CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761136Orig2s000

OFFICE DIRECTOR MEMO

Division Director and Office Director Summary Review

Date	4/02/2020
Supervisory Associate Director, Division of Non-Malignant Hematology, OCHEN, OND	Albert Deisseroth, MD, PhD
BLA #	**BLA 761136 Original-2**
Applicant	Celgene Corporation
Date of Submission	4/4/2019
PDUFA Goal Date	4/4/2020
Proprietary Name	Reblozyl
Proper Name	Luspatercept-aamt
Dosage Form(s)	Injection, lyophilized (25 mg, 75 mg)
Recommendation on Regulatory Action	Approval
Recommended Indication	For the treatment of anemia failing an erythropoiesis stimulating agent (ESA) and requiring ≥2 RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndrome with ring sideroblasts (MDS-RS) or with a myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts & thrombocytosis (MDS/MPN-RS-T). Limitations of Use: REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.
Recommended Dosing Regimen	• Start REBLOZYL at 1.0 mg/kg once every 3 weeks as a subcutaneous injection. • If the patient is 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. • If the patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose, increase the dose to 1.75 mg/kg. • Do not increase the REBLOZYL dose beyond the maximum of 1.75 mg/kg per dose.

Resources Consulted	
Primary Clinical Review	Elizabeth (Dianne) Pulte, MD
CDTL Review	Donna Przepiorka, MD, PhD
Biometrics Review	Weishi Yuan, PhD, Xu-Te Wu, PhD, and Thomas Gwise, PhD

Preamble to Division Director Summary Review:

I have read the clinical reviews and the biometrics review. The primary clinical reviewer, Dr. Elizabeth (Diane) Pulte, recommends that the application be issued a complete response letter with a request for additional data. Dr. Pulte agreed that the phase 3 clinical trial met its primary objective. However, she had concerns about the trial and the adverse reactions associated with use of the product. Therefore, she concluded the risk-benefit was negative and recommended that the Applicant submit additional data. The CDTL, Dr. Donna Przepiorka, agreed the phase 3 clinical trial met its primary and key secondary objectives. She recommends approval in the subgroup of patients requiring 2-5 RBC units over 8 weeks with recommendations for collection and reporting of long-term safety information post approval. The biometrics review team agreed that the trial met its primary and secondary objectives and deferred to the clinical team for evaluation of the clinical significance of the trial results.

Division Director's Summary Review:

(This section was derived in part from the reviews of Drs. Donna Przepiorka, Elizabeth (Diane) Pulte, and Weishi Yuan.)

Background: On April 4, 2019, Celgene submitted sBLA 761136 to the FDA, in which marketing approval was requested for luspatercept-aamt (Reblozyl) for the following indication: the treatment of adult patients with very low- to intermediate-risk myelodysplastic syndrome (MDS) associated anemia failing an ESA with ring sideroblasts (RS) and requiring red blood cell (RBC) transfusions with a limitation of use stating that luspatercept-aamt (luspatercept) is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

Luspatercept is a recombinant biological composed of a modified form of the extracellular domain of the human activin receptor type IIB receptor linked to the human immunoglobulin G1 (IgG1) fragment crystallizable (Fc) domain. By using this recombinant molecule for trapping the natural ligands to the Activin IIB receptor and therefore preventing binding of these ligands to their receptor, luspatercept relieves inhibition of differentiation of late stage erythroid precursors in the bone marrow.

On November 8, 2019, lustpatercept was approved for the treatment of anemia in adult patients with beta thalassemia who require regular RBC transfusion. This approval was based on the Ace-536-B-Thal-001 trial which met its pre-specified primary endpoint: a statistically significant increase in the proportion of patients on the luspatercept + BSC arm which exhibited a ≥33% reduction from baseline in the RBC transfusion burden with a reduction of at least 2 units from week 13 to week 24, as compared to the percentage of patients on the placebo + BSC arm. This was 21.4% (48/224) on the luspatercept + BSC arm, as compared to 4.5% on the placebo + BSC arm ($p<0.0001$).

Study ACE-536-MDS-001(MDS-001): This supplemental request for approval of luspatercept for MDS relied upon a phase 3, double blind efficacy and safety study

which randomized in a 2:1 ratio 229 patients with MDS who no longer respond to erythropoiesis stimulating agents and require ≥2 units of RBC/8 weeks to luspatercept (n=153) vs placebo (n=76) for the treatment of anemia due to IPSS-R Very Low, Low, or Intermediate risk MDS with ring sideroblasts. The randomization was stratified by baseline transfusion burden (≥ 6 RBC units/8 weeks vs. <6 RBC units/8 weeks and IPSS-r at baseline). The primary endpoint was the proportion of patients who were RBC transfusion free over any consecutive 56-day or 8-week time period (TI-8) within the treatment period of the study.

Efficacy Results: The response rate of the primary endpoint of RBC-TI ≥ 8 weeks from week 1 through Week 24, was 37.9% (95% CI: 30.2%, 46.1%) in the luspatercept arm compared with 13.2% (95% CI: 6.5%, 22.9%) in the placebo arm. The p-value from a stratified Cochran Mantel-Haenszel (CMH) test was p<0.0001.

The response rate of the first key secondary endpoint: the response rate of RBC-TI ≥ 12 weeks from Week 1 through Week 24 was 28.1% (95% CI: 21.1%, 35.9%) in the luspatercept arm compared with 7.9% (95% CI: 3.0%, 16.4%) in the placebo arm with a p-value of p=0.0002 from a CMH test.

The response rate of the second key secondary endpoint of RBC-TI ≥ 12 weeks from Week 1 through Week 48 was 33.3% (95% CI: 25.9%, 41.4%) in the luspatercept arm compared with 11.8% (95% CI: 5.6%, 21.3) in the placebo arm with a p-value of 0.0003 from a stratified CMH test.

The study was initiated on February 9, 2016, and the primary analysis data cut-off date was May 8, 2018. As of the primary analysis cut-off date, 33.2% of patients were still continuing treatment in the study, with 45.8% in the luspatercept arm and 7.9% in the placebo arm. The total number of subjects who discontinued the study was 83 (54.2%) in the luspatercept arm and 70 (92%) in the placebo arm of which 51 (33.3%) was due to lack of efficacy in the luspatercept arm and 50 (65.8%) in the placebo arm.

The overall survival (OS) was not mature at the time of the data cut-off date. With a total of 21 deaths, the median survival in the two study arms was not estimable. There were 12 deaths (7.8% of patients) in the luspatercept arm and 9 deaths (11.8% of patients) in the placebo arm.

PRO Endpoints: There were no prespecified statistical hypotheses in regard to comparison of HRQoL endpoints. This study was not powered to detect a difference between luspatercept and placebo in either HRQoL assessment: EORTC QLQ-C30 and QoL-E and therefore all of the analyses of PRO endpoints are descriptive.

Subgroup Analysis Based on Baseline Characteristics: Table 1 summarizes an exploratory subgroup analysis of the primary endpoint of RBC-TI≥ 8 response rate by transfusion burden at baseline. The luspatercept arm has a greater number (by 2-9-fold) of responses than in the placebo arm in all categories. Although the percentage of patients responding to luspatercept appears to be highest in low transfusion burden

MDS, this conclusion is based on an exploratory analysis. There is no marker which can identify the patient who will respond to luspatercept.

Table 1: Response rates (RBC-TI ≥ 8) in patients with different tumor burden

RBC units/8 weeks	Placebo	Luspatercept
<4	40.0 (19.1, 63.9)	80.4 (66.1, 90.6)
4-6	4.3 (0.1, 21.9)	36.6 (22.1, 53.1)
≥ 6	3.0 (0.1, 15.8)	9.1 (3.4, 18.7)

Safety Results:

Deaths: With less than 10% of the information available at the time of the data cut-off date, 7.8% (12/153) of patients had died in the luspatercept arm as compared to 11.8% (9/76) had died in the placebo arm. Although there were 5 patients on the luspatercept arm whose death on study was associated with adverse events (renal failure, sudden death, MOF, and general health deterioration), in only one of these patients (associated with renal failure) was there sufficient evidence available to attribute the death to luspatercept. The most common adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection. Most reactions were low grade.

Benefit-Risk Discussion: Once patients with transfusion dependent anemia due to very low to intermediate risk MDS stop responding to ESAs, there are no approved agents for treating transfusion dependent anemia until MDS progresses to the late intermediate or high-risk subsets at which time the advanced nature of the disease justifies the increased toxicities of hypomethylating agents. Because MDS is a very heterogeneous disease which is continuously undergoing progression, the boundaries separating low risk, from intermediate and high risk for purposes of therapy selection in individual patients are hard to identify.

The evidence for benefit in terms of independence from RBC transfusions from luspatercept in Study MDS-001 was consistent across the primary and key secondary endpoints and was statistically persuasive. The fact that 45.8% of patients on the luspatercept arm were still continuing on treatment at the data cut-off date over two years after the time of initiating the MDS-001 trial and only 7.9% of the patients in the placebo arm at the cut-off date were still on study also suggests that this benefit was apparent to the patients on MDS-001.

Overall, the safety profile was similar to that seen in patients with beta thalassemia except for renal injury and fatigue. Fatigue was predominantly low-grade and appeared to be less prominent later on in therapy. Given the absence of an approved agent for the proposed indication, and the persuasive evidence for benefit as measured by transfusion independence, it appears as if the benefits of luspatercept therapy outweigh the risks associated with the safety profile of luspatercept which is low-grade in most

patients. An enhanced pharmacovigilance program will be employed in the post approval setting.

Regulatory Recommendation: Approval for the following indication: For the treatment of anemia failing an erythropoiesis stimulating agent and requiring ≥2 RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndrome with ring sideroblasts (MDS-RS) or with a myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

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/s/

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04/03/2020 03:07:55 PM

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My signature indicates that I have considered the assessments and recommendations included in the reviews in determining the regulatory action