CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761136Orig2s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 18, 2020

To: Elizabeth D. Pulte, M.D.
Division of Hematologic Malignancies I (DHM1)

Rosa Lee-Alonzo, PharmD, Senior Regulatory Project Manager, DHM1

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, DHM1

From: Rebecca Falter, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for REBLOZYL® (luspatercept-aamt) for injection, for subcutaneous use

BLA: 761136 Orig-2

In response to DHM1's consult request dated May 28, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original-2 BLA submission for Reblozyl. This submission (Orig-2) provides for the addition of the indication for myelodysplastic syndromes with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring Sideroblasts and thrombocytosis.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHM1 (Rosa Lee-Alonzo) on February 4, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on February 14, 2020.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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REBECCA A FALTER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 13, 2020
To:	Rosa Lee-Alonzo, PharmD Regulatory Project Manager **Division of Hematologic Malignancies I (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	REBLOZYL (luspatercept-aamt)
Dosage Form and Route:	for injection, for subcutaneous use
Application Type/Number:	BLA 761136
Applicant:	Celgene Corporation

1 INTRODUCTION

On April 4, 2019, Celgene Corporation submitted for the Agency's review an original Biologics License Application (BLA-761136) for REBLOZYL (luspatercept-aamt) for injection, for subcutaneous use. The purpose of the submission is to seek approval for use of REBLOZYL (luspatercept-aamt) for injection, for subcutaneous use, for the treatment of adult patients with:

- very low to intermediate-risk myelodysplastic syndromes (MDS) associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions.
- beta thalassemia-associated anemia who require red blood cell (RBC) transfusions.

At the time of the April 4, 2019 submission the application was administratively split by the Agency due to the different indications. The beta thalassemia anemia indication was designated as Original 1 and the myleodysplastic syndrome (MDS) indication was designated as Original 2. Original 1 was approved on November 08, 2019, on a priority timeline.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Malignancies I (DHM1) on January 10, 2020 and May 28, 2019, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for REBLOZYL (luspatercept-aamt) for injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft REBLOZYL (luspatercept-aamt) for injection PPI received on April 4, 2019, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on February 4, 2020.
- Draft REBLOZYL (luspatercept-aamt) for injection Prescribing Information (PI) received on April 4, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 4, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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02/14/2020 07:04:37 AM

LASHAWN M GRIFFITHS
02/14/2020 07:45:26 AM

Division of Hematology Products Associate Director for Labeling Review of the Prescribing Information

Product Title	REBLOZYL® (luspatercept-aamt) for injection, for subcutaneous use
Applicant	Celgene
Application/Supplement Number	BLA 761136; Original 2
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Approved Indication(s)	The treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions. Proposed Indication: Adult patients with very low to intermediate risk myelodyplastic syndromes (MDS) who have ring Sideroblasts and require red blood cell (RBC) transfusions.
Date FDA Received Application	04/04/2019
Review Classification (Priority/Standard)	Standard
Action Goal Date	04/04/2020
Review Date	
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the Warnings and Precautions section of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background: This application requests a second indication for Reblozyl for MDS. The original-1 application was approved on 11/08/19 for "the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions".

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.

[3] See *PLR Requirements for PI* website for PLR labeling guidances.

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Reviewer Comments: I recommend inclusion of Limitations of Use (LOU) as section 1.3 since the LOU applies to both indications (1.1 & 1.2). This is consistent with the CDER Labeling Review Tool. I also recommend that the LOU be added to the Highlights Indications and Usage Section.

Michael Manning (Pharm Tox Reviewer) provided the following justifications for edits to the Pharm Tox sections after his review was archived:

> Animal-to-human exposure comparisons in sections 5.3, 8.1, and 13.1 were calculated relative to exposures at the maximum recommended human dose of 1.75 mg/kg. Exposure multiples were based on steady-state exposures in animals (excluding those with anti-drug-antibodies) compared to clinical steady-state exposures.

Regulatory Recommendation: This NDA is recommended for approval upon completion of labeling negotiations.

Attachments: Revised labeling with track changes edits and bubble comments explaining the revisions. Edits and comments are authored by the multi-disciplinary team. The labeling version attached was sent to the Applicant by Rosa Lee-Alonzo on 01/24/20.

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/s/

VIRGINIA E KWITKOWSKI
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 13, 2020
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761136
Product Name, Dosage Form, and Strength:	Reblozyl (luspatercept-aamt) for Injection, 25 mg/vial and 75 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celgene Corporation
FDA Received Date:	April 4, 2019 and December 4, 2019
OSE RCM #:	2019-994-3
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Original-2 BLA 761136 Reblozyl (luspatercept-aamt) for Injection, 25 mg per vial and 75 mg per vial, this review evaluates the proposed Prescribing Information (PI) for areas that may lead to medication errors.

1.1 REGULATORY HISTORY

Reblozyl (luspatercept-aamt) is a recombinant fusion protein that was approved on November 8, 2019 under Original-1 for the treatment of adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions. It is available as 25 mg per vial and 75 mg per vial.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Celgene Corporation submitted a 351 (a) application to obtain marketing approval of Reblozyl for Injection for 2 indications. Under Original-2, Reblozyl is being proposed for the treatment of anemia in adult patients with very low-to-intermediate-risk myelodysplastic syndromes (MDS) who have ring sideroblasts and require red blood cell transfusions.

We performed a risk assessment of the proposed PI for Reblozyl (luspatercept-aamt) for Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors. We identified areas of concern in the PI that should be revised to improve the clarity of the information presented. Specifically, we note that the PI contains a trailing zero and error prone symbols, which may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 to address

these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the PI.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGY PRODUCTS (DHP)

A. Prescribing Information

1. Dosage and Administration Section

a. In Section 2.2, [redacted] (b) (4) remove the trailing zero (e.g. 1.0 mg/kg) to avoid a ten-fold misinterpretation.

b. In Section 2.2, [redacted] (b) (4) and Section 2.3 [redacted] (b) (4) consider replacing the symbols "≥" and ">" with their intended meanings to prevent misinterpretation and confusion.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Reblozyl received on December 4, 2019 from Celgene Corporation.

Table 2. Relevant Product Information for Reblozyl	
Initial Approval Date	November 8, 2019
Nonproprietary Name	luspatercept-aamt
Indication	• Adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions. • *Adult patients with very low-to-intermediate-risk myelodysplastic syndromes (MDS) who have ring sideroblasts and require red blood cell (RBC) transfusions*.
Route of Administration	Subcutaneous
Dosage Form	for Injection
Strength	25 mg/vial and 75 mg/vial
Dose and Frequency	Starting dosage in Beta Thalassemia *and in Myelodyplastic Syndromes* • The recommended starting dose of Reblozyl is 1 mg/kg once every 3 weeks by subcutaneous injection. Dose Increases during Treatment <u>Beta Thalassemia</u> • 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. <u>*Myelodysplastic Syndromes*</u> • *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. 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.* *Dose level increases are provided in the following table*: *Table 1: Dose Level Increases in MDS* *Dose Level* | *Dose Increase*

<table>
<tr><td></td><td>
<table>
<tr><td>Starting Dose</td><td>1 mg/kg</td></tr>
<tr><td>First Dose Increase</td><td>1.33 mg/kg</td></tr>
<tr><td>Second Dose Increase</td><td>1.75 mg/kg</td></tr>
</table>

Dose level decreases are provided in the following table:

Table 2: Dose Level Decreases in MDS
<table>
<tr><td>Current Dose</td><td>Dose Reduction</td></tr>
<tr><td>1.75 mg/kg</td><td>1.33 mg/kg</td></tr>
<tr><td>1.33 mg/kg</td><td>1 mg/kg</td></tr>
<tr><td>1 mg/kg</td><td>0.8 mg/kg</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>Reblozyl (luspatercept-aamt) for injection is white to off-white lyophilized powder supplied in a single-dose vial. Each carton contains one vial.
• Reblozyl 25 mg/vial
• Reblozyl 75 mg/vial</td></tr>
<tr><td>Storage</td><td>Store vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 7, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Reblozyl. Our search identified two previous label and labeling reviews[a,b], and we confirmed that our previous recommendations were implemented.

[a] Garrison, N. Label and Labeling Review for Reblozyl (BLA 761136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 29. RCM No.: 2019-994.

[b] Mehta, Hina. Label and Labeling Review for Reblozyl (BLA 761136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 18. RCM No.: 2019-994-1.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Reblozyl labels and labeling submitted by Celgene Corporation.

- Prescribing Information (Image not shown) received on December 4, 2019, available from \\cdsesub1\evsprod\bla761136\0078\m1\us\annotated.pdf

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NICOLE F IVERSON
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Memorandum of Consultation

To: Rosa Lee-Alonzo
OHOP/Division of Hematology Products (DHP)

From: Jacqueline Cunkelman MD, MPH
Division of Bone Reproductive and Urologic Products (DBRUP)

Suresh Kaul, MD, MPH
Team Leader, Urology DBRUP

Through: Audrey Gassman, M.D.
Deputy Division Director, DBRUP

Re: Consult Response for BLA 761136, Original 2
Safety/Efficacy Question on Reblozyl (luspatercept)

Date: September 18, 2019

Introduction

The Division of Bone, Reproductive and Urologic Products (DBRUP) received a consult request on August 20, 2019 from the Division of Hematology Products (DHP) regarding a study report for BLA 761136 which raised concerns regarding the finding of BPH TEAEs in 6 subjects in the drug (luspatercept) arm and none in the placebo arm. The Division of Hematology Products is seeking DBRUP's input regarding the biological plausibility of a causal relationship between luspatercept and BPH, and request recommendations for further evaluation of the risk.

Background

This consult focuses on results from a phase 3, double-blind, randomized, placebo-controlled trial comparing the efficacy and safety of luspatercept to placebo for the treatment of anemia in subjects with myelodysplastic syndromes (MDS) who require red blood cell (RBC) transfusions. The study population represents a subset of subjects with lower-risk MDS (IPSS-R very low-, low-, or intermediate-risk) who have anemia and limited treatment options for management of the anemia. These patients often become dependent on frequent RBC transfusions resulting in diminished quality of life and increased morbidity/mortality.

The drug is administered as a subcutaneous injection and is dosed at a starting level of 1.0 mg/kg up to a maximum dose level of 1.75 mg/kg. These parameters were selected on the basis of clinical data from the ongoing Phase 2 studies (A536-03 and A536-05). Preliminary results indicated that the dose levels up to 1.75 mg/kg were generally safe and well tolerated. Selection of the dosing schedule (q3w) was based on the duration of the luspatercept responses as well as PK parameters for luspatercept in subjects with MDS.

Subjects were assigned to treatment as per 1 of the following regimens:

- Experimental group: Luspatercept at a starting dose level of 1.0 mg/kg SC injection q3w (administered on Day 1 of each 21-day treatment cycle); or
- Control group: Placebo (volume equivalent to experimental group) SC injection q3w (administered on Day 1 of each 21-day treatment cycle)

Depending upon response, luspatercept was titrated up to a maximum dose of 1.75 mg/kg SQ not to exceed a maximum total dose per administration of 168 mg.

The primary objective was to evaluate RBC-TI of luspatercept compared with placebo for the treatment of anemia due to IPSS-R very low-, low-, or intermediate-risk MDS in subjects with ring sideroblasts who require RBC transfusions. Secondary objectives were the following:

- To assess the safety and tolerability of luspatercept compared to placebo,
- To evaluate the effect of luspatercept on reduction in RBC transfusions, increase in Hgb, duration of RBC-TI, improvement in HRQoL (i.e., European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30]), increase in neutrophils, increase in platelets, decrease in serum ferritin, decrease in ICT use, and time to RBC-TI compared with placebo, and
- To evaluate population PK and exposure-response relationships for luspatercept in MDS subjects

Additionally, there were several exploratory objectives for the study that are not relevant to this consult.

Inclusion criteria were primarily focused upon parameters related to the subject's MDS and transfusion requirements. Subjects were not excluded from study participation if they had a history of BPH or an incidental histologic finding of prostate cancer (T1a or T1b). There was no pre-treatment screening (physical exam or patient questionnaire) for undiagnosed BPH.

Two hundred twenty-nine subjects were enrolled (153 drug, 76 placebo). The study subjects were predominantly male—61.4% on luspatercept, 65.8% on placebo. This report includes data through May 8, 2018. At the time of data cutoff, all subjects had either reached the week 48 visit or discontinued early. There were 70 (45.8%) subjects remaining in the luspatercept cohort and 6 (7.9%) in the placebo cohort.

Disposition Parameter	Number (%) of Subjects		
	Luspatercept (N = 153)	Placebo (N = 76)	Total (N = 229)
Number of Subjects Who Completed 24 Weeks of Treatment	128 (83.7)	68 (89.5)	196 (85.6)
Number of Subjects Who Completed 48 Weeks of Treatment	78 (51.0)	12 (15.8)	90 (39.3)
Number of Subjects Remaining on Treatment as of the Data Cutoff Date	70 (45.8)	6 (7.9)	76 (33.2)

Safety Assessment Relative to BPH

Benign Prostatic Hyperplasia (BPH) is enlargement of the prostate not associated with malignancy. Due to its physical proximity to the bladder and urethra, prostatic enlargement may result in irritative voiding symptoms (urinary urgency/frequency) and urinary retention/obstruction. If untreated, obstruction/retention may result in urinary tract infections and/or damage to the upper urinary tract (ureters and kidneys). Symptomatic BPH may be treated with medical therapy (alpha blockers such as tamsulosin or 5-alpha-reducatase inhibitors such as finasteride) or surgical intervention either to reduce the size of the prostate through destruction/removal of tissue or to physically lift the prostate to relieve obstruction.

At baseline, BPH was among the most prevalent past medical history conditions and was reported by 18 patients (11.8%) in the Luspatercept arm and 11 patients (14.5%) in the placebo arm (overall prevalence of 12.7% of the study population). Men account for 61.4% of the luspatercept cohort and 65.8% of the placebo cohort, thus the prevalence is actually higher when considering only the portion of the study population at risk for BPH.

When looking at the reported rates of BPH, it is important to recognize that this was obtained by medical history through patient reports and that screening for BPH was not a part of the baseline clinical exam. It is possible that the true prevalence in this population was underestimated, as some men may have had asymptomatic BPH or had symptoms which were not bothersome enough for them to report or seek treatment.

BPH was identified as a TEAE in 6 patients—all in the luspatercept arm—at the time of the report. BPH-related TEAEs were primarily CTCAE Toxicity Grade 1/2 (5/6). One was Grade 3 due to its association with acute retention and elevated serum creatinine necessitating intervention (catheterization). When broken down by age, one subject was ≤64, four were 65-74, and one was ≥75. Notably, 2 of the cases were reported as "worsening" BPH, implying that this was not a new diagnosis for those individuals, though I was unable to review the past medical histories for those patients.

Consult Question

Benign prostatic hyperplasia (BPH) was observed in 6 patients on the luspatercept arm of the randomized trial of luspatercept in myelodysplastic syndrome and in no patients in the placebo

arm. Is a causal relationship between luspatercept and BPH biologically plausible and, if so, do you have any recommendations for further evaluation of the risk?

DBRUP response:
Luspatercept binds with high affinity to some TGFβ ligands. Per the non-clinical reviewer, it is not known whether luspatercept is distributed to the prostate, or accumulates there, though there were no adverse prostate findings in the general toxicology studies which were performed in rats and monkeys.

The prevalence of BPH increases after the age of 40 and affects 70% of US men 60-69 years of age and 80% of those ≥70 years of age[i]. Given that BPH was prevalent at baseline in this population (median age 71.0 years) and that subjects were not screened at baseline for BPH, the adverse events designated as BPH are not unexpected from a clinical standpoint. If the 6 cases are assumed to be newly diagnosed, prevalence of BPH in the luspatercept arm increases to 26% (24/94) compared to 22% in the placebo arm. Thus, the prevalence of BPH remained clinically similar for both arms of the study, BPH was found in a lower percentage of the population than would be expected based upon age alone. In addition, 2 of the 6 cases were documented to be "worsening" BPH, implying that this is not a new diagnosis and likely reflects the natural progression of the disease process as opposed to treatment effect of luspatercept.

In summary, we do not believe that the 6 subjects with adverse events associated with BPH during participation in the study raise concerns of a clinical safety trend between luspatercept and BPH. At least 2 subjects likely represent worsening of preexisting BPH. If the remaining 4 are truly new cases, this is not unusual given the age of the population. The disparity between study arms is minimal when looking at overall prevalence. Because most subjects in the placebo arm had withdrawn from the study by the date of data closure, comparison of the incidence of BPH between study arms is not possible. No further risk evaluation or monitoring is needed at this time.

If nonclinical data or any new findings raise additional concern regarding a causal relationship, please re-consult DBRUP.

Conclusion: No recommendation for additional risk evaluation at this time.

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[i] Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. J Urol. 2005;173:1256-1261.

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AUDREY L GASSMAN
09/23/2019 12:26:00 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology Products/ OND
Center for Drug Evaluation and Research

Date: 05 September 2019

From: Eric Bastings, M.D.
Acting Division Director

Subject: BLA 761,136
ACE-536 [Luspatercept (Reblozyl®)]
Celgene & Acceleron Pharma
Study A536-05

To: Director
Division of Hematology Products

Document Type: Consult

Enclosed is the Division's response to your request

Review and Evaluation of Clinical Data

BLA (Serial Number)	**761,136**
Sponsor:	**Celgene & Acceleron Pharma**
Product:	**ACE-536 [Luspatercept (Reblozyl®)]**
Indication:	**Anemia/low-risk myelodysplastic syndrome**
Material Submitted:	**Consult**
Correspondence Date:	**8/20/19**
Date Received By Reviewer:	**8/26/19**
Date Review Completed	**9/5/19**
Reviewer:	**David A Hosford MD PhD**

1. INTRODUCTION TO LUSPATERCEPT AND THE CONSULT QUESTIONS

Luspatercept is being developed by Celgene and Acceleron Pharma for two indications:

- adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions;
- adult patients with beta thalassemia-associated anemia who require red blood cell (RBC) transfusions.

Luspatercept is a ligand trap that reduces the activation of Activin Receptor IIA (ActRIIA), and thereby prevents an ensuing receptor-mediated TGF-beta cascade from inhibiting terminal erythroid (i.e., RBC) differentiation. This mechanism of action appears suitable to reduce the number of RBC transfusions needed by patients who have anemia due to MDS or to beta-thalassemia (Fenaux et al., 2019).

The sponsor has conducted three studies of luspatercept in subjects with low or intermediate risk MDS (see classification system further below): a phase 2 open-label ascending dose study (A536-03); an open-label extension study for subjects who completed the phase 2 study (A536-05); and a phase 3 randomized, double-blind, placebo-controlled efficacy and safety study (ACE-536-MDS-001). In these studies, 260 subjects were exposed to luspatercept and 76 subjects received placebo. Three subjects exposed to luspatercept (two subjects in the phase 2 study and one subject in the open label study) had treatment-emergent adverse events (TEAEs) of normal pressure hydrocephalus (NPH). No subjects on placebo had a report of NPH. There was also an increased incidence of reports of CNS TEAEs including dizziness, headache, and confusion in subjects on luspatercept vs. placebo (see data further below).

The sponsor has also conducted four studies of luspatercept in subjects with beta-thalassemia: a phase 2 open label ascending dose study (A536-04); an open-label extension study for subjects who completed the phase 2 study (A536-06); a phase 3 randomized, double-blind, placebo-controlled efficacy and safety study in blood transfusion-dependent subjects (ACE-536-B-Thal-001); and a phase 2 randomized, double-blind, placebo-controlled study in subjects not dependent on blood transfusions

(ACE-536-B-Thal-002). In these studies, 287 subjects were exposed to luspatercept and 109 subjects received placebo. There were no reports of NPH in any of these subjects. There was an increased incidence of dizziness in subjects taking luspatercept compared to placebo in these studies (data further below).

The Division of Hematology Products (DHP) consulted DNP to address the following issue:

> In trial A536-05, a long term follow up study for patients treated with luspatercept for anemia in low-risk myelodysplastic syndrome, there were 7 reports of normal pressure hydrocephalus (NPH) occurring in three apparently unique patients. No NPH was reported in other trials, but neurological issues including headache, deliria/confusion, and dizziness were more common in the luspatercept arm. Is there a biologically plausible mechanism by which luspatercept use could result in an increased risk for NPH? If so, is there a risk of undiagnosed NPH among patients on this trial with other neurological symptoms?

Our consult response will provide a background that will enable the two questions at the end of the passage above to be addressed:

1) Is there a biologically plausible mechanism by which luspatercept could result in an increased risk for NPH?

2) If so, is there a risk of undiagnosed NPH among patients in this trial with other neurological symptoms?

2. BACKGROUND ON MYELODYSPLASTIC SYNDROME (MDS)

a) Description of the condition

MDS comprises a group of myeloid neoplasms that typically cause anemia and also, in some patients, leukopenia or thrombocytopenia. The specific types of MDS include:

- refractory anemia with ring sideroblasts (RARS)
- refractory neutropenia
- refractory thrombocytopenia
- refractory cytopenia with multilineage dysplasia
- refractory anemia with excess blasts (RAEB)

Symptoms typically begin in mid- to-later life, and the prevalence is greater in males than females (Tefferi and Vardiman, 2009). The overall prevalence of MDS in the US is approximately 4 per 100,000. Diagnosis is made through an analysis of blood cell counts, blood smears, bone marrow aspirates, and bone marrow biopsies. Although there are treatments for the syndrome (see treatment section below), the overall median

survival ranges from 6 to 61 months depending on the severity of the condition as defined by a variety of classification systems (see widely-used classification system below) (Montalban-Bravo and Garcia-Manero, 2018).

Gene mutations associated with MDS are being identified with increasing rapidity. Some mutations (e.g., in *RUNX1, TP53, and EZH2*) adversely affect the prognosis, while others (e.g., in *SF3B1)* may improve survival (Montalban-Bravo and Garcia-Manero, 2018; Malcovati et al., 2015). The *SF3B1* mutations are of particular relevance because they are present in the majority of patients who have MDS with ring sideroblasts (Malcovati et al., 2015), and this population was enrolled in the sponsor's phase 3 efficacy and safety study of luspatercept in MDS.

The TGF-beta superfamily (e.g., activins, growth differentiation factors [GDF], and bone morphogenetic proteins) plays a role in a key intracellular signaling pathway that can affect anemia in patients with MDS (Fenaux et al., 2019). TGF-beta signaling may decrease terminal erythroid differentiation after agonist activation of various subclasses of Activin Receptor II (ActRII), resulting in phosphorylation and activation of Smad2,3, a transcriptional regulator. Luspatercept is a fusion protein that traps GDF and hence decreases TGF-beta signaling, resulting in greater erythroid differentiation and a decreased need for RBC transfusions in anemic patients with MDS (Fenaux et al., 2019; see Fig. 1, below). This will be further discussed below (luspatercept section).

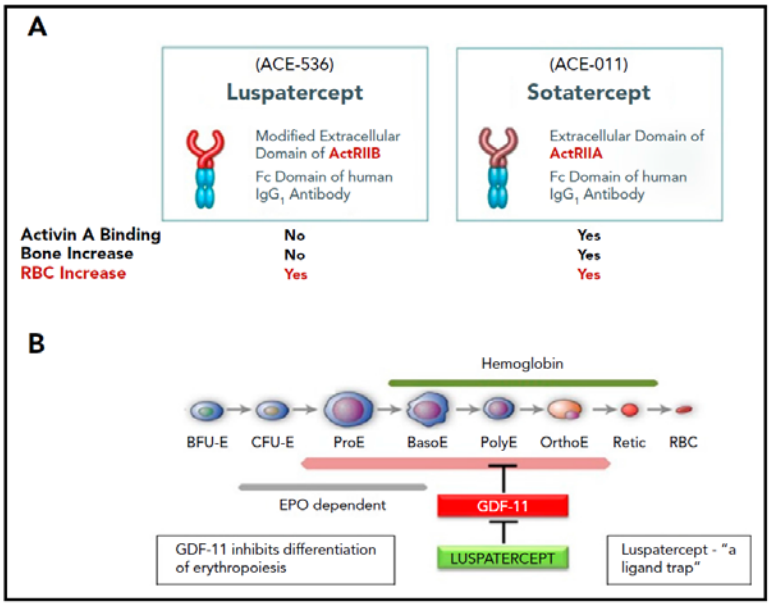

Figure 2. Luspatercept and sotatercept. (A) Molecular structure of luspatercept and sotatercept. (B) Mechanism of action of luspatercept. ACE, angiotensin-converting enzyme; BasoE, baso erythroblast; BFU-E, burst-forming unit erythroid; CFU-E, colony-forming unit erythroid; OrthoE, ortho erythroblast; PolyE, poly erythroblast; ProE, pro erythroblast; Retic, reticulocyte.

Fig. 1. Proposed mechanism of action of luspatercept. (Ref: Fenaux et al. 2019)

b) <u>Severity classification system</u>

The International Prognostic Scoring System (IPSS) is a widely used risk-stratifying classification system (Greenberg et al., 1997), and it was used by the sponsor in their trials of luspatercept in MDS. The IPSS stratifies patients into five groups based upon three factors: the percentage of bone marrow blasts (< 5% up to 30%); the prognostic

rank assigned by the karyotype (good, intermediate, or poor); and the number of cytopenias (1 vs 2 or 3). See the Table below.

Table 3. IPSS for MDS: Survival and AML Evolution

	Score Value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	—	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, ≥2.5.

* Good, normal, −Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

The sponsor enrolled patients with low (IPSS score of 0) or intermediate risk-1 (IPSS score of 0.5 – 1) scores into their trials of luspatercept in MDS.

c) Treatments

Treatment of MDS depends on transfusion requirements, IPSS staging, and patient-specific manifestations of the condition. Lower-risk patients may be maintained for a time on transfusions alone, although there are also several pharmacologic treatments that are approved (e.g. lenalidomide, 5-azacytidine, and decitabine). Higher-risk patients may be treated with erythroid-stimulating agents, 5-azacytidine, decitabine, and allogenic stem cell transplantation. Supportive methods such as antibiotic treatment or iron chelation therapy may also be needed (Montalban-Bravo and Garcia-Manero, 2018).

A number of investigational drugs are under development in the US, including luspatercept and sotatercept [each an ActRII ligand trap), proteasome inhibitors, Toll-like receptor antagonists, and immune checkpoint regulators (Montalban-Bravo and Garcia-Manero, 2018). A more detailed discussion of the luspatercept development program is below.

3. BACKGROUND ON LUSPATERCEPT (REBLOZYL®)

a) The compound and its mechanism of action

As cited above (section 2b), luspatercept is a fusion protein that consists of a modified extracellular domain of ActRIIB and the Fc domain of human IgG1. It acts as a ligand trap by binding GDFs and, to a lesser extent, activins; thereby it decreases TGF-beta signaling and allows greater erythroid differentiation (Fenaux, 2019).

Of relevance to this consult, TFG signaling is unrelated to the physiological mechanisms by which cerebrospinal fluid (CSF) is produced and absorbed (see further description of this process in the NPH section below). It is thought that alterations in CSF turnover underlie the development of NPH.

b) Subjects in trials of luspatercept in MDS

The sponsor has completed two trials of luspatercept in patients with low or intermediate-1 risk MDS, and a long-term safety extension trial is still underway. The subjects in these trials:

- are men or women > 18 years of age;
- have a documented diagnosis of MDS that is IPSS-classified as low or intermediate-1 risk (phase 2 and phase 3 studies), with additional subjects who are very low risk (phase 3 study only);
- have anemia (divided into a low transfusion burden [LTB: < 4 units of RBCs transfused within 8 weeks of treatment] or a high transfusion burden [HTB: >/= 4 units of RBCs transfused within 8 weeks of treatment]);
- are refractory or intolerant to prior erythropoiesis stimulating agents, or have stopped taking these agents before treatment;
- have not taken azacytidine or decitabine;
- have stopped taking lenalidomide, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or iron chelation therapy.

c) Efficacy in the completed phase 2 study, and general safety in the phase 2 study and its open-label extension study

The completed open-label phase 2 study (A536-03) showed that subjects treated with luspatercept had:

- a hemoglobin increase of >/= 1.5 g/dL for at least 14 days (70% of subjects);
- a reduction in RBC transfusion burden of at least 4 units or at least 50% of all units during an 8-week period (51% of subjects);
- an improvement to transfusion-independence (41%).

There were no dose-limiting toxicities and no deaths in the completed phase 2 study or its ongoing open-label safety extension study (A536-05 [data cut-off 10/13/17]). Most TEAEs were mild to moderate. TEAEs observed in more than 10% of the population included hypertension (24.3%), headache (13.1%), upper respiratory tract infection (20.6%), diarrhea (16.8%), fatigue (23.4%), peripheral edema (13.1%), myalgia (13.1%), cough (11.2%), and dyspnea (13.1%) [Source: Summary of Clinical Safety, Table 15]. There were three TEAEs resulting in drop-out: disease progression of MDS to high risk; physical health deterioration; and dyspnea. The reports of NPH in two unique subjects in this study will be described and discussed further below.

d) Efficacy and general safety in phase 3 study

The completed double-blind, randomized, placebo-controlled phase 3 study (ACE-536-MDS-001 showed that:

- transfusion-independence was achieved significantly more often in luspatercept-treated than placebo-treated subjects ($p = 0.0003$ or better depending on the measure);
- significantly more luspatercept-treated than placebo-treated subjects had hematologic improvements that included a hemoglobin increase of at least 1 mg/dL ($p < 0.0001$).

The general safety profile in subjects treated with luspatercept in the phase 3 study was similar to that in the open-label phase 2 study. TEAEs observed in more than 10% of the luspatercept group and also numerically greater in the luspatercept than the placebo group included: dizziness (19.6% luspatercept vs. 5.3% placebo); headache (15.7% vs. 6.6%); bronchitis (11.1% vs. 5.3%); urinary tract infection (11.1% vs. 5.3%); diarrhea (22.2% vs. 9.2%); nausea (20.3% vs. 7.9%); constipation (11.1% vs. 9.2%; fatigue (26.8% vs. 13.2%); asthenia (20.3% vs. 11.8%; back pain (19.0% vs. 6.6%); cough (17.6% vs. 13.2%); and dyspnea (15.0% vs. 6.6%) [Source: Summary of Clinical Safety, Table 15]. There were more deaths in the placebo group than in the luspatercept group, and there was a similar drop-out rate due to TEAEs in the two groups. Serious adverse events occurred approximately evenly between the two groups. The report of NPH in one unique subject in this study will be described and discussed further below.

4. BACKGROUND ON NORMAL PRESSURE HYDROCEPHALUS (NPH) AND ITS PREVALENCE

Hakim and Adams described NPH in 1965. In their description, patients exhibited what is now considered to be the classic triad of gait abnormality, mental deterioration that can reach a state of overt dementia, and urinary incontinence (Hakim and Adams, 1965). These signs resulted from a non-obstructive (i.e., communicating) hydrocephalus that was not accompanied by the range of higher intracranial pressures that characterize obstructive (i.e., noncommunicating) hydrocephalus. Instead, in spite of the ventriculomegaly that is present in NPH, intracranial pressures in this condition are normal or only mildly elevated (Kiefer and Unterberg, 2012).

The generally accepted explanation for the mechanics of normal intracranial pressure and for the development of the classic neurological signs is as follows. Ventriculomegaly is thought to arise from an imbalance in cerebrospinal fluid (CSF) production and absorption, resulting in an excess CSF volume and initially higher intracranial pressure. It is relevant to briefly describe the mechanisms of CSF production and absorption here. CSF is produced via an ATP-dependent transport mechanism through which sodium is transported into the CSF by choroidal ependymal

cells, followed by passive diffusion of water. CSF absorption is medicated by arachnoidal villi as a function of venous pressure (Cutler and Spertell, 1982; Ropper and Samuels, 2009). Neither of these functions involve intracellular signaling, whether via a TGF-beta-mediated cascade or through other intracellular cascades.

After the initial alteration of CSF turnover in people who will progress to development of NPH, gradual alterations in periventricular brain parenchyma and lowering of cerebral blood flow stabilize CSF turnover, resulting in the combination of a non-obstructive hydrocephalus with the paradoxical combination of ventriculomegaly yet relatively normal intracranial pressure (Kiefer and Unterberg, 2012). Ventriculomegaly, in turn, is thought to stretch descending cortical fibers as they pass through the white matter overlying the ventricles, thereby impairing the neural network that subserves control of both gait and of bladder detrusor muscle activity. Mental deterioration and dementia typically develop later in the course of the disease due to frontal subcortical damage, a result of the compression of periventricular brain parenchyma by ventriculomegaly (Kiefer and Unterberg, 2012).

The features of NPH described above can arise from either idiopathic NPH (iNPH), or from secondary NPH (sNPH). sNPH can be caused by etiologies that include subarachnoid hemorrhage, meningitis, or traumatic brain injury (Kiefer and Unterberg, 2012). NPH of either type is diagnosed via: brain imaging to demonstrate both communicating ventriculomegaly and preservation of the cortical mantle; measurement of intracranial pressure via lumbar puncture (LP); and the exclusion of other conditions that can present with dementia. A typical radiographic finding in iNPH is shown in the figure below (Source: Kiefer and Unterberg, 2012).

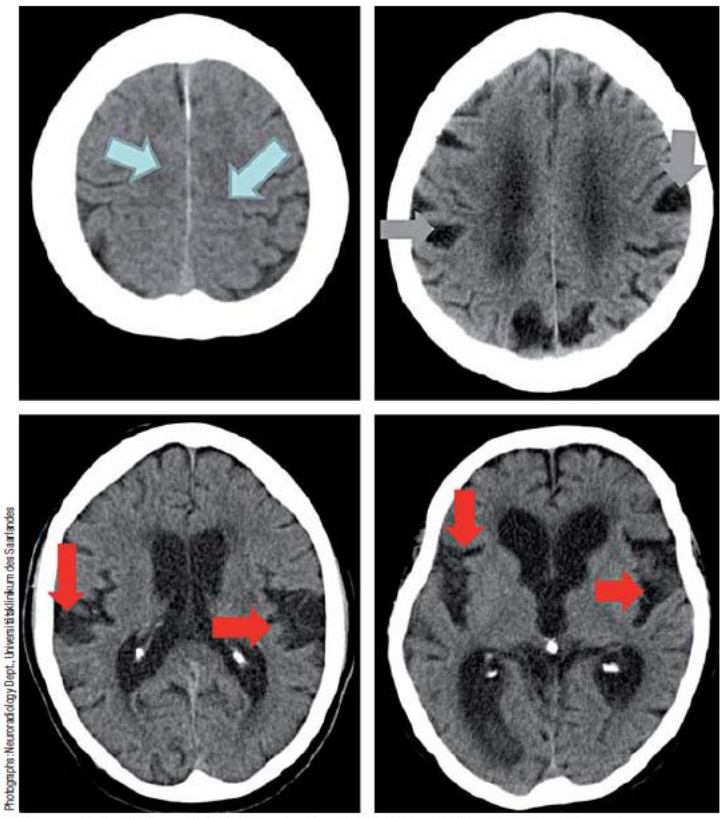

Figure 4: Typical cranial CT of a patient with iNPH. The CSF spaces near the vertex are narrow (blue arrows); the few wide sulci that are seen on the cerebral convexity (gray arrows) are all in the vicinity large, superficial arteries. Widening of the insular cisterns (red arrow) is a good indicator of iNPH that will respond to treatment

Treatment of NPH is typically via ventriculoperitoneal shunting, following which the majority of patients exhibit a rapid and sustained improvement in clinical signs of gait abnormality and urinary incontinence. Mental deterioration or dementia will stabilize, but it may take longer to recognize the absence of progression.

Several features of NPH are relevant to the reports of NPH in the sponsor's studies of luspatercept in people with MDS. First, headache is uncommon as a symptom of NPH (in either iNPH or sNPH), because the intracranial pressure in NPH is relatively normal. Instead, the headaches that are commonly ascribed to hydrocephalus are present in obstructive hydrocephalus, a condition characterized by high intracranial pressure. Second, psychiatric features such as delirium or hallucinations are rarely present in NPH. Third, dementia in NPH typically follows the onset of earlier signs of urinary incontinence and gait instability. Finally, a sense of disequilibrium may be present in NPH because of gait instability; however, this symptom is usually manifested when the patient is standing with eyes closed rather than as a constant symptom (Kiefer and Unterberg, 2012). This sense of disequilibrium is quite different than sensations of dizziness, which are more constant features and occur irrespective of stance or of eye closure. These points will be discussed more fully in section 6.

The prevalence of NPH in an older population is also relevant to the reports in NPH in the sponsor's studies. The prevalence of NPH in Japan has been reported to range from 1.4% to 2.9%, and to increase with age in older populations who are more than 65 years of age (Schneck, 2018). In Sweden, the prevalence of NPH ranges from 0.2% in younger populations to 5.9% as people approach 80 years of age (Jaraj et al., 2014). These prevalence rates will be discussed further in section 6.

5. CASES OF NPH IN STUDIES A536-03 AND A536-05

Three subjects had reports of NPH in study A536-05: subject (b) (6); subject (b) (6); and subject (b) (6). Features of each case are briefly cited below. Sources for the details in the relevant studies (phase 2 study A536-03 and open-label extension study A536-05) are Listings 16.2.7.1 [AE]; 16.2.8.1 [lab measurements]; and 16.2.8.16 [concomitant procedures].

a) Subject (b) (6)

i) Case presentation

This 78-year-old male subject in the HTB cohort had a report of NPH with a date of onset during the phase 2 study (A536-03) on Day 49. The report of NPH was made on the same day as a report of memory impairment (i.e., on Day 49), and following an earlier report of ataxia on Day 21. The report of NPH was apparently based on a head CT that was performed on Day 49 (listed as "suspected NPH"). A LP was performed on day 105 (listed as NPH). A subsequent head CT was performed on Day 208 (listed as NPH). A ventriculoperitoneal shunt was inserted on Day 209, and the event of NPH is reported as resolved on Day 211. Although there were several reports of NPH in this subject, it is clear that the condition continued from the initial report until it was reported as resolved on Day 211.

In this subject there were no reports of any other events in the Nervous Systems Disorders or Psychiatric Disorders SOCs, and also no report of urinary incontinence. He had a later event of epistaxis following resolution of the event of NPH. However, his platelet counts were in the normal range throughout the studies (e.g., 273 X 10^9/L at Screening into study A536-05 [ref range 150 – 400]). It is therefore doubtful that he had intracranial bleeding as a potential etiology for sNPH.

ii) Discussion

This is a likely case of NPH. The subject had the onset of ataxia before memory impairment; he had a LP that revealed an intracranial pressure which was apparently consistent with NPH; and he was shunted with subsequent resolution of the event of NPH. This was also likely a case of iNPH. He had a later event of

epistaxis but no prior events of intracranial bleeding that could have led to sNPH, and he also had a normal platelet count.

b) Subject (b) (6)

i) Case presentation

This 78-year-old female in the LTB cohort had a report of NPH with an onset on Day 56 of the phase 2 study (A536-03). A head CT was also performed on Day 56, listed as "suspicion of apoplexy;" apoplexy can be used to describe a variety of events that include stroke or intracranial hemorrhage. The event of NPH was reported to have resolved on Day 65. However, a second event of "suspected NPH" [verbatim term] was reported on Day 66. This event on Day 66 could not have been a new event, but rather was a continuation of the original event. The event of NPH had not resolved more than 400 days later, at the cut-off date for data from the long-term extension study (A536-05). Ataxia was reported on Day 358 of the long-term extension study. "Worsening of pre-existing ataxia" [verbatim term] was reported on Day 408 and a number of diagnostic procedures were performed for ataxia on Days 407 and 408, including another head CT.

In this subject there was a report of depression after the onset of NPH, but no other events in the Nervous System Disorders or Psychiatric Disorders SOCs. Of relevance to the event of apoplexy is that the subject had a low platelet count at Screening (113 X 10^9/L) and at numerous other measurement dates during the studies.

ii) Discussion

This is a possible case of NPH. There is no report of ataxia preceding the onset of the event of NPH; ataxia was first reported hundreds of days later. There is also no report of urinary incontinence or memory impairment, and no LP is reported to have been performed. These factors would tend to lower the likelihood that NPH was actually present, except that the preceding event of apoplexy in a setting of thrombocytopenia may provide a basis for a possible event of intracranial bleeding as an etiology for sNPH.

c) Subject (b) (6)

i) Case presentation

This 78-year-old male subject had the onset of a reported event of NPH on Day 114 of the long-term extension study (A536-05). A shunt was placed on Day 156, but there is no recording of any prior head CT or LP. A head CT was performed following shunt placement, on Day 167, and it is listed as NPH. The initial event of NPH is reported to have resolved on Day 307. However, a

subsequent event of NPH is reported to have started on Day 308, and the verbatim term is "worsening of preexisting NPH." Clearly this is not a new event. A head CT was performed on Day 450, and it is listed as "worsening NPH."

This subject had no other AEs of urinary incontinence, ataxia, or memory impairment. He also had no other AEs in the Nervous System Disorders or Psychiatric Disorders SOCs. His platelet count was high at Screening (536 X 10^9/L), and it remained high throughout the study.

ii) Discussion

This is an uncertain and perhaps unlikely case of NPH. There is no basis provided for the initial diagnosis (i.e., no brain imaging study and no LP), and the subject is not reported to have had ataxia, urinary incontinence, or memory impairment. Subsequent CTs are listed as NPH. It appears possible that the subject had ventriculomegaly as a CT finding, but that ventriculomegaly was due to some other cause, particularly since the subject did not improve after placement of a shunt. Nevertheless, to adhere to a principle of safety conservatism, this event of NPH will be considered to be a true event in the discussions below.

In summary, there are three unique subjects with probable or possible NPH in the 153 subjects exposed to luspatercept in studies of MDS, which equals a rate of 2.0%. There were no reports of NPH in the 76 subjects who received placebo. A rate of 2.0% of NPH in luspatercept-treated subjects is within the range of prevalence of NPH in older subjects, as cited above (section 4). Hence these cases of NPH may simply reflect a condition that occurs with increasing frequency in older people; all three subjects were 78 years of age.

In the four studies of luspatercept in patients with beta-thalassemia, there were no reports of NPH in subjects exposed to luspatercept (n = 287) nor in subjects who received placebo (n = 109). However, it is not possible to perform a balanced comparison between these patient populations, because the mean and median age of subjects in the MDS studies (mid-70s) are within the age range in which MDS is observed, in contrast to the far lower age range (mid-30s) of subjects in the beta-thalassemia studies.

6. OTHER ADVERSE EVENTS OF RELEVANCE IN THESE STUDIES

The consult from DHP refers to certain specific neurologic and psychiatric TEAEs (i.e., dizziness, headache, and delirium/confusion) in the MDS studies. There is only one placebo-controlled MDS study (ACE-536-MDS-001) that was conducted by the sponsor, and hence this study comprises the only available comparison of event rates between subjects taking luspatercept and those taking placebo. The complete Nervous System

Disorders and Psychiatry Disorders SOCs from this study are listed below, followed by a discussion about the relevance of individual TEAEs. The source for these data is Table 14.3.1.2.1.

System Organ Class Preferred Term	Luspatercept (N=153) n (%)	Placebo (N=76) n (%)
Nervous system disorders	72 (47.1)	21 (27.6)
Dizziness	30 (19.6)	4 (5.3)
Headache	24 (15.7)	5 (6.6)
Syncope	7 (4.6)	1 (1.3)
Paraesthesia	4 (2.6)	3 (3.9)
Lethargy	3 (2.0)	0
Presyncope	3 (2.0)	0
Sciatica	3 (2.0)	0
Balance disorder	2 (1.3)	0
Burning sensation	2 (1.3)	0
Cerebral atrophy	2 (1.3)	0
Dysgeusia	2 (1.3)	1 (1.3)
Memory impairment	2 (1.3)	0
Peripheral sensory neuropathy	2 (1.3)	0
Amnesia	1 (0.7)	1 (1.3)
Cerebral haemorrhage	1 (0.7)	0
Cognitive disorder	1 (0.7)	0
Disturbance in attention	1 (0.7)	0
Dyskinesia	1 (0.7)	0
Head discomfort	1 (0.7)	0
Lacunar infarction	1 (0.7)	0
Loss of consciousness	1 (0.7)	0
Mental impairment	1 (0.7)	0
Neuropathy peripheral	1 (0.7)	0
Parkinson's disease	1 (0.7)	0
Polyneuropathy	1 (0.7)	0
Quadrantanopia	1 (0.7)	0
Seizure	1 (0.7)	0
Speech disorder	1 (0.7)	0
Tension headache	1 (0.7)	0
Transient ischaemic attack	1 (0.7)	0
Tremor	1 (0.7)	0
Ageusia	0	1 (1.3)
Cerebral ischaemia	0	1 (1.3)
Cerebrospinal fluid leakage	0	1 (1.3)
Dysaesthesia	0	1 (1.3)
Haemorrhage intracranial	0	1 (1.3)
Hypoaesthesia	0	1 (1.3)
Neuralgia	0	1 (1.3)
Somnolence	0	1 (1.3)
Psychiatric disorders	30 (19.6)	10 (13.2)
Insomnia	9 (5.9)	4 (5.3)
Depression	8 (5.2)	5 (6.6)
Confusional state	7 (4.6)	0
Anxiety	5 (3.3)	1 (1.3)
Disorientation	2 (1.3)	0
Abnormal behaviour	1 (0.7)	0
Agitation	1 (0.7)	0
Delirium	1 (0.7)	1 (1.3)
Psychomotor retardation	1 (0.7)	0
Sleep disorder	1 (0.7)	0
Tension	1 (0.7)	0
Suicide attempt	0	1 (1.3)

The rates of dizziness (19.6% in subjects who received luspatercept vs. 5.3% in subjects who received placebo), headache (15.7% vs. 6.6%), syncope (4.6% vs. 1.3%), confusional state (4.6% vs. 0), and anxiety (3.3% vs. 1.3%) are greater in the luspatercept group. The other TEAEs in these SOCs occur at either a lower rate in the luspatercept than in the placebo group; or they occur more frequently in the luspatercept group but are numerically low and hence of low clinical significance.

First, the rates of these CNS TEAEs that can be associated with cases of NPH will be considered. Ataxia is not reported in these listings. Moreover, the only event term that might represent the mental deterioration, memory disturbance, or dementia in cases of NPH is “mental impairment;” this term was reported in 1 subject who received luspatercept (0.7%) and in no subject who received placebo. Urinary incontinence is not reported in the Renal and Urinary Disorders SOC. Due to the absence of a clinically

significant number of event terms that might be harbingers of NPH, it is unlikely that these listings represent undiagnosed cases of NPH.

Second, the rates of the five CNS TEAEs that appear to be over-represented in the luspatercept group will be considered. These TEAEs are dizziness, headache, syncope, confusional state, and anxiety. As presented above, disequilibrium may be present in subjects who have gait instability and are standing with eyes closed. This is a distinctly different symptom than a sensation of dizziness that may be present for longer periods of time, irrespective of stance or eye closure. Nevertheless, from a principle of safety conservatism, consider other evidence that these twelve cases of dizziness may mask an underlying condition of NPH. If this is true, then ataxia or gait instability should be present in these subjects to cause the event term of dizziness. However, there are no reports of ataxia or gait instability in these listings. There are two events of "balance disorder" reported in the luspatercept group (1.3%) and none in the placebo group, and it is possible that these cases could represent gait instability. This is a low number, and the absence of a clinically significant number of potential reports of ataxia again suggests that the over-representation of dizziness is not a clue of undiagnosed cases of NPH.

The remaining CNS TEAEs that appear to be over-represented in the luspatercept group will now be considered. These include headache, syncope, confusional state, and anxiety. Headache is not a feature of NPH. Syncope, confusional state, and anxiety are likewise nonspecific, and are not thought to represent signs or symptoms or NPH.

Taken together, these points suggest that it is unlikely that there are undiagnosed cases of NPH in this study. From a principle of safety conservatism, however, consider the prevalence of NPH in this study if the two reports of "balance disorder are considered to represent covert cases of NPH. In this situation, there are actually five and not three unique subjects with NPH in this study in which 153 subjects were exposed to luspatercept. Five out of 153 subjects would represent a rate of 3.3%, which is still within an expected prevalence rate of MDS in this older population.

Of incidental interest is that dizziness and headache were also observed in the placebo-controlled beta-thalassemia study (ACE-536-B-Thal-001) at higher rates in luspatercept-exposed subjects compared to subjects who received placebo. Ataxia, urinary incontinence, and terms that could reflect mental impairment are not reported. This increases the likelihood that EAEs of dizziness and headache may reflect the safety profile of luspatercept in general, rather than masking undiagnosed cases of NPH.

7. REVIEWER'S DISCUSSION, AND RESPONSES TO CONSULT QUESTIONS

a) Discussion

Luspatercept is a fusion protein that traps specific ligands (Growth Differentiation Factors) that activate ActRII, thereby preventing a receptor-mediated TGF-beta signaling cascade that can disturb erythroid differentiation. This mechanism of action does not appear to be relevant to the dynamic factors that change CSF production or absorption in the condition of NPH. It is often possible for compounds to have off-target activities that produce unanticipated and even surprising adverse events, but it is unlikely that luspatercept is causing NPH through such off-target activity for the following reason. Sotatercept (ACE-011, developed by Celgene for MDS and beta-thalassemia (b) (4)) acts as a similar ligand trap for agonists of ActRII, but sotatercept is less selective than luspatercept because it traps a larger range of ligands, and hence has a greater opportunity for off-target activity. Examination of TEAEs in the only completed study of sotatercept in low-risk patients with MDS (study ACE-011-MDS-001; table 14.3.1.3) reveals no reports of NPH in the 74 subjects exposed to sotatercept, but a reporting rate of dizziness (16.2%) and headache (18.9%) that are similarly common as compared to luspatercept. The absence of cases of NPH caused by sotatercept does not prove that the more selective compound, luspatercept, cannot cause NPH. However, together with the absence of a plausible relationship between TGF-beta signaling and CSF dynamics, there is no current evidence that luspatercept's mechanism of action could potentially cause NPH.

Three subjects had a number of reports of NPH during the conduct of two of the three studies of luspatercept in MDH (A536-03 and A536-05). Although only one of the three cases has sufficient documentation to justify it as a likely case of NPH, from a principle of safety conservatism all three cases will be accepted as true diagnoses of NPH. The rate of NPH in the sponsor's studies (2.0%) appears to be in the range reported for the prevalence of NPH in an elderly population (1.4 – 5.9%). Of the hallmark signs that characterize NPH (i.e., ataxia, urinary incontinence, and mental deterioration that can be consistent with dementia), only one other subject in these trials had a potential sign (event term of "mental impairment) of undiagnosed NPH. Two other subjects had terms of "balance disorder," which from a principle of safety conservatism can be considered to represent two potential subjects with ataxia. But even so, there would be five cases of NPH in 153 subjects exposed to luspatercept, resulting in a rate of 3.3%. This rate is well within the expected prevalence rate of NPH in an older population.

Likewise, the over-representation of other terms in the Nervous System Disorders and Psychiatric Disorders SOCs (i.e., dizziness, headache, syncope, confusional state, and anxiety) do not characterize NPH. Dizziness is a relatively constant feature when present, whereas the disequilibrium that can be observed in people with NPH occurs only when they have ataxia and are standing with eyes closed. There are no reports of ataxia in these studies, and the above discussion of two reports of "balance disorder" do not result in an overall rate of overt or potentially covert NPH out of range of normal prevalence rates of this condition.

b) Responses to the consult questions

1) Is there a biologically plausible mechanism by which luspatercept could result in an increased risk for NPH?

> Based upon the data, interpretations, and discussion points that are presented in the sections above, there does not appear to be a biologically plausible mechanism by which luspatercept could result in an increased risk for NPH. Indeed, the rate of NPH in unique subjects in the sponsor's studies of luspatercept in MDS (2.0%) falls well within the expected prevalence of NPH in this elderly population (1.4 – 5.9%).

2) If so, is there a risk of undiagnosed NPH among patients in this trial with other neurological symptoms?

> There does not appear to be a risk of undiagnosed NPH in other subjects in the trials. First, the hallmark signs of NPH (i.e., gait instability/ataxia, urinary incontinence, and mental deterioration that can reach the stage of dementia) are not over-represented in the luspatercept-exposed subjects. Second, the neurological and psychiatric signs or symptoms that are over-represented in the luspatercept-exposed subjects (i.e., dizziness, headache, syncope, confusional state, and anxiety) are not characteristic *per se* of the condition of NPH.

8. REFERENCES (in order of citation)

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CLINICAL INSPECTION SUMMARY

Date	September 6, 2019
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Elizabeth Dianne Pulte, M. D., Medical Officer Donna Przepiorka, M.D., Ph.D. Clinical Team Leader Ann Farrell, M.D., Director Rosa Lee-Alonzo, Regulatory Project Manager Division of Hematology Products
BLA	761136
Applicant	Celgene
Drug	Luspatercept
NME	Yes
Division Classification	Recombinant fusion protein
Proposed Indication	Treatment of adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anemia
Consultation Request Date	May 3, 2019
Summary Goal Date	September 1, 2019 (Original) September 23, 2019 (Extension)
Action Goal Date	December 4, 2019 (CDER priority review)
PDUFA Date	December 4, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites and the sponsor were selected for inspection in support of BLA 761136.

Data as reported by the sponsor to the BLA from Dr. Katja Sockel's sites in Germany (Study A536-03 Site 301 and Study ACE-536-MDS-001 Site 104), Dr. Ghulam Mufti's site in London, U.K. (Study A536-MDS-001 Site 500) and Dr. Pierre Fenaux's site in France (Study A536-MDS-001 Site 200) are considered to be reliable in support of the requested indication. These are based on preliminary clinical inspection findings. An amended report may be submitted as needed.

The inspection of the sponsor found no significant deficiencies with oversight and monitoring of the trial. In general, the sponsor maintained adequate oversight of the clinical trial and appeared to be in compliance with Good Clinical Practices.

II. BACKGROUND

Luspatercept (ACE-536) is a recombinant fusion protein consisting of a modified extracellular domain (ECD) of the human activin receptor type IIB (ActRIIB) linked to the human IgG1 Fc domain. The ActRIIB receptor and its ligands are members of the transforming growth factor (TGF)-β superfamily of proteins, which are negative regulators of red blood cell development. The presumed mechanism of luspatercept action involves the maturation phase of erythroblast differentiation, and maturation in the bone marrow.

In this submitted application, the sponsor proposes the following drug indication for luspatercept: Treatment of adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions.

A Phase 3 study ACE-536-MDS-001 and a Phase 2 study A536-03 will form the basis for the regulatory decision-making process for this application. Clinical study sites were selected for inspection because they enrolled high number of subjects with large numbers of protocol deviations, high response rates, and/or a quantitative impact on study outcomes.

Study ACE-536-MDS-001

Study ACE-536-MDS-001 was a Phase 3, double-blind, randomized study to compare the efficacy and safety of luspatercept (ACE-536) versus placebo for the treatment of anemia, based upon the Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes in subjects with ring sideroblasts who required red blood cell transfusions. The primary objective of the study was to evaluate red blood cell transfusion independence of luspatercept compared with placebo for the treatment of anemia classified as very low-risk, low-risk, or intermediate-risk myelodysplastic syndromes in subjects with ring sideroblasts who required RBC transfusions.

The primary efficacy endpoint was red blood cell transfusion independence at least for 8 weeks duration, defined as the proportion of subjects who were RBC transfusion free over any consecutive 56-day (8-week) period, during Week 1 through Week 24. Efficacy measures required the absence of any red blood cell transfusion during any consecutive 56-day (8-week) period, during the Primary Phase of the Treatment Period (covering the first 24 weeks of double-blind treatment), specifically, Days 1 to 56, Days 2 to 57, Days 3 to 58, etc.

A total of 229 subjects were randomized between February 9, 2016 and May 8, 2018. The study was conducted at 60 clinical study centers, in several countries including the United States, United Kingdom, Lebanon, Jamaica, Canada, Turkey, France, Italy, Netherlands, Egypt, Kenya, and Oman.

Study A536-03

Study A536-03 was a Phase 2 study to evaluate the proportion of subjects who had a modified erythroid response, defined as (1) a hemoglobin increase of 1.5 g/dL or greater, from baseline for 14 days or more (in the absence of red blood cell transfusions) in low transfusion burden subjects or (2) reduction of either 4 units and greater, or at least 50% of units of RBCs transfused compared to pretreatment in high transfusion burden subjects.

The primary efficacy endpoint was erythroid response for up to 24 weeks following initiation of treatment. Erythroid response endpoints were determined by monitoring hematologic laboratory values and RBC transfusions.

There were 12 participating centers in Germany. The first study subject enrolled on January 21, 2013. The last subject completed on August 9, 2017. A total of 107 subjects enrolled onto the study, 95 subjects completed five doses of treatment, and 101 subjects completed the study.

III. RESULTS (by site):

1. **Katja Sockel, M.D. (Previous P.I. -Uwe Plazbecker, M.D.)**
   Study ACE-536-MDS-001, Site 104 & Study A536-03 Site 301
   Universitätsklinikum C G Carus Medizinische Klink und Poliklinik Fetscherstrasse 74, House 66, Dresden, Germany 01307
   Inspection dates: August 12 to 16, 2019

For Study A536-MDS-01, six subjects were screened, and four subjects were enrolled at the site. Three subjects completed the treatment phase of the study. Three subjects discontinued due to refusal to participate or withdrawal of consent.

For Study A536-03, 50 subjects were screened, and 38 subjects were enrolled at the site. All enrolled patients completed the treatment phase of the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also reviewed.

Source documents for four enrolled subjects in Study A536-MDS-01 and for 17 enrolled subjects in Study A536-03 whose records were reviewed were verified against the case report forms and BLA subject line listings for study eligibility, informed consent form documentation, primary study endpoint assessment, adverse events, and serious adverse event reporting. Records review of these subjects indicated that the eligibility criteria for enrollment were met. Further, records for 38 subjects enrolled in Study A536-03 were reviewed comprehensively for blood transfusion dates and hemoglobin count levels.

Source documents for the raw data used to assess the primary efficacy endpoint were verifiable at the study site for both studies. There was no under-reporting of adverse events for Study A536-MDS-01 and Study A536-03. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Ghulam Mufti, M.D., Study ACE-536-MDS-001, Site 500
King's College Hospital NHS Foundation Trust
Denmark Hill, London SE 9RS UK
Inspection dates: August 5 to 9, 2019

A total of 13 subjects were screened and 11 subjects were enrolled for Study ACE-536-MDS-001. Ten subjects, who received treatment, completed the study. One patient withdrew further consent to participate in this study.

For this inspection, a complete review of all regulatory documentation at the study site was performed. Source records for all the subjects enrolled at the site were reviewed. The records reviewed included medical records, regulatory binder documents, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for all enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings for eligibility, adverse events, and serious adverse event reporting. Source documents for the primary efficacy raw data endpoint were verifiable at the study site. There was no under-reporting of adverse events. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

3. Pierre Fenaux, M.D., Study ACE-536-MDS-001, Site 200
Hopital St Louis
1 Avenue Claude Vellefaux
Paris 75475 France
Inspection dates: August 19 to 23, 2019

For Study ACE-536-001, a total of 13 subjects were screened and 11 subjects were enrolled. Five subjects, who received treatment, completed this study. Five subjects discontinued treatment due to lack of efficacy. One subject discontinued treatment from the study due to an adverse event.

For this inspection, a complete review of all regulatory documentation at the study site was performed. Source records for all the subjects enrolled at the site were reviewed. The records reviewed included medical records, regulatory binder documents, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for the 11 enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings for eligibility, adverse events, and serious adverse event reporting. Source documents for the primary efficacy raw data endpoint were verifiable at the study site. There was no under-reporting of adverse events. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

4. Celgene Corporation (Sponsor)
86 Morris Avenue, Summit, NJ 07901
Inspection dates: July 8 to 16, 2019

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Phase 3 study ACE-536-MDS-001 and a Phase 2 study A536-03. The inspection included review of organizational charts, vendor list, vendor oversight, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events, protocol deviations, and standard operating procedures. Interim Site Visiting Monitoring Reports for three clinical study sites [Sites #301 (Study 03 and Study 001), #500 (Study 001) and #200 (Study 001)] were selected and reviewed. No underreporting of significant adverse events to the Agency was noted.

There were no deficiencies with oversight and monitoring of the trial. In general, the sponsor appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

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