CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761136Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: October 25, 2019

To: Rosa Lee-Alonzo, PharmD, Senior Regulatory Health Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, 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

In response to DHP's consult request dated May 28, 2019, OPDP has reviewed the proposed product labeling (PI) for the original BLA submission for Reblozyl.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Rosa Lee-Alonzo) on October 16, 2019, and are provided below.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	October 18, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761136
Product Name and Strength:	Reblozyl (luspatercept-aamt) For Injection, 25 mg/vial and 75 mg/vial
Applicant/Sponsor Name:	Celgene
OSE RCM #:	2019-994-1
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 9 and 10, 2019 for Reblozyl (luspatercept-aamt). We reviewed the revised container label and carton labeling for Reblozyl (luspatercept-aamt) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

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

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 9 AND 10, 2019

Container labels

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HINA S MEHTA
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DIVISION OF HEMATOLOGY PRODUCTS
Associate Director for Labeling Review of the Prescribing Information

Product Title	**REBLOZYL (luspatercept-aamt)**
Applicant	Celgene
Application/Supplement Number	BLA 761136, Original 1
Type of Application/Submission[1]	NME
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
Proposed Indication(s) (if applicable)	Adult patients with beta thalassemia-associated anemia who require red blood cell (RBC) transfusions
Approved Indication(s) (if applicable)	tba
Date FDA Received Application	04/04/2019
Review Classification (Priority/Standard)	Priority
Action Goal Date	12/4/2019 (Internal goal date 11/06/19)
Review Date	09/09/19
Reviewer	Virginia E. Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format 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[2]
- 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

The applicant is seeking approval of luspatercept-aamt for the treatment of adult patients with transfusion-dependent beta thalassemia-associated anemia who require red blood cell (RBC) transfusions. This review is being completed after labeling meeting #2. In the attached PI, ADL comments (in balloons) begin with my initials "KV".

This review includes a high-level summary of the rationale for major changes to the PI as compared with the applicant's draft PI.

[1] Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

[2] 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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09/09/2019 11:46:46 AM

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:	August 29, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761136
Product Name 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
OSE RCM #:	2019-994
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

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

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. Reblozyl is indicated for the treatment of adult patients with beta thalassemia-associated anemia who require red blood cell (RBC) transfusions.

We performed a risk assessment of the proposed container labels, carton labeling, and Prescribing Information 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 the proposed labels and labeling that could be revised to improve clarity and readability of important information.

For the Division, we recommend removing trailing zeros, relocating complex preparation instructions in a tabular format, revising reconstitution and storage statements for clarity.

For the Applicant, we recommend changes to the carton and container labels to improve readability and prominence of important information. Specifically, we recommend increasing prominence of the proprietary name, strength presentation, including reconstitution instructions, and revising the storage information on the labeling.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for Celgene Corporation to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information

1. Dosage and Administration Section

a. Remove the trailing zero (e.g. 1.0 mg/kg) to avoid a ten-fold misinterpretation.

b. Remove the dangerous abbreviation, "SC" as the intended meaning, "subcutaneous" is used in the dosage and administration section and thus is not necessary.

c. Add the statement "See full prescribing information for preparation and administration instructions (2.4)." as the preparation involves several steps.

B. Prescribing Information

1. Dosage and Administration Section

a. Remove all instances of trailing zeros (e.g. 1.0 mg/kg) to avoid a ten-fold misinterpretation.

b. In Section 2.4, *Preparation and Subcutaneous Administration,* consider including reconstitution volumes in a table to mitigate the risk of preparation errors. For example,

Reconstitution Volumes

Strength	Amount of Sterile Water for Injection, USP required for reconstitution	Final Concentration
25 mg vial	0.68 mL	50 mg/mL
75 mg vial	1.6 mL	50 mg/mL

c. In Section 2.4, *Preparation and* [redacted] *Administration,* revise the statement, "Reconstitute the [redacted] number of REBLOZYL vials to achieve the [redacted] dose." to " Reconstitute the [redacted] number of REBLOZYL vials to achieve the [redacted] dose [redacted] the patient's weight."

d. In Section 2.4, *Preparation and* [redacted] *Administration,* revise the statements, "Reconstitute REBLOZYL with Sterile Water for Injection, USP. [redacted] We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked and the warning may be misinterpreted as an affirmative action.

e. For Step 1 of the Reconstitution Instructions, revise the statement, [redacted] to "Reconstitute with Sterile Water for Injection, USP using volumes described in Table x (Reconstitution volumes) with the stream directed onto the lyophilized powder."

2. How Supplied/Storage and Handling Section

a. Revise the storage statement as follows, "Store refrigerated at 2°C-8°C (36°F-46°F) in the original carton. Do not freeze."

4.2 RECOMMENDATIONS FOR CELGENE CORPORATION

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. The placement of the graphic at the end of the proprietary name competes with the readability of the proprietary name, which may lead to misinterpretation of the proprietary name as "Reblozylo". We recommend moving or decreasing the prominence of the graphic at the end of the proprietary name competes with the readability of the proprietary name, which may lead to misinterpretation of the proprietary name.

2. Increase the prominence of the 75 mg vial strength presentation by changing the font color from [redacted] to black to mitigate the risk of product selection errors.

3. The [redacted] colored line located on the left side of the principal display panels competes in prominence with the colored boxing used to differentiate the strength presentation. Consider removing or lightening the [redacted] colored line on the principal display to bring prominence to the strength presentation.

B. Container Labels

1. Revise the statement, [redacted] (b) (4) to "Dosage: See Prescribing Information".
2. On the side display panel, revise the storage information as follows, "Store refrigerated at 2°C-8°C (36°F-46°F) in the original carton. Do not freeze"
3. Revise the statement, [redacted] (b) (4) to "Reconstitute prior to administration."
4. If possible, consider deleting the numbers, "VL77501.001" on the side display to ensure it will not be confused with the lot number.

C. Carton Labeling

1. The Rx Only Statement appears prominent the principal display panel of the carton labeling. Decrease the prominence by debolding the Rx Only statement.
2. We note that both side display panels contain redundant storage, reconstitution, dosage and administration information. We recommend removing redundant statements as this increases visual clutter on the side display panels.
3. Revise the statement, "[redacted] (b) (4) to "Dosage: See Prescribing Information".
4. Revise the storage information as follows, "Store refrigerated at 2°C-8°C (36°F-46°F) in the original carton. Do not freeze.
5. Consider revising the statement on the principal display panel, [redacted] (b) (4) to "Reconstitute with Sterile Water for Injection, USP prior to administration." to highlight the importance of only using sterile water for reconstitution.
6. Include the following reconstitution instructions on the side display panel. For example, using the 25 mg/vial, "Reconstitute each Reblozyl vial with 0.68 mL of Sterile Water for Injection, USP to obtain a concentration of 50 mg/mL of luspatercept-aamt"

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

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

Table 2. Relevant Product Information for Reblozyl	
Initial Approval Date	N/A
Active Ingredient	luspatercept-aamt
Indication	For the treatment of adult patients with beta thalassemia-associated anemia who 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	1 mg/kg once every 3 weeks by subcutaneous injection
How Supplied	Reblozyl for injection is supplied as a lyophilized powder in a 3 mL single-dose vial packaged in cartons of 1 vial. • Reblozyl 25 mg powder for solution for injection • Reblozyl 75 mg powder for solution for injection
Storage	Store unreconstituted vials at 2°C - 8°C (36°F - 46°F) in original carton. Do not freeze.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 5, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, luspatercept. Our search did not identify any previous reviews.

APPEARS THIS WAY ON ORIGINAL

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,[a] along with postmarket medication error data, we reviewed the following Reblozyl labels and labeling submitted by Celgene Corporation.

- Container label received on April 4, 2019
- Carton labeling received on April 4, 2019
- Prescribing Information (Image not shown) received on April 4, 2019

G.2 Label and Labeling Images

Container labels

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

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HINA S MEHTA
08/29/2019 09:50:31 AM

CLINICAL INSPECTION SUMMARY

Date	August 14, 2019
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Min Lu, M.D., M.P.H., GCPAB Acting Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Laurel Menapace, M. D., Medical Officer Tanya Wroblewski, M.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 beta thalassemia-associated anemia who require red blood cell transfusions
Consultation Request Date	May 23, 2019
Summary Goal Date	October 10, 2019
Action Goal Date	November 6, 2019
PDUFA Date	December 4, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites and the sponsor's site were selected for inspection in support of BLA 761136.

Data from Dr. Thomas Coates's site in California (Site 001) and Dr. Maria Cappellini's site in Italy (Site 481) in Study ACE-536-B-THAL-001, as reported by the sponsor to the BLA, are considered to be reliable in support of the requested indication.

The inspection of sponsor's site 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 involving Study ACE-536-B-THAL-001, the sponsor proposes the following drug indications for luspatercept: Treatment of adult patients with beta thalassemia-associated anemia who require red blood cell (RBC) transfusions

Study ACE-536-B-THAL-001
Study was an ongoing Phase 3, double-blind, randomized, placebo-controlled, multicenter study subjects aged at least 18 years and who required regular RBC transfusions due to β-thalassemia. The study consisted of a Screening/Run-in Period (12 weeks), a double-blind treatment period (48 weeks), and a double-blind long-term treatment period (up to 48 weeks).

The primary objective of the study was to determine the proportion of subjects treated with luspatercept plus best supportive care *versus* placebo plus best supportive care who achieved erythroid response. Erythroid response was defined as a thirty-three percent or greater reduction from baseline, in transfusion burden (units red blood cells/time), with a reduction of at least two units, from Week 13 to Week 24.

The primary efficacy endpoint was the proportion of subjects with hematologic improvement, defined as 33% or greater reduction from baseline in RBC transfusion burden, with a reduction of at least 2 units from Week 13 to Week 24, compared with the 12-week interval prior to randomization for luspatercept plus best supportive care *versus* placebo plus best supportive care.

A total of 336 subjects were randomized in a 2:1 ratio to the luspatercept plus placebo treatment group (224 subjects) and the placebo plus best supportive care treatment group (112 subjects). The calendar date of the first subject visit was May 2, 2016. The calendar date of the last subject completing the Week 48 visit was May 14, 2018. The study is ongoing. This study was conducted at 65 clinical study sites in 15 countries.

Rationale for Site Selection
ACED-536-B-THAL-001 Sites 481(Maria Cappellini) and 001 (Thomas M. Coates) were selected because they were high number of subjects enrolling sites with large numbers of protocol deviations. In addition, Site 481 had also a relatively higher serious adverse event reporting profile compared to other high enrollee sites.

III. RESULTS (by site):

1. **Thomas M. Coates, M.D. Site 001**
   Children's Hospital Los Angeles, 4560 Sunset Blvd. Los Angeles, CA 90027
   Inspection dates: July 25 to August 2, 2019

A total of 12 subjects were screened and 11 patients enrolled. Eleven study subjects received treatment in this ongoing study. One enrolled subject withdrew consent due to an adverse event.

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 11 enrolled subjects 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.

Source documents for the raw data used to assess the primary efficacy endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

At the conclusion of the inspection, a Form FDA 483 was issued for inaccurate or inadequate study record documentation. Specifically, for Subject (b) (6) the medication stop date was not included in the concomitant medication patient data listing for vitamin B complex prophylaxis (start date of (b) (6)). For Subject (b) (6) a Grade 1 abdominal pain adverse event date (an incorrect calendar entry (b) (6)]) in the patient data listing was captured inaccurately; however, the start and stop dates were recorded in the CRF.

The Form FDA 483 (List of inspectional observations) was shared with the Division of Hematology Products (DHP).

Although the above observation is a regulatory violation, the findings were found not significant for this ongoing clinical investigation and would unlikely affect the overall reliability of safety and efficacy data of the study.

2. Maria Cappellini, M.D. Site 481
Fondazione Ca Granada IRCCS, Ospedale Maggiore PoliclinicoVia Francesco Sforza 35, Milan, 20122, Italy
Inspection dates: July 29 to 31, 2019

A total of 15 subjects were screened and 12 subjects were enrolled. Ten subjects, who received treatment, are participating in this ongoing study. Two subjects discontinued from the study due to adverse events.

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

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of ACE-536-B-THAL-001. 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 two clinical study sites (Sites #001 and #481) 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, 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.

{See appended electronic signature page}
Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Interdisciplinary Review Team for QT Studies Consultation Review

Submission	BLA 761136
Submission Number	001
Submission Date	4/4/2019
Date Consult Received	4/26/2019
Clinical Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- CQT report: ACE-536-MPS-003 (Submission 0001);
- Clinical trial report for A536-03, A536-04, ACE-536-MDS-001, and ACE-536-B-THAL-001 (Submission 0001); and
- Proposed label (Submission 0001).

1 SUMMARY

Luspatercept is a large targeted protein (76 kDa) with low likelihood of direct cardiac ion channel interactions and a dedicated QT evaluation is not necessary as per ICH E14 Q&A 6.3.

The safety QTc data do not suggest any off-target effects for QTc prolongation – the incidence of patients with QTc categorical outliers (e.g., QTc > 500 ms or increase in QTc > 60 ms) is similar between placebo and luspatercept arms. The quality of the ECG acquisition and measurement is not appropriate for characterizing the QTc effects using central tendency analysis and concentration-QTc analysis.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable

2 PROPOSED LABEL

Below are proposed edits to the proposed label (Submission 0001). Our changes are highlighted (addition, ~~deletion~~). We recommend removing the text below from the label because only safety ECGs were collected in phase 2 and 3 clinical trials and are not adequate for excluding small QTc effects.

12.2 Pharmacodynamics
(b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Luspatercept (ACE-536) is an erythroid maturation agent. Luspatercept 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 kDa. Luspatercept is produced in Chinese hamster ovary cells by recombinant DNA technology.

The proposed indication is for the treatment of adult patients with β-thalassemia and myelodysplastic syndromes (MDS) associated anemia who require red blood cell transfusion. The recommended starting dose is 1 mg/kg once every 3 weeks (Q3W) by subcutaneous (SC) injection. The maximum recommended therapeutic dose is (b) (4) mg/kg Q3W.

Study report ACE-536-MPS-003 described the findings of the sponsor's concentration-QTc analysis using data collected from four clinical trials. A summary of individual study features is provided below. Single 12-lead ECGs were collected near the trough or the maximum concentration at steady-state ($C_{max,ss}$). Because luspatercept concentrations change slowly over time, ECG and concentration measurements collected on the same day were considered to be time-matched. The primary endpoint is QTcF. Baseline QTcF was defined as the QTcF measurement taken at screening.

Study	A536-03	A536-04	ACE-536-MDS-001	ACE-536-B-THAL-001
Study population	MDS	β-Thalassemia	MDS	β-Thalassemia
Dose levels (mg/kg)	0.125 – 1.75	0.2 – 1.25	0.45 – 1.75	0.45 – 1.25
Visit for baseline ECG	Screening	Screening	Screening	Screening
Visit for paired ECG/PK	C2D1, EOT, Unscheduled	C2D1, EOT, Unscheduled	C5D8, EOT, Unscheduled	C6D8, EOT, Unscheduled
Study day from first dose for paired ECG/PK	21, 112, varies	21, 112, varies	92, varies, varies	113, varies, varies

C = dose for study ACE-536-B-THAL-001 or cycle for other studies; D = day; ECG = electrocardiogram; EOT = end of treatment (28 days after the last dose); MDS = myelodysplastic syndromes.

Source: Table 2 in CQT report ACE-536-MPS-003

Reviewer's comments:

- *T_{max} is approximately 7 days postdose. The half-life is 13 days for patients with MDS and 11 days for patients with beta thalassemia. Steady state is reached after 3 doses.*
- *The dose and exposure appears adequate to cover maximum exposure at the therapeutic dose levels.*
- *Only safety ECGs were collected in clinical trials. These data are appropriate for assessing categorical outliers, but not for characterizing the QTc effect using central tendency or concentration-QTc analyses.*

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

The sponsor did not conduct central tendency analysis.

3.2.2 Categorical Analysis

All available data from all subjects by visit were included in the summaries, regardless of whether they were included in the concentration-QTc analysis.

	Indication	Starting dose	N	Maximum QTcF, n (%)		
				> 450 ms	> 480 ms	> 500 ms
Baseline	MDS	Placebo	76	13 (17.1)	4 (5.3)	3 (3.9)
		< 1 mg/kg	14	2 (14.3)	1 (7.1)	1 (7.1)
		1-1.75 mg/kg	246	26 (10.6)	6 (2.4)	5 (2.0)
	BTHAL	Placebo	109	10 (9.2)	3 (2.8)	0
		< 0.8 mg/kg	18	0	0	0
		0.8-1.25 mg/kg	269	20 (7.4)	5 (1.9)	3 (1.1)
Post-baseline	MDS	Placebo	64	12 (18.8)	5 (7.8)	2 (3.1)
		< 1 mg/kg	14	2 (14.3)	0	0
		1-1.75 mg/kg	225	32 (14.2)	7 (3.1)	6 (2.7)
	BTHAL	Placebo	102	5 (4.9)	0	0
		< 0.8 mg/kg	18	0	0	0
		0.8-1.25 mg/kg	256	20 (7.8)	7 (2.7)	4 (1.6)

BTHAL = β-thalassemia; MDS = myelodysplastic syndromes; N = total number of subjects for each dose group; n = number of subjects in each outlier category.

Source: Table 10 in CQT report ACE-536-MPS-003

Indication	Starting Dose	N	Δ QTcF, n (%)	
			>30 ms	>60 ms
Myelodysplastic Syndrome	Placebo	64	8 (12.5)	3 (4.7)
	< 1 mg/kg	14	3 (21.4)	1 (7.1)
	1-1.75 mg/kg	225	21 (9.3)	6 (2.7)
β-Thalassemia	Placebo	102	11 (10.8)	3 (2.9)
	< 0.8 mg/kg	18	1 (5.6)	0
	0.8-1.25 mg/kg	256	27 (10.5)	10 (3.9)

N = total number of subjects for each dose group; n = number of in each outlier category.

Source: Table 11 in CQT report ACE-536-MPS-003

Reviewer's comment: *Compared to baseline and placebo arm, there is no overreporting of QTc prolongation in the treatment groups.*

3.2.3 Exposure-Response Analysis

The sponsor used a direct effect, linear concentration-QTc model to evaluate the effect of luspatercept on the QTc interval.

Reviewer's comments:

- *The use of a direct effect concentration-QTc model is not appropriate for large therapeutic proteins because these proteins do not directly inhibit hERG channel.*
- *The reviewers did not conduct an independent analysis of the data because a dedicated QTc assessment is not necessary for large targeted proteins and not supported by the safety ECGs.*

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/s/

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06/20/2019 12:15:34 PM

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