CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761136Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication/First Biosimilar/Expedited or Breakthrough Review: Yes

Recommendation: BLA Approval

BLA Number: 761136
Review Number: 1
Review Date: 09/24/2019

Drug Name/Dosage Form	REBLOZYL- Luspatercept, ACE-536/lyophilized powder for injection
Strength/Potency	25 or 75 mg of lyophilized powder in a 2 mL vial to be reconstituted to 50 mg/mL with sterile water for injection
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Beta-thalassemia-associated anemia; Low to intermediate risk myelodysplastic syndromes (MDS)-associated anemia
Applicant/Sponsor	Celgene
US agent, if applicable	n/a

Product Overview

REBLOZYL (luspatercept) is a recombinant fusion protein. REBLOZYL is supplied as a sterile, white lyophilized powder for subcutaneous injection, following reconstitution with sterile Water for Injection.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Sarah Johnson	OPQ/OBP/DBRR II
Drug Product	Sarah Johnson	OPQ/OBP/DBRR II
Immunogenicity	Sarah Johnson	OPQ/OBP/DBRR II
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Facility	Viviana Matta	OPQ/OPF/DIA
Microbiology	Madushini Dharmasena (DS) Aimee Cunningham (DP)	OPQ/OPF/DMA
Facility Team Lead	Peter Qiu	OPQ/OPF/DIA
Microbiology Team Lead	Reyes Candau-Chacon	OPQ/OPF/DMA
Regulatory Business Project Manager	Kelly Ballard	OPQ/OPRO/DRBPMI/RBPMBI
Application Team Lead	Yanming An	OPQ/OBP/DBRR II
OBP Tertiary Reviewer	Xianghong Jing	OPQ/OBP/DBRR II

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Rosa Lee-Alonzo	OHOP/DHP
Cross-disciplinary Team Lead	Tanya Wroblewski (Beta-thalassemia) Danna Przepiorka (MDS)	OHOP/DHP
Medical Officer	Laurel Menapace (Beta-thalassemia) Dianne Pulte (MDS)	OHOP/DHP
Pharm/Tox	Michael Manning/Chris Sheth	OHOP/DHOT

Clinical Pharmacology	Lili Pan/George Shen	OCP/DCPV
Statistics	Weishi (Vivian) Yuan / Lei Nie (Beta-thalassemia), Yute We (MDS)	OB/DB V

1. Names:
   a. Proprietary Name: REBLOZYL
   b. Trade Name: REBLOZYL
   c. Non-Proprietary/USAN: Luspatercept
   d. INN Name: Luspatercept
   e. CAS Registry Number: 1373715-00-4
   f. OBP systematic name: FUS:MABFRAG HUMAN (IGG1 FC); RPRPTFRAG Q13705 (AVR2B_HUMAN) [ACE536]
   g. Other name(s): ACE-536

Submissions Reviewed:

Submission(s) Reviewed	Document Date
761136/0001	04/04/2019
761136/0004 (response to DIA IR on 04/30/2019)	05/10/2019
761136/0005 (response to DIA IR on 05/06/2019)	05/15/2019
761136/0012 (response to DMA IR on 05/28/2019)	06/07/2019
761136/0016 (response to OBP IR on 06/07/2019)	06/24/2019
761136/0017 (response to DMA IR on 06/17/2019)	07/01/2019
761136/0022 (stability update)	08/01/2019
761136/0023 (response to OBP IR on 07/24/2019)	08/07/2019
761136/0024 (response to DMA IR on 08/01/2019)	08/08/2019
761136/0027 (response to OBP IR on 08/06/2019)	08/20/2019
761136/0029 (response to OBP IR on 08/21/2019) Telecon with Sponsor on 08/23/2019	08/27/2019
761136/0030 (response to DMA IR 08/26/2019)	08/29/2019

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed
(b) (4)	3		(b) (4)	2	Adequate	N/A
	3			2	Adequate	N/A
	3			2	Adequate	N/A

(b) (4)	5	(b) (4)	2	Adequate	N/A
	3		2	Adequate	N/A
	3		2	Adequate	N/A

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	112562	Celgene-sponsored IND under which luspatercept was developed and meetings were held

3. Consults: None.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761136 for luspatercept manufactured by Celgene Corporation. The data submitted in this application are adequate to support the conclusion that the manufacture of luspatercept is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  (b) (4)

- Fill size and dosage form:
  25 mg lyophilized powder in a single-use 2.0 mL vial to be reconstituted with 0.68 mL sterile water for injection;

  75 mg lyophilized powder in a single-use 2.0 mL vial to be reconstituted with 1.6 mL sterile water for injection

- Dating period:
  - Drug Product: 18 months: 2 to 8 °C
  - Drug Substance (b) (4) months: (b) (4) °C
  - For packaged products: "Not packaged"
  - Stability Option:
    We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
  - Yes
  - Rationale, if exempted: Per FR notice 95-29960 well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products are exempt from 21 CFR 601.2a lot release requirement.

- Celgene claimed a categorical exclusion from the requirements of environmental assessment for luspatercept in accordance with 21 CFR 25.31 (c). The claim is because the estimated concentration of the substance at the point of entry into the aquatic environment will nonetheless be below 1 ppb. To the best of the sponsor's knowledge, no extraordinary circumstances exist that may significantly affect the quality of the human environment.

  The claim of a categorical exclusion is accepted.

C. Benefit/Risk Considerations:

Luspatercept is a recombinant fusion protein consisting of the modified form of the extracellular domain (ECD) of human activin receptor type IIB (ActRIIB). Luspatercept is designed to bind specifically to the growth differentiation factor 11 (GDF-11) and activin B ligands of the TGF-β superfamily. By binding to GDF-11 and activin B, luspatercept inhibits the Smad 2/3 transcriptional regulator signaling cascade and allows for erythroid maturation to occur through differentiation of late-stage erythroid precursors (normoblasts) in the bone marrow. Celgene seeks licensure for the following 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; and
- Adult patients with beta-thalassemia-associated anemia who require red blood cell (RBC) transfusions.

The overall control strategy includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The conditions used in manufacturing have been sufficiently validated, and the data submitted in this application support the conclusion that the manufacture of luspatercept is well controlled and yields a consistently high-quality product.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective.

The DIA assessor is recommending approval of the commercial manufacture of luspatercept (b) (4)

The OBP assessments including DS quality, DP quality, and validation of immunogenicity assays, DMA DS and DP microbiological assessments, and DIA facility technical assessment are located as separate documents in Panorama.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

Implement a test monitoring the (b) (4) oxidation and (b) (4) isomerization into luspatercept drug substance release and stability specification and drug product release specification. Submit the proposed release specification and supporting validation results following 21 CFR 601.12(b).

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRRII and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPF/DMA.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Binding and sequestering GDF-11 and activin B and preventing it from binding to the ActRIIB. (Potency)	Efficacy	Intrinsic to molecule	(b) (4)	
Primary Sequence and corresponding variants	Efficacy and immunogenicity	Intrinsic to molecule		
High-molecular weight species (HMWS) (product-related impurity)	Efficacy, pharmacokinetics, and immunogenicity	Manufacturing process and storage conditions. Can form due to agitation, temperature, or light exposure.		
Low-molecular weight species (LMWS) (product-related impurities)	Efficacy, pharmacokinetics, and immunogenicity	Manufacturing process and storage conditions. LMWS may be caused by agitation, temperature, or light		
(b) (4) (product related impurity)	Pharmacokinetics and half-life	DS manufacturing process and storage conditions		
(b) (4) (product related impurity)	Efficacy	DS manufacturing process and storage conditions		
(b) (4) (product related impurity)	Efficacy	DS manufacturing process		
(b) (4)	Pharmacokinetics, and immunogenicity	DS manufacturing process		

CQA (type)	Risk	Origin	Control Strategy	Other
Higher order structure	Efficacy immunogenicity	Intrinsic to molecule	(b) (4)	

B. Drug Substance [luspatercept] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below summarizes the critical quality attributes and their control strategy that are relevant specifically to the Drug Substance. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRRII and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPF/DMA.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance, color and clarity	Safety	Manufacturing process	(b) (4)	
Protein Concentration	Efficacy, pharmacokinetics, safety	Manufacturing process		
pH	Efficacy, safety	Formulation and stability		
Host Cell Proteins (process-related impurity)	Safety and immunogenicity	Derived from host cell line		
Host Cell DNA (process-related impurity)	Safety	Derived from host cell line		
(b) (4) (process-related impurity)	Safety and immunogenicity	Process-related impurity (b) (4)		
(b) (4)	Safety	(b) (4		
(b) (4) (process-related impurity)	Safety			

CQA (type)	Risk	Origin	Control Strategy	Other
(b) (4) (process-related impurity)	Safety	(b) (4)	(b) (4)	
(b) (4) (process-related impurity)	Safety			
(b) (4) (process-related impurity)	Safety			
(b) (4) (process-related impurity)	Safety			
(b) (4) (process-related impurity)	Safety			
(b) (4) impurity)	Safety			
Virus (enveloped and non-enveloped (contaminant)	Safety			
Endotoxin	Safety, Purity			
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination			

- Description: Luspatercept is a recombinant fusion protein consisting of (b) (4) the extracellular domain (ECD) of human activin receptor type IIB (ActRIIB) linked to the human IgG1 Fc domain, including the hinge, CH_2, and CH_3 domains, through a linker (b) (4)

(b) (4) The final amino acid sequence of luspatercept comprises 107 amino acids of the ActRIIB ECD, 225 amino acids of the human IgG1 Fc region and 3 amino acids linker. Luspatercept contains a total of 16 cysteine residues per chain. The ActRIIB ECD region forms five intra-chain disulfide bonds, and the IgG1 Fc region forms two intra-chain and two inter-chain disulfide bonds. The average calculated molecular mass of luspatercept is 75701.1 Da (non-glycosylated) and approximately 94 kDa with the most abundant glycoforms.

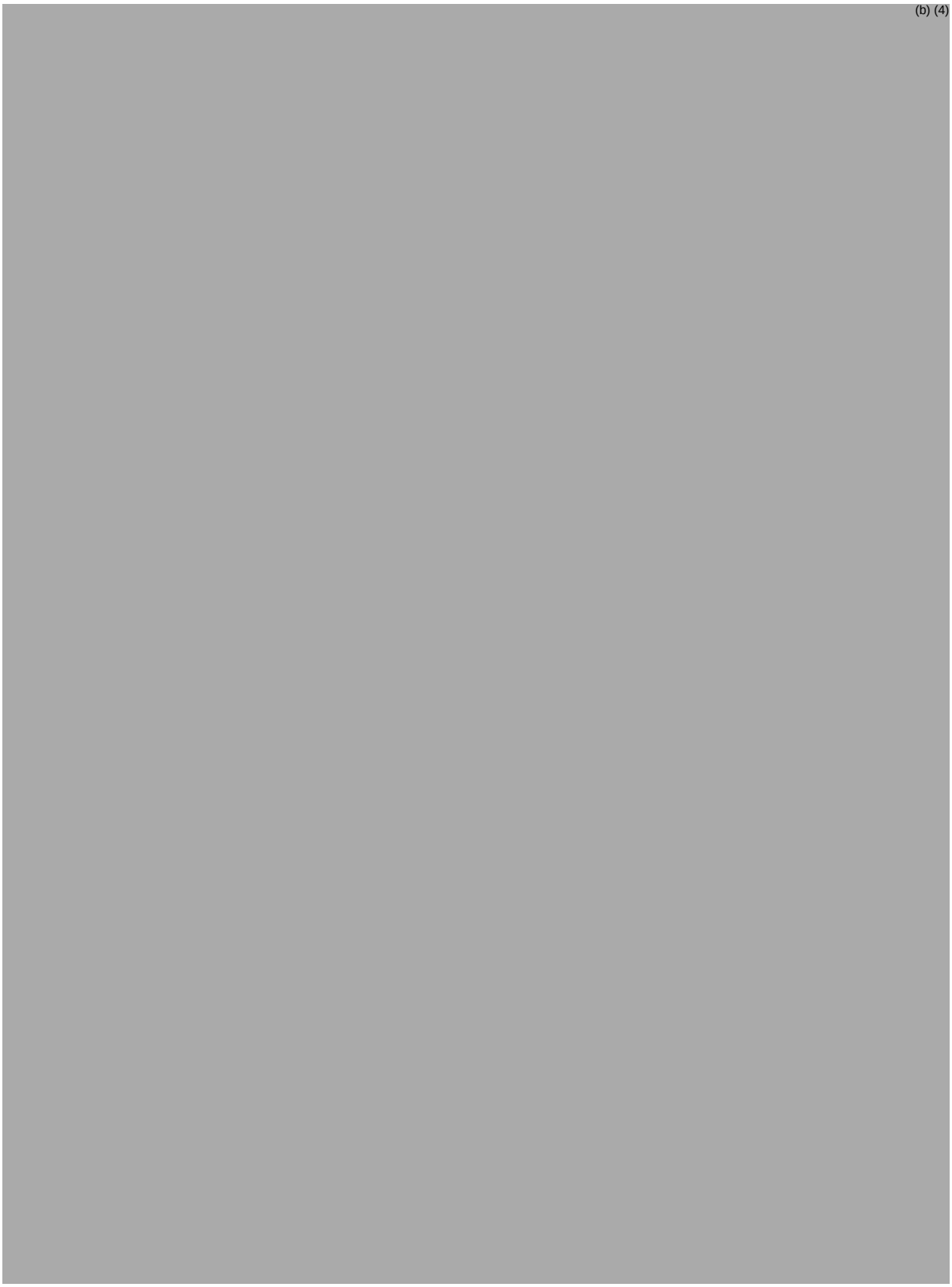
- Mechanism of Action (MoA): Luspatercept binds specifically to growth differentiation factor 11 (GDF-11) and activin B, blocks them from binding to the ActRIIB on cell surface. The ActRIIB receptor and its ligands are members of the transforming growth factor-β (TGF-β) superfamily that induce signaling pathways regulating cellular development and differentiation, including erythropoiesis. Binding of GDF-11 and activin B to ActRIIB on cell surface induces the phosphorylation of the transcriptional regulators Smad2 and Smad3, resulting in the inhibition of late-stage erythropoiesis. Smad2/3 signaling is abnormally high in disease models characterized by ineffective erythropoiesis, i.e. myelodysplastic syndromes (MDS) and β-thalassemia, and in the bone marrow of MDS patients. By binding to GDF-11 or activin B luspatercept inhibits Smad2/3 signaling, resulting in erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts) in the bone marrow.

- Potency Assay: A cell-based reporter gene assay measures inhibition of Smad2/3 signaling stimulated by GDF-11 binding in a cell line (A204-CAGA12-Luc) that expresses Activin Type IIB (ActIIB) and Activin Type I receptors. The cell line contains the firefly luciferase reporter gene under the control of a Smad2/3 responsive promoter, CAGA12. The assay measures firefly luciferase luminescent signal stimulated by a constant amount of the recombinant human growth and differentiation factor II (rhGDF-11). Luspatercept causes a dose-dependent loss in luminescent signal by binding and sequester rhGDF-11. This activity is reported as a percentage of the activity of the reference standard.

- Reference Materials: (b) (4)

(b) (4)

(b) (4)



C. Drug Product [REBLOZYL] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance (lyophilized (b) (4)	Safety	Manufacturing process	(b) (4)	White to off-white powder, free of visible foreign matter
Appearance (reconstituted product)	Safety	Manufacturing process		Clear to slightly opalescent solution, essentially free of particulate matter
Protein content	Efficacy	Manufacturing process		
Polysorbate-80	Safety, stability	Manufacturing process		
Uniformity of Dosage	Control of dosing	Manufacturing process		
Sub-visible particles (general)	Safety	Manufacturing process, product degradation		
pH (general)	Safety, efficacy	Formulation		
Reconstitution time (general)	Safety, efficacy	Manufacturing process, storage conditions		
Moisture content (general)	Stability	Manufacturing process, loss of container closure integrity		
Osmolality	Safety, stability	Formulation		
Endotoxin (contaminant)	Safety, purity and immunogenicity	Raw materials; microbial contamination during the manufacturing process		
Sterility (contaminant)	Safety, purity, efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced during DP manufacture or through a container closure integrity failure		
Container closure integrity	Safety (maintenance of sterility during shelf-life)	Container closure breaches during storage. May be impacted by storage conditions.		

- Potency and Strength: Potency of luspatercept is considered, for the purposes of this review, as the percent inhibition of luciferase activity relative to the current reference standard. The potency assay is the same as those described in the Drug Substance section of this review.

  Luspatercept is available in two presentations, 25 mg/vial and 75 mg/vial. The 25 mg/vial DP is to be reconstituted in 0.68 mL sterile water for injection (WFI), yielding a 50 mg/mL solution. The reconstituted volume accommodates delivery of up to 0.5 mL of 50 mg/mL luspatercept. The 75 mg/vial DP is to be reconstituted in 1.6 mL sterile WFI, yielding a 50 mg/mL solution. The reconstituted volume accommodates delivery of up to 1.5 mL of 50 mg/mL luspatercept. There is a (b) (4) overfill to assure that adequate reconstituted solution can be withdrawn per the product labeling.

- Summary of Product Design: Luspatercept for injection will be supplied as a single-use sterile, preservative-free lyophilized powder for subcutaneous administration. The lyophilized powder is to be reconstituted in water for injection (WFI).

- List of Excipients: Excipients include (b) (4) citric acid monohydrate, tri-sodium citrate dihydrate, sucrose, polysorbate 80, (b) (4) Except for the protein itself, all ingredients meet compendial requirements (USP/NF, Ph. Eur. and/or JP) and are commonly used for formulation of biopharmaceuticals. No excipients are of human or animal origin.

- Reference Materials: (b) (4)

- Manufacturing process summary: (b) (4)
  (b) (4)

- Container closure: The primary packaging material for luspatercept Drug Product consists of a (b) (4) glass vial with (b) (4)

[redacted] (b) (4)
aluminum flip-off seal [redacted] (b) (4)

- Dating period and storage conditions: The sponsor conducted real-time, accelerated, and thermal-stressed stability studies on 3 PPQ lots and 3 clinical Drug Product lots for each presentation. These data support a dating period of 18 months when stored at 2 to 8°C.

- List of co-package components: None.

D. Biopharmaceutics Considerations: None

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations: None

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacture, release, and stability testing: • Appearance, color, clarity, pH • CE-SDS (reduced and non-reduced) • Size exclusion chromatography • Protein concentration • Bioburden, endotoxin • Peptide mapping Working cell bank manufacture and storage.	[redacted] (b) (4)		VAI	1. The procedures in place are inadequate to prevent the use of defective material for the manufacture of luspatercept drug substance. 2. Corrective actions did not include implementation of adequate procedures to prevent similar deviations from recurring.	Approve
Master cell bank and working cell bank storage			-----	Waived	Approve
Master and working cell bank testing and storage In-process cell culture testing: [redacted] (b) (4)			-----	Waived	Approve

(b) (4)					
Master cell bank, End of production cell banks, and Unprocessed (b) (4) (harvest) testing: Transmission electron microscopy Working cell bank 2 testing: DNA fingerprinting assay	(b) (4)		-----	Waived	Approve
Drug substance and drug product release and stability testing: cell-based potency assay (reporter gene bioassay)			-----	Waived	Approve
Drug substance and drug product release and stability testing: cell-based potency assay (reporter gene bioassay)			----	Waived	Approve
Drug substance and drug product release testing: Imaged capillary isoelectric focusing (icIEF)			----	Waived	Approve
Drug substance and drug product release testing: icIEF			----	Waived	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug product manufacturing Primary packaging Visual inspection Drug product release and stability testing: • Compendial methods • Protein content	(b) (4)		-----	Waived	Approve

• SE-HPLC • Peptide map • Reconstitution time					
Visual inspection Drug product release and stability testing: • Compendial methods • Protein content • Reduced CE-SDS • Non-reduced CE-SDS • Reconstitution time	(b) (4)		-----	Waived	Approve
Visual inspection Drug product release and stability testing: • Compendial methods • Protein content • Reconstitution time			----	Waived	Approve
Visual inspection Drug product stability testing: CCI			----	Waived	Approve
Drug product release testing: Polysorbate-80			----	Waived	Approve
Labeling Secondary packaging			----	Waived	Approve

H. **Facilities:** A pre-license inspection for luspatercept drug substance manufacture was conducted (b) (4) FDA Form 483 was issued and the initial

recommendation is approval for the BLA. The final classification of the (b) (4) pre-license inspection was acceptable.

The pre-license inspection of the drug product site (b) (4) was waived because of the site's compliance status and its recent surveillance inspection (b) (4)

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved: Stability protocol for the extension of shelf life, annual stability protocol, Production of a replacement WCB, annual stability protocol for primary and working reference standards.
ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved: stability protocol for the extension of shelf life, annual stability protocol, end of shelf-life (EOSL) leachables assessment.
ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		x		
2.	Naturally Derived Product			x	
3.	Botanical			x	
4.	Human Cell Substrate/source material			x	
5.	Non-Human Primate Cell Substrate/Source Material			x	
6.	Non-Primate Mammalian Cell Substrate/source material		x		
7.	Non-Mammalian Cell Substrate/Source Material			x	
8.	Transgenic Animal source			x	
9.	Transgenic Plant source			x	
10.	New Molecular Entity			x	
11.	PEPFAR drug			x	
12.	PET drug			x	
13.	Sterile Drug Product		x		
14.	Other: [fill in information]				
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			x	
16.	Comparability Protocol(s)			x	
17.	End of Phase II/Pre-NDA Agreements tem			x	
18.	SPOTS (special products on-line tracking system)			x	
19.	USAN assigned name		x		
20.	Other [fill in]				
	Quality Considerations				
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process		x	
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements			x	
27.	Real Time release testing (RTRT)			x	
28.	Parametric release in lieu of Sterility testing			x	
29.	Alternative Microbiological test methods			x	
30.	Process Analytical Technology in Commercial Production			x	
31.	Non-compendial analytical procedures	Drug Product	x		
32.		Excipients		x	
33.		Drug Substance	x		
34.	Excipients	Human or Animal Origin		x	
35.		Novel		x	
36.	Nanomaterials			x	
37.	Genotoxic Impurities or Structural Alerts			x	
38.	Continuous Manufacturing			x	
39.	Use of Models for Release			x	
40.	Other {fill-in}				

Yanming An

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Xianghong Jing

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Date: 9/26/2019 09:13:23AM
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BLA STN 761136

REBLOZYL™ (luspatercept)

Celgene Corporation

Sarah A. Johnson, Ph.D., Primary Assessor
Yanming An, Ph.D., Application Technical Lead

Division of Biotechnology Review & Research II (DBRR II)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Review Data Sheet

1. BLA#: STN 761136, Original-1 (Priority) Beta thalassemia (b) (4)

2. Review Date: 4 September 2019

3. Primary Review Team:

    a. **Medical Officer:** Laurel Menapace/ Tanya Wroblewski (Original-1)
    Dianne Pulte/ Donna Przepiorka (b) (4)
    b. **Pharm/Tox:** Michael Manning / Chris Sheth
    c. **Product Quality Team:**
    OPQ/OBP: Sarah Johnson/ Yanming An (ATL)
    OPQ/OPF/DMA: Madushini Dharmasena (DS), Amy Cunningham (DP)/Maria Candauchacon
    OPQ/OPF/DIA: Viviana Matta/Peter Qiu
    OPQ/OBP (labeling): Vicky Borders-Hemphill
    d. **Clinical Pharmacology:** Lili Pan/ George Shen
    e. **Statistics:** Weishi (Vivian) Yuan / Lei Nie (Original-1), Yute Wu (b) (4)
    f. **RPM:** Rosa Lee-Alonzo (OND/ODEI/DHP)
    g. **RBPM**: Kelly Ballard (OPQ)

4. Major GRMP Deadlines:
    a. Filing meeting: 17 May 2019
    b. Application orientation meeting: 17 May 2019
    c. Mid-cycle internal meeting:
    Original 1 9 July 2019
    (b) (4)
    d. Mid-cycle communication:
    Original 1 19 July 2019
    (b) (4)
    e. Late-cycle internal meeting:
    Original-1 11 September 2019
    (b) (4)
    f. Late-cycle sponsor meeting:
    Original 1 2 October 2019
    (b) (4)
    g. Primary review (CMC) due:
    Original 1 (b) (4) 4 September 2019
    h. Secondary review (CMC) due:
    Original 1 (b) (4) 25 September 2019
    i. Wrap-up meeting:
    Original 1 15 October 2019
    (b) (4)
    j. PDUFA goal date:
    Original 1 4 December 2019
    (b) (4)

5. Communications and submissions:

Communication/Document	Date	Submission	Review status
Original submission	4/4/2019	STN 761136/SN 0001, 4/4/2019	Complete
Filing review memo	5/21/2019	N/A	Complete
Stability Update	8/1/2019	STN 761136/SN0022, 8/1/2019	Complete
Information Request #1	6/7/2019	STN 761136/SN0016, 6/24/2019	Complete
Information Request #2	7/24/2019	STN 761136/ SN0023, 8/7/2019	Complete
Information Request #3	8/6/2019	STN 761136/SN0027, 8/20/2019	Complete
Information Request #4	8/21/2019	Telecon with Sponsor, 8/23/2019 STN 761136/SN0029, 8/27/2019	Complete

6. Drug Product Name/Code/Type:
   a. Proprietary Name: REBLOZYL™
   b. Trade Name: REBLOZYL™
   c. Non-Proprietary Name/USAN: Luspatercept
   d. CAS Registry Number: 1373715-00-4
   e. Common Name: Homodimeric fusion IgG1 Fc region to extracellular domain (ECD) of activin receptor type IIB (ActRIIB), anti-TGFβ superfamily ligands (GDF-11, activin B)
   f. INN Name: Luspatercept
   g. OBP systematic name: FUS: MABFRAG HUMAN (IGG1 FC); RPROTFRAG Q13705 (AVR2B_HUMAN) [ACE536]
   h. Other name(s): ACE-536

7. Pharmacological Category: Erythroid maturation agent

8. Dosage Form: 25mg or 75 mg powder for solution for injection

9. Strength/Potency:
   (i): The concentration/strength of the Drug Product: 50mg/mL after reconstitution
   (ii): Type of potency assay(s): Potency is defined as percent activity relative to reference standard, using the A204-CAGA12-Luciferase cell line which expresses both Activin Type IIB (ActIIB) and Activin Type I receptors, and the firefly luciferase reporter gene under the control of a Smad2/3 responsive promoter, CAGA12. Cell response to recombinant human growth and differentiation factor II (rhGDF11) can be measured by the decrease in luciferase signal that occurs when cells are exposed to rhGDF-11 due to luspatercept.

10. Route of Administration: Subcutaneous injection

11. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
[redacted]	[redacted]	(b) (4)	Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA.
			Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA
			Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA

(b) (4)	Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA
	Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA
	Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA

12. Inspectional Activities: The pre-license inspection on the drug substance manufacturing site (b) (4) was conducted on (b) (4) by Madushini Dharmasena (OPF/DMA), Viviana Matta (OPF/DIA/IABI), Sarah Johnson (OPQ/OBP) and Yanming An (OPQ/OBP). The inspection covered the manufacture of drug substance from (b) (4), manufacture and storage of working cell bank (WCB), and specific release and stability testing methods for drug substance performed by (b) (4). The inspection was risk-based and covered Quality, Production, Laboratory Control, Materials, and Facilities and Equipment Systems. Form FDA 483 was issued with two observations (b) (4) Form 483 was issued to (b) (4) on (b) (4) with no refusals. It was recommended that the inspection be classified as voluntary action indicated.

The pre-license inspection on the drug product manufacturing site (b) (4) was waived.

13. Consults Requested by OBP: None

14. Quality by Design Elements: The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
	Design of Experiments
x	Formal Risk Assessment/Risk Management
x	Multivariate Statistical Process Control
x	Process Analytical Technology
	Expanded Change Protocol

15. Precedents: None.

16. Administrative:
Signature Block

Name and Title	Signature and Date
Yanming An, Ph.D. Application Technical Lead, DBRRII/OBP/OPQ/CDER	See electronic signature and date
Sarah A. Johnson, Ph.D. Primary assessor, DBRRII/OBP/OPQ/CDER	See electronic signature and date

Summary of Quality Assessments

1. Primary Assessor Summary Recommendation: The data submitted in this Biologics License Application (STN 761136) support the conclusion that the manufacture of REBLOZYL™ (luspatercept)

is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents and meets the standards recommended by FDA. The conditions used in the manufacturing process had been adequately validated, and the product had been consistently manufactured from multiple production runs. It is recommended that REBLOZYL™ (luspatercept) be approved for human use under conditions specified in the package insert.

2. List of Deficiencies to be Communicated: None.

3. List of Post-Marketing Commitments/Requirements:
"Celgene commits to implement a new peptide map method for monitoring the (b) (4) oxidation and (b) (4) isomerization post-translational modifications. The new method will be implemented for luspatercept drug substance release and stability testing and for drug product release. Updated method and supporting data will be submitted as a prior approval supplement (PAS) by December 2020."

Product quality-related protocols to be approved within BLA 761136 are listed in the table below:

eCTD Section	Protocol	Brief Summary	Proposed reporting category in the BLA submission
(b) (4)			

Product quality-related commitments to be approved within BLA 761136 are listed in the table below:

eCTD Section	Commitment	Proposed Implementation	Proposed Reporting
(b) (4)			

4. Review of Common Technical Document - Quality Module 1:

A. Environmental Assessment of Claim of Categorical Exclusion

Celgene Corporation claims a categorical exclusion from the requirements of environmental assessment (BLA section 1.12.14) based on 21 CFR §25.15(d) under the provisions of 21 CFR 25.31(b and c). Thus, no environmental assessment needs to be performed. Categorical Exclusion is appropriate for this product and should be granted.

5. Primary Container Labeling Review: The carton and container labels are reviewed by OBP. The OBP carton and container labeling review will be uploaded as a separate file in Panorama.

6. Review of Common Technical Document - Quality Module 3.2 and Module 2.3 Quality Overall Summary: The review of Modules 2.3 and 3.2 is included in this review memorandum.

7. Review of Immunogenicity Assays - Module 5.3.1.4: The current immunogenicity assay, a modified Meso Scale Discovery electrochemiluminescence assay (MSD-ECL), has neat sufficient sensitivity 41 ng/mL and can detect 500 ng/mL anti-drug antibody (ADA) when 5µg/mL or 1600ng/mL ADA when 100 µg/mL of luspatercept was on board, which exceeded the maximum C_{trough} luspatercept levels detected in patient serum (b) (4) 8.37µg/mL in β-thalassemia patients) in the steady state with starting doses of (b) (4) 0.8mg/kg (β-thalassemia) treatment. The two competitive binding-based enzyme-linked immunosorbent assays (ELISA) to detect for neutralizing antibodies (NAbs) to luspatercept, or the endogenous version of the Activin RIIB extracellular (ActRIIB ECD) were also validated for parameters such as sensitivity, drug tolerance, selectivity, robustness and stability. The immunogenicity assays were adequately validated. The review of these assays are conducted below in 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies.

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Sarah Johnson

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Yanming An

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Aimee L. Cunningham, Ph.D., M.P.H.
Quality Assessment Lead: Reyes Candau-Chacon, Ph.D.

BLA:	761136/0
Applicant:	Celgene
US License Number:	2114
Submission Reviewed:	Original BLA
Product:	Reblozyl (luspatercept)
Indication:	MDS (myelodysplstic syndrome)- or β-thalassemia associated anemia with ring sideroblasts requiring RBC transfusion
Dosage Form:	lyophilized powder for s.c. administration after reconstitution (25 or 75 mg)
Manufacturing Sites:	(b) (4)
FDA Receipt Date:	04/04/2019
Action Date:	12/04/2019

Conclusion and Approvability Recommendation

The drug product portion of this BLA was reviewed from a sterility assurance and product quality microbiology standpoint and is recommended for approval.

Review Summary

Celgene has submitted BLA 761136 to license luspatercept and its associated drug substance and drug product manufacturing processes. BLA 761136 was submitted via eCTD on April 5, 2019. This review contains the assessment of the manufacturing process of luspatercept drug product from a microbiological quality perspective. For review of drug substance aspects of this application, please see the review by Dr. Madushini Dharmasena.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	04/05/2019	Original BLA

Sequence number	Date	Description
0017	07/01/2019	IR responses
0024	08/08/2019	IR responses
0027	08/20/2019	IR responses
0030	08/29/2019	IR responses

Letters of authorization (LOAs) to the following drug master files (DMFs) related to product quality microbiology were provided in Module 1. The review status of each DMF is documented below.

DMF #	Content	Date Reviewed	Finding	Document Name
(b) (4)		05/08/2018	Adequate	(b) (4)

Module 1

1.14 Labeling

Recommended dosing for luspatercept is 1 mg/kg every 3 weeks by s.c. injection; dosing can be increased to maximum dose (b) (4) 1.25 mg/kg for β-thalassemia. Reconstitution should be performed by a healthcare professional and uses sterile WFI. Reconstituted solution can be stored in the original vial either at room temperature for up to 8 hrs or for up to 24 hrs at 2-8°C; it cannot be frozen. Multiple injections require a new syringe and needle be used. Vials are single (b) (4)

Reviewer's Comment: *A microbial challenge hold time study supporting the reconstituted DP hold conditions is provided in P.2.6.*

SATISFACTORY

Module 3.2

P.1 Description and Composition of the Drug Product

Luspatercept is a single (b) (4) sterile, preservative-free, lyophilized powder for s.c. administration. It is reconstituted with WFI. DP is provided in 2 presentations: 25 mg or 75 mg per vial (both for a final concentration of 50 mg/mL after reconstitution); the composition of each vial is outlined below.

Component	Function	25 mg Vial	75 mg Vial
Luspatercept	(b) (4)		
Citric acid monohydrate			
Tri-sodium citrate dihydrate			
Polysorbate 80			
Sucrose			
(b) (4)			
WFI			

SATISFACTORY

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
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Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761136/0**

From: Madushini Dharmasena, Ph.D., DMA Branch IV

Through: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead, DMA Branch IV

Subject: New BLA for the treatment of adult patients with very low to intermediate risk myelodysplastic syndrome (MDS)-associated anemia who have ring sideroblasts and require red blood cell transfusions and for the treatment of adult who have beta-thalassemia-associated anemia and require red blood cell transfusions

US License: 2114

Applicant: Celgene Corporation

Product: Luspatercept (REBLOZYL, ACE-536)

Dosage: 75mg/vial and 25mg/vial powder for subcutaneous injection after reconstitution

Facilities: (b) (4)

Receipt Date: 04/04/2019

Action Date: 10/04/2019

Recommendation for Approvability: The DS (DS) portion of STN 761136/0 was reviewed from a product quality microbiology perspective and is recommended for approval.

Review Summary

Celgene Corporation submitted a new Biologics License Application (BLA) for the liquid formulation of Luspatercept (ACE-536) at doses of 75mg/vial and 25mg/vial powder to be administered subcutaneously (SC) after reconstitution. Luspatercept is a recombinant Fc fusion protein consisting of the modified extracellular domain (ECD) of human activin receptor IIB (ActRIIB) linked to the human IgG1 Fc domain acts as an erythroid maturation agent. The luspatercept production (b) (4) is a CHO cell (b) (4)

DS Quality Microbiology Information Reviewed

Sequence number	Date	Description

eCTD 0001	04/04/2019	Original BLA
00012	06/07/2019	Response to information request sent on 5/28/2019
00016	6/24/2019	Response to request at the pre-licensing inspection

3.2.S DRUG SUBSTANCE (DS)

3.2.S.1 GENERAL INFORMATION

3.2.S.2 MANUFACTURE

3.2.S.2.1 Manufacturer

(b) (4) performs analytical and microbial testing, including bioburden and endotoxin. This is a multiproduct facility that manufactures clinical and commercial-grade biopharmaceutical products.

3.2.S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

The figure below provided in the submission provides an overview of the Luspatercept (b) (4) manufacturing process.

(b) (4)

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