg/kg to 1.75 mg/kg (0.125 to 1.75 times the recommended starting dosage) in patients with MDS. The geometric mean (% coefficient of variation [%CV]) steady-state AUC at the starting dose of 1 mg/kg was 126 (35.9%) day•µg/mL for patients with beta thalassemia and 154 (37.4%) day•µg/mL for patients with MDS. Luspatercept-aamt serum concentration reached steady state after 3 doses when administered every 3 weeks. The accumulation ratio of luspatercept-aamt was approximately 1.5.

Absorption

The median [range] time to maximum concentration (T_{max}) of luspatercept-aamt was observed at approximately 5 [3 to 8] days post-dose in adult patients with beta thalassemia or 6 [3 to 7] days post-dose in adult patients with MDS. The absorption of luspatercept-aamt was not significantly affected by the subcutaneous injection sites (upper arm, thigh, or abdomen).

Distribution

The geometric mean (%CV) apparent volume of distribution (V_d/F) of luspatercept-aamt was 7.1 (26.7%) L for patients with beta thalassemia and 9.6 (26.7%) L for patients with MDS.

Elimination

The geometric mean (%CV) half-lives ($t_{1/2}$) of luspatercept-aamt were approximately 11 (25.7%) days in patients with beta thalassemia and 14 (31.7%) days in patients with MDS. The geometric

mean (%CV) apparent total clearance (CL/F) of luspatercept-aamt was 0.44 (38.5%) L/day in patients with beta thalassemia and 0.47 (42.9%) L/day in patients with MDS.

Metabolism

Luspatercept-aamt is expected to be catabolized into small peptides and amino acids by general catabolic degradation processes in multiple tissues.

Specific Populations

No clinically significant differences in the luspatercept-aamt PK were observed based on age (18 to 95 years), sex, race/ethnicity (Asian, White), mild to severe hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransaminase [AST] or alanine transaminase [ALT] > ULN, or total bilirubin > ULN and any AST or ALT), mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min), baseline albumin (30 to 56 g/L), baseline serum erythropoietin (2.4 to 2920 U/L), red blood cell (RBC) transfusion burden (0 to 43 units/24 weeks), beta thalassemia genotype (β0/β0 vs. non-β0/β0), splenectomy, and ring sideroblasts status in MDS (negative vs. positive). The effect of AST or ALT >3 x ULN and the effect of severe renal impairment (eGFR <30 mL/min) on luspatercept-aamt PK is unknown.

Body Weight

The apparent CL/F and V_d/F of luspatercept-aamt increased with increasing body weight in patients with beta thalassemia (34 to 97 kg) and in patients with MDS (33 to 124 kg).

Drug Interaction Studies

Effect of Iron-chelating Agents on Luspatercept-aamt

No clinically significant differences in luspatercept-aamt PK were observed when used concomitantly with iron-chelating agents.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of REBLOZYL or of other luspatercept products.

In the BELIEVE trial, the median duration of exposure was 64 weeks, with a median ADA sampling period of 50 weeks. Of the 220 patients in the BELIEVE trial with beta thalassemia who require regular RBC transfusions treated with REBLOZYL and evaluable for the presence of anti-luspatercept-aamt antibodies, 4 patients (1.81%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 2 patients (0.9%) who had neutralizing antibodies detected. The majority of anti-luspatercept-aamt antibodies were of low titers.

In the COMMANDS trial, the median duration of exposure was 42 weeks, with the median ADA sampling period of 27 weeks. In the MEDALIST trial, the median duration of exposure was 49 weeks, with the median ADA sampling period of 46 weeks. Of the 331 ESA-naïve (COMMANDS trial) and ESA-refractory or -intolerant (MEDALIST trial) patients with MDS who were treated with REBLOZYL, 21 patients (6.3%) tested positive for treatment-emergent anti-

luspatercept-aamt antibodies, including 14 patients (4.2%) who had neutralizing antibodies. The majority of anti-luspatercept-aamt antibodies were of low titers.

There were no severe acute systemic hypersensitivity reactions reported for patients with anti-luspatercept-aamt antibodies in REBLOZYL clinical trials, and there was no association between hypersensitivity type reaction or injection site reaction and presence of anti-luspatercept-aamt antibodies. There was no apparent effect of anti-luspatercept-aamt antibodies on clinical response.

Anti-Drug Antibody Effects on Pharmacokinetics

Among patients in the BELIEVE trial with luspatercept-aamt exposure data available, luspatercept-aamt mean trough concentration (C_{trough}) was approximately 35% lower in 4 patients with beta thalassemia who tested positive for treatment-emergent anti-luspatercept-aamt antibodies (2.19 μg/mL) compared to patients with beta thalassemia who did not develop treatment-emergent anti-luspatercept-aamt antibodies (3.38 μg/mL). There is insufficient data to assess whether the observed anti-luspatercept-aamt antibody associated pharmacokinetic changes reduce effectiveness in patients with beta thalassemia.

Among 21 ESA-naïve and ESA-refractory or -intolerant patients with MDS in the COMMANDS and MEDALIST trials who tested positive for treatment-emergent anti-luspatercept-aamt antibodies, there were no identified clinically significant effects of anti-luspatercept-aamt antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of luspatercept-aamt over the treatment duration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies have been conducted with luspatercept-aamt.

In a repeat-dose toxicity study, juvenile rats were administered luspatercept-aamt subcutaneously at 1, 3, or 10 mg/kg once every 2 weeks from postnatal day 7 to 91. Hematologic malignancies (granulocytic leukemia, lymphocytic leukemia, malignant lymphoma) were observed at 10 mg/kg resulting in exposures (based on area under the curve [AUC]) approximately 4.4 times the maximum recommended human dose (MRHD) of 1.75 mg/kg.

In a combined male and female fertility and early embryonic development study in rats, luspatercept-aamt was administered subcutaneously to animals at doses of 1 to 15 mg/kg. There were significant reductions in the average numbers of corpora lutea, implantations, and viable embryos in luspatercept-aamt-treated females. Effects on female fertility were observed at the highest dose with exposures (based on AUC) approximately 7-times the MRHD of 1.75 mg/kg. Adverse effects on fertility in female rats were reversible after a 14-week recovery period. No adverse effects were noted in male rats.

14 CLINICAL STUDIES

14.1 Beta Thalassemia

The efficacy of REBLOZYL was evaluated in adult patients with beta thalassemia in the BELIEVE trial (NCT02604433). BELIEVE was a multicenter, randomized, double-blind, placebo-controlled trial in which (n=336) patients with beta thalassemia requiring regular red blood cell transfusions (6-20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that

period were randomized 2:1 to REBLOZYL (n=224) or placebo (n=112). In BELIEVE, REBLOZYL was administered subcutaneously once every 3 weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity. All patients were eligible to receive best supportive care, which included RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and/or nutritional support, as needed.

The BELIEVE trial excluded patients with a diagnosis of Hemoglobin S/β-thalassemia or isolated alpha (α)-thalassemia (e.g., Hemoglobin H) or who had major organ damage (liver disease, heart disease, lung disease, renal insufficiency). Patients with recent deep vein thrombosis or stroke or recent use of ESA, immunosuppressant, or hydroxyurea therapy were also excluded. The median age was 30 years (range: 18-66). The trial was comprised of patients who were 42% male, 54.2% White, 34.8% Asian, and 0.3% Black or African American. The percent of patients reporting their race as "other" was 7.7%, and race was not collected or reported for 3% of patients.

Table 12 summarizes the baseline disease-related characteristics in the BELIEVE study.

Table 12: Baseline Disease Characteristics of Patients with Beta Thalassemia in BELIEVE

Disease Characteristic	REBLOZYL (N=224)	Placebo (N=112)
Beta thalassemia diagnosis, n (%)		
Beta-thalassemia	174 (77.7)	83 (74.1)
HbE/beta thalassemia	31 (13.8)	21 (18.8)
Beta thalassemia combined with alpha-thalassemia	18 (8)	8 (7.1)
Missing [a]	1 (0.4)	0
Baseline transfusion burden 12 weeks prior to randomization		
Median (min, max) (Units/12 weeks)	6.12 (3, 14)	6.27 (3, 12)
Beta thalassemia gene mutation grouping, n (%)		
β0/β0	68 (30.4)	35 (31.3)
Non-β0/β0	155 (69.2)	77 (68.8)
Missing [a]	1 (0.4)	0
Baseline serum ferritin level (µg/L)		
N	220	111
Median (min, max)	1441.25 (88, 6400)	1301.50 (136, 6400)
Splenectomy, n (%)		
Yes	129 (57.6)	65 (58)
No	95 (42.4)	47 (42)
Age patient started regular transfusions (years)		
N	169	85
Median (min, max)	2 (0, 52)	2 (0, 51)

HbE=hemoglobin E.

[a] "Missing" category includes patients in the population who had no result for the parameter listed.

The efficacy of REBLOZYL in adult patients with beta thalassemia was established based upon the proportion of patients achieving RBC transfusion burden reduction (≥33% reduction from baseline) with a reduction of at least 2 units from Week 13 to Week 24.

Efficacy results are shown in Table 13.

Table 13: Efficacy Results in Beta Thalassemia - BELIEVE

Endpoint	REBLOZYL (N=224)	Placebo (N=112)	Risk Difference (95% CI)	p-value
≥33% Reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks				
Primary endpoint – Week 13 to Week 24	48 (21.4)	5 (4.5)	17.0 (10.4, 23.6)	<0.0001
Week 37 to Week 48	44 (19.6)	4 (3.6)	16.1 (9.8, 22.4)	<0.0001
≥50% Reduction from baseline in RBC transfusion burden with a reduction of at least 2 units for 12 consecutive weeks				
Week 13 to Week 24	17 (7.6)	2 (1.8)	5.8 (1.6, 10.1)	0.0303
Week 37 to Week 48	23 (10.3)	1 (0.9)	9.4 (5, 13.7)	0.0017

14.2 Treatment of Myelodysplastic Syndromes with Associated Anemia in ESA-naïve Patients

The efficacy of REBLOZYL was evaluated in the COMMANDS trial (NCT03682536), a multi-center, open-label, randomized active-controlled trial comparing REBLOZYL *versus* epoetin alfa in patients with anemia due to IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN RS-T) in ESA-naïve patients (with endogenous sEPO levels of < 500 U/L) who require regular red blood cell transfusions. For eligibility, patients were required to have had 2 to 6 RBC units/8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization.

The COMMANDS trial included 356 patients randomized 1:1 to REBLOZYL (N=178) or epoetin alfa (N=178). Randomization was stratified by RBC transfusion burden, RS status, and endogenous serum erythropoietin (sEPO) level at baseline. Treatment was started at 1 mg/kg subcutaneously every 3 weeks. Two dose level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg). Doses were held and subsequently reduced for adverse reactions, reduced if the hemoglobin increased by ≥ 2 g/dL from the prior cycle, and held if the predose hemoglobin was ≥ 12 g/dL.

All patients received best supportive care, which included RBC transfusions as needed. Patients were treated for 24 weeks and were assessed for efficacy at that time point. Treatment beyond 24 weeks was optional based upon response to treatment and absence of disease progression.

The median age of the 356 study participants was 74 years (range: 33, 93 years). The trial population was 56% male and 44% female; 79.5% were White, 0.6% Black or African American, 12.1% Asian, and race was not reported in 7.9% of patients. Ethnicities were reported as 85.4% for Not Hispanic or Latino patients, 6.5% for Hispanic or Latino patients, 7.6% for patients with no ethnicity reported, and 0.6% were unknown. IPSS-R risk classification at baseline was 9.3% very low, 72.2% low, 17.4% intermediate, 0.3% high, and 0.8% missing. Table 14 summarizes the baseline disease-related characteristics in the COMMANDS study.

Table 14: Baseline Disease Characteristics of Patients in COMMANDS

Disease Characteristic	REBLOZYL (N=178)	Epoetin Alfa (N=178)
Hemoglobin (g/dL) – n (%)		
Median (min, max)	7.80 (4.7, 9.2)	7.80 (4.5, 10.2)
Serum EPO (U/L) – n (%)		
Median (min, max)	78.7 (7.8, 495.8)	85.9 (4.6, 462.5)
IPSS-R risk classification at baseline – n (%)		
Very low	16 (9.0)	17 (9.6)
Low	126 (70.8)	131 (73.6)
Intermediate	34 (19.1)	28 (15.7)
High	1 (0.6)	0 (0)
Missing	1 (0.6)	2 (1.1)
Ring sideroblast status (per WHO criteria) – n (%)		
RS+	130 (73.0)	128 (71.9)
RS-	48 (27.0)	49 (27.5)
Missing	0 (0)	1 (0.6)
SF3B1 mutation status – n (%)		
Mutated	111 (62.4)	99 (55.6)
Non-mutated	65 (36.5)	72 (40.4)
Missing	2 (1.1)	7 (3.9)

The efficacy of REBLOZYL in the treatment of anemia in ESA-naïve adult patients with MDS was established at the time of the interim efficacy analysis based upon the proportion of patients who experienced both red blood cell transfusion independence (RBC-TI) [defined as the absence of any RBC transfusion during any consecutive 12-week period] and an associated concurrent mean improvement in hemoglobin by at least 1.5 g/dL for any consecutive 12 week period during Weeks 1-24.

At the time of the interim efficacy analysis, 301 subjects were included in the efficacy analysis, of which 147 were in the luspatercept arm and 154 were in the epoetin alfa arm, which is about 85% of the total information. The key efficacy results are shown in Table 15.

Table 15: Key Efficacy Results in COMMANDS

Endpoint	REBLOZYL (N=147)	Epoetin Alfa [a] (N=154)
RBC-TI for ≥12 weeks with associated concurrent mean Hgb increase of ≥ 1.5 g/dL (Weeks 1-24)		
Response rate, n (%) (95% CI)	86 (58.5) (50.1, 66.6)	48 (31.2) (24.0, 39.1)
Common Rate Difference (95% CI) [b]	26.6 (15.8, 37.4)	
p-value [c]	<0.0001	
Mean Hgb increase ≥ 1.5 g/dL (Weeks 1-24)		
Response rate, n (%) (95% CI)	106 (72.1) (64.1, 79.2)	75 (48.7) (40.6, 56.9)
Common Rate Difference (95% CI) [b]	23.2 (12.2, 34.1)	
HI-E per IWG ≥8 weeks (Weeks 1-24)		
Response rate, n (%) (95% CI)	109 (74.1) (66.3, 81.0)	79 (51.3) (43.1, 59.4)
Common Rate Difference (95% CI) [b]	22.3 (11.8, 32.8)	
p-value [c]	<0.0001	
RBC-TI for 24 weeks (Weeks 1-24)		
Response rate, n (%) (95% CI)	70 (47.6) (39.3, 56.0)	45 (29.2) (22.2, 37.1)
Common Rate Difference (95% CI) [b]	17.0 (6.7, 27.2)	
p-value [c]	0.0012	
RBC-TI for ≥12 weeks (Weeks 1-24)		
Response rate, n (%) (95% CI)	98 (66.7) (58.4, 74.2)	71 (46.1) (38.1, 54.3)
Common Rate Difference (95% CI) [b]	19.1 (8.6, 29.6)	
p-value [c]	0.0003	

EOT = End of treatment; HI-E = Hematologic Improvement – Erythroid Response; NE = Not Estimable; RBC-TI = red blood cell transfusion independence

[a] The majority of study participants (>90%) were outside of the United States and a non-U.S.-licensed epoetin alfa product was used in the control arm for such patients. Direct comparisons have not been established between REBLOZYL and U.S. licensed epoetin alfa product for the treatment of patients with anemia due to IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes or MDS/MPN RS-T in ESA-naïve patients.

[b] Common rate difference is based on the Mantel-Haenszel stratum weights.

[c] Based on CMH test stratified by baseline RBC transfusion burden (< 4, ≥ 4 pRBC units), RS status (RS+, RS-) and sEPO level (≤ 200, > 200 U/L). 2-sided p-value is presented. The statistical significance level at the second interim analysis is two-sided p-value 0.03.

No major outliers were observed in clinically relevant baseline demographic and disease characteristic subgroups.

14.3 Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia in ESA-refractory or -intolerant Patients

The efficacy of REBLOZYL was evaluated in the MEDALIST trial (NCT02631070), a multi-center, randomized, double-blind, placebo-controlled trial in patients with IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes who have ring sideroblasts and require red blood cell transfusions (2 or more RBC units over 8 weeks). For eligibility, patients were required to have had an inadequate response to prior treatment with an erythropoiesis-stimulating agent (ESA), be intolerant of ESAs, or have a serum erythropoietin > 200 U/L. The MEDALIST trial excluded patients with deletion 5q (del 5q), white blood cell count > 13 Gi/L, neutrophils < 0.5 Gi/L, platelets < 50 Gi/L, or with prior use of a disease modifying agent for treatment of MDS.

The MEDALIST trial included 229 patients randomized 2:1 to REBLOZYL (n=153) or placebo (n=76). Randomization was stratified by baseline RBC transfusion burden and baseline IPSS-R. Treatment was started at 1 mg/kg subcutaneously every 3 weeks; the dose could be increased after completion of the first 2 cycles if the patient had at least one RBC transfusion in the prior 6 weeks. Two dose level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg). Doses were held and subsequently reduced for adverse reactions, reduced if the hemoglobin increased by ≥ 2 g/dL from the prior cycle, and held if the predose hemoglobin was ≥ 11.5 g/dL.

All patients received best supportive care, which included RBC transfusions as needed. The primary efficacy assessment was conducted after completion of 24 weeks on study drug. Patients with a decrease in transfusion requirement or increase in hemoglobin could continue on blinded study drug thereafter until unacceptable toxicity, loss of efficacy, or disease progression.

The median age of the 229 study participants was 71 years (range: 26, 95 years). The trial population was 63% male and 69% White. Table 16 summarizes the baseline disease-related characteristics in the MEDALIST study.

Table 16: Baseline Disease Characteristics of Patients in MEDALIST

Disease Characteristic	**REBLOZYL (N=153)**	**Placebo (N=76)**
Time Since Original MDS Diagnosis [a] (months)		
Median (range)	44.0 (3, 421)	36.1 (4, 193)
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
Diagnosis per WHO Criteria, n (%)		
MDS-RS [c]	135 (88.2)	65 (85.5)

Disease Characteristic	REBLOZYL (N=153)	Placebo (N=76)
MDS/MPN-RS-T	14 (9.2)	9 (11.8)
Other [d]	4 (2.6)	2 (2.6)
IPSS-R Classification Risk Category, n (%)		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75)
Intermediate	25 (16.3)	13 (17.1)
High	1 (0.7)	0
RBC Transfusions/8 Weeks Over 16 Weeks Categories, n (%)		
< 4 units	46 (30.1)	20 (26.3)
≥ 4 and < 6 units	41 (26.8)	23 (30.3)
≥ 6 units	66 (43.1)	33 (43.4)

EPO=erythropoietin; IPSS R=International Prognostic Scoring System-Revised; ITT=intent-to-treat; MDS=myelodysplastic syndromes; RARS=refractory anemia with ring sideroblasts; RBC=red blood cell; RCMD=refractory cytopenia with multilineage dysplasia; SD=standard deviation; WHO=World Health Organization.

[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] Includes MDS-RS-MLD and MDS-RS-SLD.

[d] Includes MDS-EB-1, MDS-EB-2, and MDS-U.

The efficacy of REBLOZYL in adult patients with MDS-RS and MDS-RS-T was established based upon the proportion of patients who were red blood cell transfusion independent (RBC-TI), defined as the absence of any RBC transfusion during any consecutive 8-week period occurring entirely within Weeks 1 through 24.

The efficacy results are shown in Tables 17 and 18.

Table 17: Efficacy Results in MEDALIST

Endpoint	REBLOZYL (N=153) n, % (95% CI)	Placebo (N=76) n, % (95% CI)	Common Risk Difference (95% CI)	p-value
RBC-TI ≥ 8 weeks during Weeks 1-24	58 (37.9) (30.2, 46.1)	10 (13.2) (6.5, 22.9)	24.6 (14.5, 34.6)	<0.0001
RBC-TI ≥ 12 weeks during Weeks 1-24	43 (28.1) (21.1, 35.9)	6 (7.9) (3.0, 16.4)	20.0 (10.9, 29.1)	0.0002
RBC-TI ≥ 12 weeks during Weeks 1-48*	51 (33.3) (25.9, 41.4)	9 (11.8) (5.6, 21.3)	21.4 (11.2, 31.5)	0.0003

* The median (range) duration of treatment was 49 weeks (6 to 114 weeks) on the REBLOZYL arm and 24 weeks (7 to 89 weeks) on the placebo arm.

Table 18 shows the proportion of patients who achieved RBC-TI ≥ 8 weeks during Weeks 1-24 by diagnosis and baseline transfusion requirement.

Table 18: RBC-TI ≥ 8 Weeks during Weeks 1-24 By Diagnosis and Baseline Transfusion Burden in MEDALIST

	Responders / N		% Response (95% CI)	
	REBLOZYL	**Placebo**	**REBLOZYL**	**Placebo**
WHO 2016 Diagnosis				
MDS-RS	46 / 135	8 / 65	34.1 (26.1, 42.7)	12.3 (5.5, 22.8)
MDS/MPN-RS-T	9 / 14	2 / 9	64.3 (35.1, 87.2)	22.2 (2.8, 60.0)
Other [a]	3 / 4	0 / 2	75.0 (19.4, 99.4)	0.0 (0.0, 84.2)
Baseline RBC Transfusion Burden				
2 - 3 units/8 weeks [b]	37 / 46	8 / 20	80.4 (66.1, 90.6)	40.0 (19.1, 63.9)
4 - 5 units/8 weeks [c]	15 / 41	1 / 23	36.6 (22.1, 53.1)	4.3 (0.1, 21.9)
≥ 6 units/8 weeks	6 / 66	1 / 33	9.1 (3.4, 18.7)	3.0 (0.1, 15.8)

[a] Includes MDS-EB-1, MDS-EB-2, and MDS-U.

[b] Includes patients who received 3.5 units.

[c] Includes patients who received 5.5 units.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

REBLOZYL (luspatercept-aamt) for injection is a white to off-white lyophilized powder supplied in a single-dose vial. Each carton contains one vial.

REBLOZYL 25 mg/vial (NDC 59572-711-01)
REBLOZYL 75 mg/vial (NDC 59572-775-01)

16.2 Storage

Store vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to and during treatment with REBLOZYL.

Thromboembolic Events

Advise beta thalassemia patients of the potential risk of thromboembolic events. Review known risk factors for developing thromboembolic events and advise patients to reduce modifiable risk factors (e.g., smoking, use of oral contraceptives) *[see Warnings and Precautions (5.1)]*.

Effects on Blood Pressure

Caution patients that REBLOZYL may cause an increase in blood pressure *[see Warnings and Precautions (5.2)]*.

Extramedullary Hematopoietic Masses

Advise patients with beta thalassemia of the potential risk of extramedullary hematopoietic masses. Review possible risk factors for developing extramedullary hematopoietic masses. Instruct patients to report possible signs and symptoms of EMH masses *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving REBLOZYL and for at least 3 months after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with REBLOZYL *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]*.

Lactation

Advise females not to breastfeed during treatment with REBLOZYL and for 3 months after the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:

Celgene Corporation, a Bristol-Myers Squibb Company
86 Morris Avenue
Summit, NJ 07901
U.S. License No. 2252

REBLOZYL® is a registered trademark of Celgene Corporation, a Bristol-Myers Squibb Company.

REBPI.006

PATIENT INFORMATION
REBLOZYL® (REB-low-zil)
(luspatercept-aamt)
for injection, for subcutaneous use

What is REBLOZYL?

REBLOZYL is a prescription medicine used to treat anemia (low red blood cells) in adults with:

- beta thalassemia who need regular red blood cell (RBC) transfusions.
- myelodysplastic syndromes who may need regular RBC transfusions and have never received an erythropoiesis stimulating agent (ESA).
- myelodysplastic syndromes with ring sideroblasts (MDS-RS) or myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) who need 2 or more RBC units over 8 weeks and have not responded well to an ESA.

REBLOZYL is not for use as a substitute for RBC transfusions in people who need immediate treatment for anemia.
It is not known if REBLOZYL is safe and effective in children.

Before receiving REBLOZYL, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had blood clots
- take hormone replacement therapy or birth control pills (oral contraceptives)
- have had your spleen removed (splenectomy)
- smoke
- have or have had high blood pressure (hypertension)
- have a history of extramedullary hematopoietic (EMH) masses
- have or have had enlarged spleen or liver
- are pregnant or plan to become pregnant. REBLOZYL may harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with REBLOZYL.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with REBLOZYL.
  - You should use effective birth control (contraception) during treatment with REBLOZYL and for at least 3 months after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if REBLOZYL passes into your breast milk.
  - Do not breastfeed during treatment with REBLOZYL and for 3 months after the last dose. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive REBLOZYL?

- Your healthcare provider will prescribe REBLOZYL in a dose that is right for you. Depending on how you respond to REBLOZYL, your healthcare provider may adjust your dose or stop treatment.
- REBLOZYL is given as an injection under your skin (subcutaneous) in the upper arm, thigh, or stomach (abdomen) by your healthcare provider.
- Your healthcare provider will do regular blood tests to check your hemoglobin to monitor if your anemia is getting better before each injection and during your treatment with REBLOZYL.

If your scheduled REBLOZYL dose is delayed or missed, your healthcare provider will give your dose of REBLOZYL as soon as possible and continue your treatment as prescribed with at least 3 weeks between doses.

What are the possible side effects of REBLOZYL?

REBLOZYL may cause serious side effects, including:

- **Blood clots.** Blood clots in the arteries, veins, brain, and lungs have happened in people with beta thalassemia during treatment with REBLOZYL. The risk of blood clots may be higher in people who have had their spleen removed or who take hormone replacement therapy or birth control (oral contraceptives). Call your healthcare provider or get medical help right away if you get any of these symptoms:
  - chest pain
  - trouble breathing or shortness of breath
  - pain in your leg, with or without swelling
  - a cold or pale arm or leg
  - sudden numbness or weakness that are both short-term or continue to happen over a long period of time, especially on one side of the body
  - severe headache or confusion
  - sudden problems with vision, speech, or balance (such as trouble speaking, difficulty walking, or dizziness)
- **High blood pressure.** REBLOZYL may cause an increase in your blood pressure. Your healthcare provider will check your blood pressure before you receive your REBLOZYL dose. Your healthcare provider may prescribe you medicine to treat high blood pressure or increase the dose of medicine you already take to treat high blood pressure if you develop high blood pressure during treatment with REBLOZYL.

- **Extramedullary Hematopoietic (EMH) Masses.** EMH masses have happened in people with beta thalassemia during treatment with REBLOZYL. You may have a higher risk for developing EMH masses if you have a history of EMH masses, have had your spleen removed, have or have had an enlarged spleen or liver, or have low hemoglobin levels. Your healthcare provider will monitor you before you start and during treatment with REBLOZYL. Call your healthcare provider or get medical help right away if you get any of these symptoms:
  - severe pain in the back
  - numbness, weakness, or loss of voluntary movement in feet, legs, hands, or arms
  - loss of bowel and bladder control

The most common side effects of REBLOZYL include:

- tiredness
- headache
- back, joint, muscle, or bone pain
- joint pain
- dizziness
- nausea
- diarrhea
- cough
- stomach (abdominal) pain
- trouble breathing
- swelling of your hands, legs, or feet
- high blood pressure
- allergic reactions

REBLOZYL may cause fertility problems in females. This could affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of REBLOZYL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of REBLOZYL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about REBLOZYL that is written for health professionals.

What are the ingredients in REBLOZYL?

Active ingredient: luspatercept-aamt

Inactive ingredients: citric acid monohydrate, polysorbate 80, sucrose, and tri-sodium citrate dihydrate.

For more information, go to www.REBLOZYL.com or call 1-888-423-5436.

Manufactured by: Celgene Corporation, a Bristol-Myers Squibb Company, 86 Morris Avenue, Summit, NJ 07901

REBPPI V5 8/2023

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 8/2023

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M WROBLEWSKI
08/28/2023 02:02:43 PM