

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761136Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 112562

MEETING MINUTES

Celgene Corporation
Attention: Christina Kish
Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Ms. Kish:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for luspatercept.

We also refer to the meeting between representatives of your firm and the FDA on October 4, 2018. The purpose of the meeting was to discuss the top line results for the clinical efficacy and safety data from the Phase 3 MEDALIST pivotal study (ACE-536-MDS-001) and two Phase 2 studies (A536-03/05); and the Phase 3 BELIEVE pivotal study (ACE-536- B-THAL-001) and two Phase 2 studies (A536-04/06) to support the BLA submission of luspatercept for the treatment of myelodysplastic syndromes (MDS) and beta-thalassemia.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Laura Wall, Regulatory Project Manager at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: October 4, 2018 from 2:00 PM to 3:00 PM (EST)
Meeting Location: White Oak Building 22, Conference Room: 1311

Application Number: IND 112562
Product Name: luspatercept
Indication: Proposed for the treatment of MDS and beta-thalassemia
Sponsor/Applicant Name: Celgene Corporation

Meeting Chair: Donna Przepiorka, MD, PhD, Clinical Team Leader
Meeting Recorder: Laura Wall, MS, APHN, Senior Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products

Ann Farrell, MD, Division Director
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Nicole Gormley, MD, Deputy Director (Acting)
R. Angelo de Claro, MD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Clinical Team Leader
Aviva Krauss, MD, Clinical Reviewer
Virginia Kwitkowski, MS, ACNP-BC, Clinical Team Leader
Laurel Menapace, MD, Clinical Reviewer
Diane Leaman, BS, Safety Regulatory Project Manager
Laura Wall, MS, APHN, Senior Regulatory Project Manager

Office of Biostatistics, Division of Biometrics V

Thomas Gwise, PhD, Deputy Division Director
Yuan-Li Shen, DrPH, Statistical Team Leader
Yaping Wang, PhD, Statistical Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology V

Liang Li, PhD, Clinical Pharmacology Reviewer

Product Quality - OBP

Yanming An, PhD, Product Quality Reviewer, Division of Biotechnology Review and Research II/OBP

SPONSOR ATTENDEES

Jay Backstrom, MD, MPH, Chief Medical Officer, Celgene Corporation
Abderrahmane Laadem, MD, Executive Director, Clinical Research & Development, Celgene Corporation
Paul McNulty, Vice President, Regulatory Affairs, Celgene Corporation
Steve Ritland, PhD, MBA, Executive Director, Project Leadership, Celgene Corporation
Mary Vandekauter, MS, RAC, Director, Regulatory Affairs, Celgene Corporation
Xianjuan Zhang, Associate Director, Biostatistics, Celgene Corporation
James Desiderio, PhD, Sr. Vice President, Regulatory Affairs, Acceleron Pharma
Peter Linde, MD, Vice President, Medical Research, Acceleron Pharma
Jennifer Dudinak, PharmD, Senior Vice President, Regulatory Affairs, Celgene Corporation

1.0 BACKGROUND

Luspatercept (ACE-536), a recombinant homodimeric fusion protein consisting of the extracellular domain (ECD) of activin receptor type IIB (ActRIIB) linked to the human IgG1 Fc domain, is being developed for the treatment of anemia. Orphan Drug Designation was granted on 3/11/2013 for treatment of beta-thalassemia, and on 3/18/2013 for treatment of myelodysplastic syndrome. Fast Track Designation was granted on 5/5/2015 for treatment of transfusion-dependent (TD) and nontransfusion-dependent (NTD) beta-thalassemia, (b) (4)

(b) (4). FDA provided advice on the clinical development program for MDS at a Type B meeting on 7/29/2015. FDA provided written advice on the content and format of the proposed BLA on 5/25/2018 and at a Type B meeting on 9/5/2018.

The purpose of this meeting was to discuss the top line results for the clinical efficacy and safety data from the (b) (4)

(b) (4) Phase 3 BELIEVE pivotal study (ACE-536- B-THAL-001) and two Phase 2 studies (A536-04/06) to support the BLA submission of luspatercept for the treatment of (b) (4) beta-thalassemia.

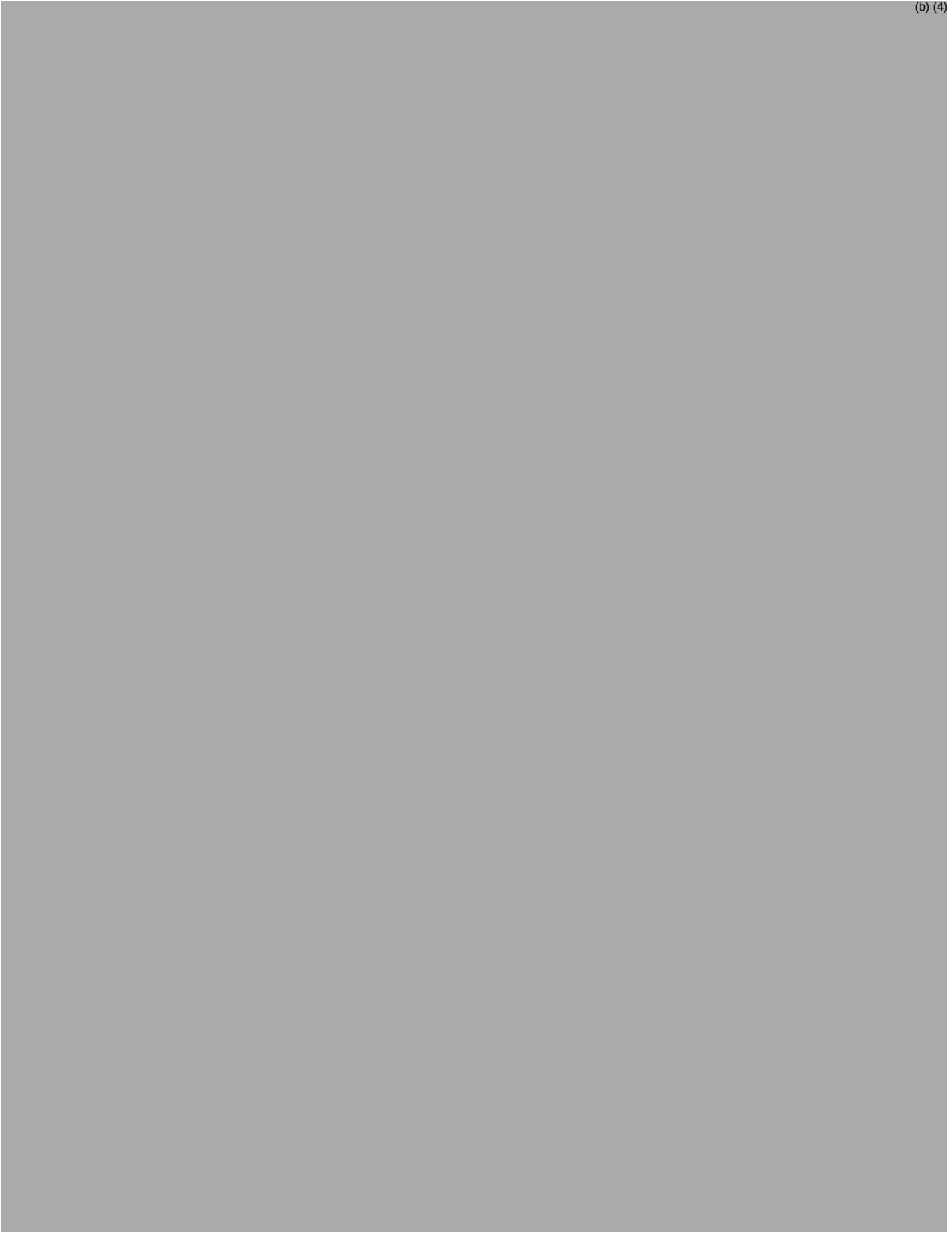
2.0 DISCUSSION

2.1. Clinical

(b) (4)

(b) (4)

(b) (4)



Meeting Discussion: None

Question 5: *Does the Agency agree that the efficacy results for the primary endpoint of Study ACE- 536-B-THAL-001 (≥ 33 percent reduction from baseline in red blood cell (RBC) transfusion burden with a reduction of at least 2 units during the protocol-defined period of 12 consecutive weeks, from week 13 to week 24; 21.4% luspatercept vs 4.5% placebo) in conjunction with the results for the four key secondary endpoints (including ≥ 50 percent reduction from baseline in red blood cell (RBC) transfusion burden during the period from week 13 to week 24 and ≥ 50 percent reduction from baseline in red blood cell (RBC) transfusion burden during the period from week 37 to week 48; (10.3% luspatercept vs 0.9% placebo)) supports the filing and review of the luspatercept BLA?*

FDA Response to Question 5: The efficacy results for the primary and secondary endpoints in Study ACE-536-B-THAL-001 appear adequate to consider submission of the proposed BLA. The filing review is completed after submission of the BLA.

Meeting Discussion: Please see discussion for question 1.

Question 6: *Understanding that this is a review issue, does the Agency agree that the efficacy results of the phase 3 ACE-536-B-THAL-001 study as presented in this meeting package demonstrate a meaningful clinical benefit of luspatercept in this patient population?*

FDA Response to Question 6: It is premature at this juncture to comment on whether the efficacy results confer meaningful clinical benefit in patients with beta thalassemia. Assessment of overall risk and benefit in this specific patient population will be a review issue.

Meeting Discussion: The Agency invited the Sponsor to submit a 12 and 24-week rolling analyses for the beta-thalassemia indication in the proposed BLA package. It was highlighted that labeling claims based on the submitted data will be an internal review issue. It was also brought to the Sponsor's attention that while rolling analyses were prespecified, they were not included in the key secondary endpoints and hence no alpha was allocated. The Sponsor also offered to provide additional approaches to analyses should FDA need those during the review.

Question 7: *Does the Agency have any comments or questions on the efficacy data as presented that could further inform the presentation in the proposed BLA?*

FDA Response to Question 7: No, the Agency does not have additional comments or questions at this time.

Meeting Discussion: None

Question 8: *Does the Agency agree that the proposed BLA safety data base of 287 patients with Beta- Thalassemia including 261 patents exposed for greater than or equal to 1 year is acceptable for filing and review?*

FDA Response to Question 8: The proposed safety database appears adequate to support submission of the BLA.

Meeting Discussion: None

Question 9: *Does the Agency agree that the data are adequate to support the filing and assessment of the safety profile of luspatercept observed from the pivotal Phase 3 study, Study ACE-536-B-THAL-001, and the two Phase 2 Studies (A536-04/06) for this patient population?*

FDA Response to Question 9: The outlined data appear adequate to support submission of the proposed BLA. Whether the results are sufficient to support filing and approval will be a review issue.

Meeting Discussion: None

Question 10: *Does the Agency agree that Study ACE-536-B-THAL-001, a Phase 3, double-blind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in adults who require regular red blood cell transfusions due to beta (β)-thalassemia (BELIEVE), along with data from the two Phase 2 Studies (A536-04 and 06) are adequate to support the filing and review of a BLA for the proposed indication?*

FDA Response to Question 10: The studies described appear adequate to support submission of the proposed BLA. Whether the results are sufficient to support filing and approval for the indication will be a review issue.

Meeting Discussion: None

2.2. General and/or Regulatory Questions

Question 11: *Based on the data presented, does the Agency support the Sponsor's intention to request a priority review for one or both indications?*

FDA Response to Question 11: You may submit a request for priority review and your justification for the request. Whether the application will be granted priority review will be determined at the time of filing.

Meeting Discussion: None

Question 12: *In our content and format meeting package for which Celgene received written feedback from the Agency on 25 May 2018, Celgene suggested that should both studies be positive a combined BLA for both MDS and beta-thalassemia would be submitted. Based on the data presented in the current meeting package, our plan is to proceed with two indications in one BLA. Does the Agency have any comments or concerns regarding the proposed format of this submission?*

FDA Response to Question 12: No.

Meeting Discussion: None

Question 13: *Modules for the luspatercept BLA will be completed beginning in December 2018, with the exception of Module 3 (and the corresponding Module 2 sections), Module 3 and the corresponding Module 2 sections will be available in Q1 2019. Both MDS and beta-thalassemia indications have been granted Fast Track Designation. Celgene proposes to submit a request for a rolling application later this year which will include a schedule for when each section of the BLA will be completed and submitted. Does the Agency have any comments on this proposal?*

FDA Response to Question 13: No.

Meeting Discussion: None

Question 14: *Based on the data presented, does the Agency foresee a potential need for an advisory committee for one or both indications?*

FDA Response to Question 14: Whether the application warrants an Advisory Committee meeting will be a review issue.

Meeting Discussion: None

Question 15: *Does the Agency have any other comments or advice that may aid in the preparation and submission of the BLA?*

FDA Response to Question 15:

- a.  (b) (4)
- b. Please include an analysis of overall survival for your pivotal and supporting studies as part of the BLA submission.
- c. Data sets (including the ISS data set) should have one unique subject identifier for each patient. If patients transition between studies, the unique subject identifier should not change.
- d. With regard to the revised BLA Table of Contents, as communicated to you in the responses to the Type C WRO meeting dated 5/25/2018, it is unclear why sections 5.3.1 and 5.3.2 will not contain any study reports.

- e. In addition to the clinical pharmacology comments provided in the Written Responses dated May 25, 2018, address the following questions in the Summary of Clinical Pharmacology:
- What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
 - What are the exposure-response relationships for efficacy, safety and biomarkers?
 - How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
 - What is the impact of immunogenicity on exposure, efficacy and safety?

Meeting Discussion: None

Post Meeting Notes

1. The Agency confirms that you may submit a single original BLA with both indications. (b) (4)
[REDACTED]
2. [REDACTED] (b) (4)
[REDACTED] you should provide support for why the observed response duration is clinically meaningful to patients with [REDACTED] (b) (4) beta-thalassemia. This support is critical for the Agency's risk benefit analyses.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

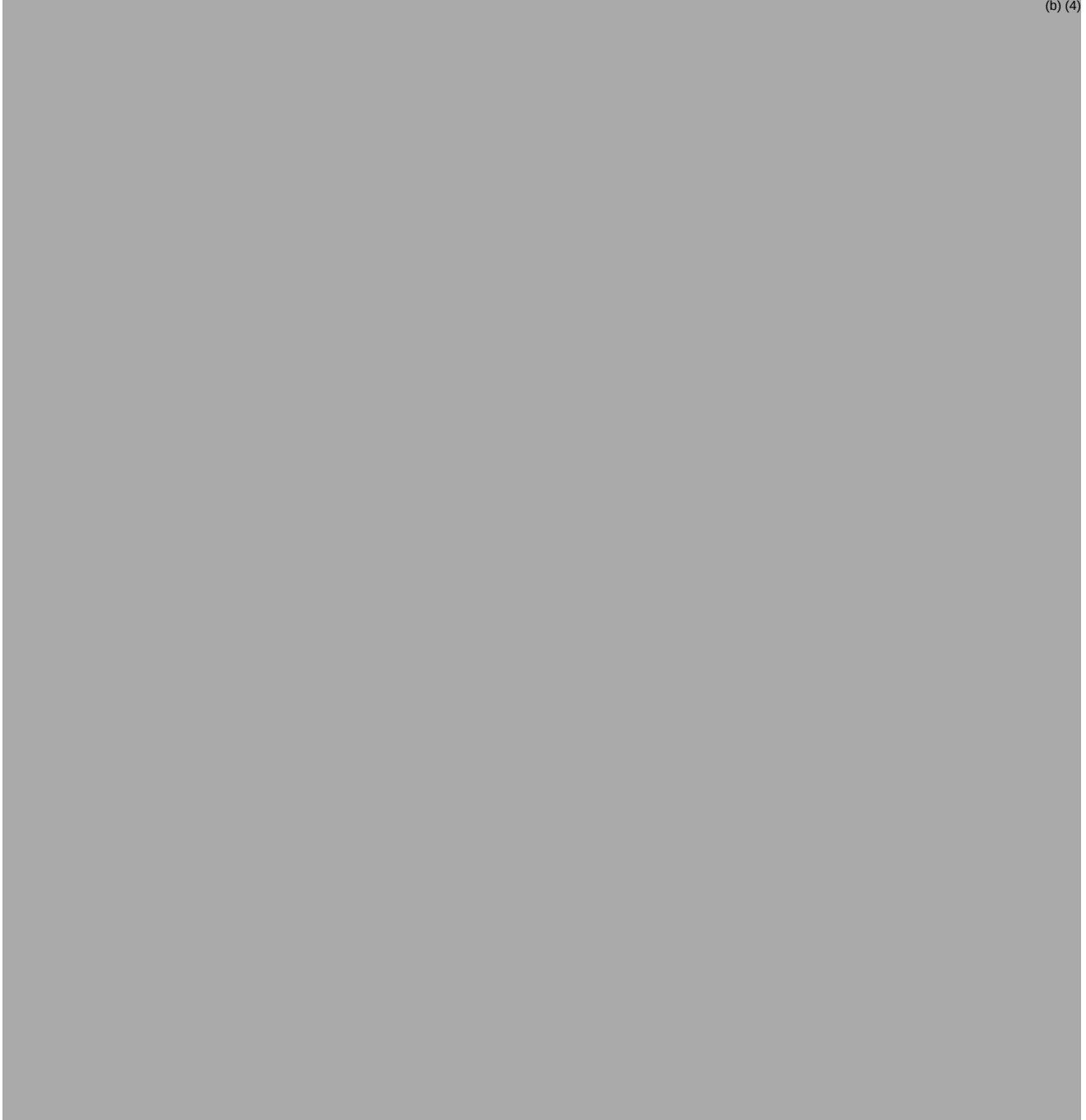
- The content of a complete application was discussed. The Sponsor agreed to submit a complete application at the time of initial submission of the BLA.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that the need for a REMS will be a review issue.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry presubmission meeting was held on September 5, 2018. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

(b) (4)



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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the

available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module

1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Celgene submitted the attached responses to the Agency's Meeting Preliminary Comments on October 1, 2018 via e-mail.

CELGENE RESPONSE TO FDA COMMENTS DATED 25 SEP 2018

Product Name: Luspatercept (ACE-536)
Application Number: IND 112562
Sponsor: Celgene Corporation (Celgene)

Provided below are Celgene's responses to the FDA comments and questions received on 25 Sep 2018 in reference to the questions included in the briefing package dated 31 Aug 2018 (SN0218). The briefing package submitted was in support of the pre-BLA Type B meeting scheduled for 04 Oct 2018 from 3:00 pm to 4:00 pm ET.

At the meeting on 04 Oct 2018, Celgene would like to focus on our additional responses and clarifications as provided below, and is seeking additional discussion on the following questions (in the specified order):

- Question 1 (15 minutes)
- Question 2 (5 minutes)
- Question 5 (15 minutes)
- Question 6 (15 minutes)

1. CLINICAL

(b) (4)



(b) (4)

(b) (4)

Beta-Thalassemia**Question 5:**

Does the Agency agree that the efficacy results for the primary endpoint of Study ACE- 536-B-THAL-001 (≥ 33 percent reduction from baseline in red blood cell (RBC) transfusion burden with a reduction of at least 2 units during the protocol-defined period of 12 consecutive weeks, from week 13 to week 24; 21.4% luspatercept vs 4.5% placebo) in conjunction with the results for the four key secondary endpoints (including ≥ 50 percent reduction from baseline in red blood cell (RBC) transfusion burden during the period from week 13 to week 24 and ≥ 50 percent reduction from baseline in red blood cell (RBC) transfusion burden during the period from week 37 to week 48; (10.3% luspatercept vs 0.9% placebo)) supports the filing and review of the luspatercept BLA?

FDA Response Dated 25 Sep 2018:

The efficacy results for the primary and secondary endpoints in Study ACE-536-B-THAL-001 appear adequate to consider submission of the proposed BLA. The filing review is completed after submission of the BLA.

Celgene Response:

Celgene thanks the Agency for its comments.

Celgene acknowledges that the results are subject to Agency review but would appreciate the opportunity to discuss any concerns regarding the filing of the BLA for this indication that the Agency may have.

<i>Would the Agency provide more information regarding any filing concerns for the Beta-Thalassemia indication?</i>

Question 6:

Understanding that this is a review issue, does the Agency agree that the efficacy results of the phase 3 ACE-536-B-THAL-001 study as presented in this meeting package demonstrate a meaningful clinical benefit of luspatercept in this patient population?

FDA Response Dated 25 Sep 2018:

It is premature at this juncture to comment on whether the efficacy results confer meaningful clinical benefit in patients with beta thalassemia. Assessment of overall risk and benefit in this specific patient population will be a review issue.

Celgene Response:

Celgene thanks the Agency for its comments.

In addition to the defined endpoints according to fixed periods per the protocol, analyses per the rolling 12-week and 24-week periods were performed and these analyses were prespecified in the SAP. Celgene believes these analyses have clinical value for the labeling, as the rolling analysis method is consistent with real world clinical practice and has been used to support approvals of other products.

<i>Does the Agency agree, or could the Agency provide further comment?</i>
--

Question 7:

Does the Agency have any comments or questions on the efficacy data as presented that could further inform the presentation in the proposed BLA?

FDA Response Dated 25 Sep 2018:

No, the Agency does not have additional comments or questions at this time.

Celgene Response:

Celgene thanks the Agency for its comments.

No further discussion is needed for this question.

Question 8:

Does the Agency agree that the proposed BLA safety data base of 287 patients with Beta-Thalassemia including 261 patents exposed for greater than or equal to 1 year is acceptable for filing and review?

FDA Response Dated 25 Sep 2018:

The proposed safety database appears adequate to support submission of the BLA.

Celgene Response:

Celgene thanks the Agency for its comments.

No further discussion is needed for this question.

Question 9:

Does the Agency agree that the data are adequate to support the filing and assessment of the safety profile of luspatercept observed from the pivotal Phase 3 study, Study ACE-536-B-THAL-001, and the two Phase 2 Studies (A536-04/06) for this patient population?

FDA Response Dated 25 Sep 2018:

The outlined data appear adequate to support submission of the proposed BLA. Whether the results are sufficient to support filing and approval will be a review issue.

Celgene Response:

Celgene thanks the Agency for its comments.

No further discussion is needed on this question.

Question 10:

Does the Agency agree that Study ACE-536-B-THAL-001, a Phase 3, doubleblind, randomized, placebo-controlled, multicenter study to determine the efficacy and safety of luspatercept (ACE-536) versus placebo in adults who require regular red blood cell transfusions due to beta (β)-thalassemia (BELIEVE), along with data from the two Phase 2 Studies (A536-04 and 06) are adequate to support the filing and review of a BLA for the proposed indication?

FDA Response Dated 25 Sep 2018:

The studies described appear adequate to support submission of the proposed BLA. Whether the results are sufficient to support filing and approval for the indication will be a review issue.

Celgene Response:

Celgene thanks the Agency for its comments and has asked an additional question in the response to the Agency's comment on question 5.

No further discussion of this question is needed on this question.

General and/or Regulatory Questions**Question 11:**

Based on the data presented, does the Agency support the Sponsor's intention to request a priority review for one or both indications?

FDA Response Dated 25 Sep 2018:

You may submit a request for priority review and your justification for the request. Whether the application will be granted priority review will be determined at the time of filing.

Celgene Response:

Celgene thanks the Agency for its comments.

No further discussion of this question is needed.

Question 12:

In our content and format meeting package for which Celgene received written feedback from the Agency on 25 May 2018, Celgene suggested that should both studies be positive a combined BLA for both MDS and beta-thalassemia would be submitted. Based on the data presented in the current meeting package, our plan is to proceed with two indications in one BLA. Does the Agency have any comments or concerns regarding the proposed format of this submission?

FDA Response Dated 25 Sep 2018:

No.

Celgene Response:

Celgene thanks the Agency for its comments.

No further discussion of this question is needed.

Question 13:

Modules for the luspatercept BLA will be completed beginning in December 2018, with the exception of Module 3 (and the corresponding Module 2 sections), Module 3 and the corresponding Module 2 sections will be available in Q1 2019. Both MDS and beta-thalassemia indications have been granted Fast Track Designation. Celgene proposes to submit a request for a rolling application later this year which will include a schedule for when each section of the BLA will be completed and submitted. Does the Agency have any comments on this proposal?

FDA Response Dated 25 Sep 2018:

No.

Celgene Response:

Celgene thanks the Agency for its comments.

No further discussion of this question is needed.

Question 14:

Based on the data presented, does the Agency foresee a potential need for an advisory committee for one or both indications?

FDA Response Dated 25 Sep 2018:

Whether the application warrants an Advisory Committee meeting will be a review issue.

Celgene Response:

Celgene thanks the Agency for its comments.

No further discussion of this question is needed.

Question 15:

Does the Agency have any other comments or advice that may aid in the preparation and submission of the BLA?

FDA Response Dated 25 Sep 2018:

a.

(b) (4)

(b) (4)

- b. Please include an analysis of overall survival for your pivotal and supporting studies as part of the BLA submission.
- c. Data sets (including the ISS data set) should have one unique subject identifier for each patient. If patients transition between studies, the unique subject identifier should not change.
- d. With regard to the revised BLA Table of Contents, as communicated to you in the responses to the Type C WRO meeting dated 5/25/2018, it is unclear why sections 5.3.1 and 5.3.2 will not contain any study reports.
- e. In addition to the clinical pharmacology comments provided in the Written Responses dated May 25, 2018, address the following questions in the Summary of Clinical Pharmacology:
- What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
 - What are the exposure-response relationships for efficacy, safety and biomarkers?
 - How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
 - What is the impact of immunogenicity on exposure, efficacy and safety?

Celgene Response:

Celgene thanks the Agency for its comments.

Regarding the Agency's comment "a" above, Celgene plans to provide the following

(b) (4)

(b) (4)

Regarding the Agency's comment "d", Celgene will be providing method validation reports for the PK and ADA assays and bioanalytical reports for ADA and PK sample assays in the clinical studies in Module 5.3.1.4.

Celgene will also address the remaining Agency comments in the BLA submission including the clinical pharmacology comments which will be addressed in the summary of clinical pharmacology and the QBA.

Additional Administrative Questions (as Written Responses Only):

Celgene understands that there is a reorganization planned for the Office of Hematology and Oncology Products. As a result, Celgene would also like to take this opportunity to ask the following administrative questions regarding our BLA submission, estimated for 1Q 2019.

- *Can the Agency advise if both indications (MDS and beta-thalassemia) will likely be under the same review division?*
- *Will the Agency require Celgene to submit one application or two applications (one per indication per division, if applicable)? If two applications are required Celgene would plan to submit a full submission for the first indication and propose that the submission for the second indication would cross reference to the first submission for the non-clinical modules (Modules 2.4, 2.6, and 4) and the CMC modules (Modules 2.3 and 3) as well as to Module 2.7.4 for the Summary of Clinical Safety and Module 5 for the ISS and ISI, would that be acceptable to the Agency?*
- *Should Celgene prepare for one Application Orientation meeting covering both indications, or separate Application Orientation meetings?*

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

/s/

DONNA PRZEPIORKA
10/15/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112562

MEETING MINUTES

Celgene Corporation &
Acceleron Pharma
Attention: Penny Ng, MSc, MBA RAC
Regulatory Affairs
Corporate Woods, Bldg 32, Suite 900
9225 Indian Creek Parkway,
Overland Park, KS 66210

Dear Ms. Ng:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for for Luspatercept (ACE-356).

We also refer to the meeting between representatives of your firm and the FDA on May 15, 2015. The purpose of the meeting was to meeting to discuss the clinical development program and registration strategy for luspatercept.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me CAPT Diane Hanner, Regulatory Project Manager at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, Ph D, Clinical Team Leader
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: End of Phase 2

Meeting Date and Time: May 15, 2015 @ 3:00 p.m.

Meeting Location: White Oak Campus, Building 22, Room 1313

Application Number: IND 112562

Product Name: Luspatercept (ACE-536)

Indications:

- Luspatercept for the treatment of adults who require regular red-blood cell transfusion due to β -thalassemia (including transfusion dependent hemoglobin E/ β -thalassemia)

(b) (4)

Sponsor/Applicant Name: Celgene Corporation in partnership with Acceleron Pharma

Meeting Chair: Albert Deisseroth, MD, Ph D

Meeting Recorder: CAPT Diane Hanner, MPH, MSW

FDA ATTENDEES

- o Ann T. Farrell, MD, Division Director , Division of Hematology Products (DHP)
- o Albert Deisseroth, MD, PhD, Medical Officer, Clinical Team Leader, DHP
- o Donna Przepiorka, MD, PhD, Medical Officer, DHP
- o Virginia Kwitkowski, MS, R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
- o Kathy Robie-Suh, MD, Clinical Team Leader, DHP
- o Kallappa Koti, PhD, Statistical Reviewer. DB 5
- o Lei Nie, PhD, Statistical Team Leader, DB 5
- o Michael Manning, PhD, Pharmacology/Toxicology Reviewer, DHOT
- o Linan Ha , PhD, Biologist. Division of Monoclonal Antibodies, OBP
- o Tura Camilli , PhD, Biologist. Division of Monoclonal Antibodies, OBP
- o Christopher Sheth, PhD, (acting) Pharmacology/Toxicology Supervisor, DHOT
- o Olanreqaju Okusanya, Pharm D, Clinical Pharmacology Reviewer, DCP5
- o Gene Williams, Pharm D, Clinical Pharmacology Team Leader, DCP5
- o CAPT Diane Hanner, MPH., MSW, Senior Program Management Officer, DHP

SPONSOR ATTENDEES

- o Kenneth Attie, MD, Vice President, Medical Research, Acceleron Pharma
- o Jay Backstrom, MD, MPH, Senior Vice President, Global Head Hematology/Oncology Clinical R&D, Regulatory Affairs
- o Nianhang Chen, Senior Principal Scientist, Clinical Pharmacology, Celgene Corporation
- o Nathaniel Collins, DVM, PhD, Senior Director, Toxicology, Celgene Corporation
- o James Desiderio, PhD, Vice President, Regulatory Affairs, Acceleron Pharma
- o Carolina Giuseppi, MD, Senior Director, Lead Product Safety Physician, Celgene Corporation
- o [REDACTED] (b) (4)
- o [REDACTED]
- o Dalia Mahmoud, Executive Director, Outcomes Research, Celgene Corporation
- o [REDACTED] (b) (4)
- o Penny Ng, M.Sc, MBA, RAC, Director, Regulatory Affairs, Celgene Corporation
- o Steve Ritland, PhD, MBA, Executive Director, Project Leadership, Celgene Corporation
- o Xiaosha Zhang, Vice President, Biostatistics, Acceleron Pharma
- o Jun Zou, M.Sc, Principal Statistician, Biostatistics, Celgene Corporation

1.0 BACKGROUND

The Sponsor requested a Type B- IND meeting to discuss questions concerning the study design and their interim results from on-going trial and to obtain feedback regarding the following:

Luspatercept is being developed for the following indications:

- Luspatercept for the treatment of adults who require regular red-blood cell transfusion due to β -thalassemia (including transfusion dependent hemoglobin E/ β -thalassemia)

(b) (4)

The meeting was granted on March 31, 2015, and was scheduled for May 15, 2015.

FDA sent Preliminary Comments to the Sponsor on May 6, 2015.

2. DISCUSSION

FDA Introductory Comment:

FDA acknowledged the Sponsor's reply documents (received via email on May 14, 2015 p.m.) to the FDA preliminary responses to the meeting questions. These documents are attached at the end of the Meeting Minutes. While the information in the Sponsor's reply will serve as the basis for discussion at this meeting, this meeting should not be considered a complete review of the additional material provided.

Question 1 – Non-Clinical Program for Phase 3 Initiation and Initial Registration

Does the Agency agree that the luspatercept nonclinical program supports the conduct of the proposed Phase 3 clinical studies in β -thalassemia and ultimately the initial registration of luspatercept in adults with β -thalassemia?

FDA RESPONSE to Question 1: The type of studies and nonclinical data available outlined in your meeting package appears to be sufficient to support the proposed clinical trial and BLA submission. A final decision regarding the adequacy of the nonclinical studies will be a review issue.

MEETING DISCUSSION – Question 1:

None

Question 2 – Immunogenicity Testing Plan

Does the Agency agree that the proposed immunogenicity testing plan is adequate to support the conduct of the proposed Phase 3 clinical studies in β -thalassemia and initial registration of luspatercept in adults with β -thalassemia?

FDA RESPONSE to Question 2: Regarding the ADA and Neutralizing assays, insufficient information is provided to assess the adequacy of the assays. The adequacy of the assays will be a review issue upon submission of the validation studies to the IND.

MEETING DISCUSSION – Question 2:

None

Question 3 – Clinical Development Program

Does the Agency agree that the proposed clinical development program is adequate to support the initial registration of luspatercept for the treatment of adult subjects with β -thalassemia?

FDA RESPONSE to Question 3: No. You propose to conduct one randomized trial for each indication. In order for a single trial to support registration for an indication, the trial must be well conducted, and the results of the trial must be internally consistent, clinically meaningful, and statistically very persuasive. See also the comments below regarding the design of the individual trials.

MEETING DISCUSSION – Question 3:

None

Question 4 – Key Study Design Elements Agreed (b) (4) EOP 1 Meeting

Does the Agency agree that the agreements reached at the (b) (4) EOP1 meeting (b) (4) on the following key study design elements of the proposed Phase 3 study in (b) (4) subjects are applicable to the proposed luspatercept Phase 3 study in TD subjects?

FDA RESPONSE to Question 4: No. Our comments will reflect review of your proposal for clinical trials of luspatercept.

Question (4a)

- *Definition of Patient Population*

FDA RESPONSE to Question (4a): The key enrollment criteria that you identified are acceptable for this protocol.

MEETING DISCUSSION – Question 4 (a):

None

Question (4b)

- *Control Arm*

FDA RESPONSE to Question (4b): We agree that a placebo control would be of value, but there is a concern about dropouts in the control arm when subjects do not see a quick response despite repeated injections. Please provide a plan for mitigating this bias.

MEETING DISCUSSION – Question (4b):

The Sponsor agreed that there was potential for early drop out after 6 months in the placebo arm and proposed an primary efficacy analysis evaluation at week 24. FDA recommended a comparison between week 24 and one year as a key secondary or co-primary comparison to ensure persistence of the treatment effect, to capture time to response data, and to continue to follow all patients on the placebo arm for one year independent of treatment.

Question 4c.

o *Primary Endpoint*

FDA RESPONSE to Question (4c): No. The clinical benefit of a 33% reduction in transfusion burden is not clear, especially with the limited treatment effect that you are targeting. We recommend that you modify the definition to require 50% reduction in transfusion burden AND a reduction of at least 2 units over a 12-week period.

MEETING DISCUSSION – Question 4(c):

None

Question 4d.

o *2:1 Randomization*

FDA RESPONSE to Question(4d): Yes.

MEETING DISCUSSION – Question 4(d):

None

Question 5 – Secondary Endpoints

Does the Agency agree with the proposed secondary efficacy endpoints and their ranking to support clinical benefit in subjects with transfusion dependent β -thalassemia?

FDA RESPONSE to Question 5: We have no objection to the ranking of key secondary endpoints in the order that you have provided. We do recommend that if you choose to use 33% reduction in transfusion burden as the primary endpoint, you should consider using 50% reduction in transfusion burden AND a reduction of at least 2 units over a 12-week period as the

first key secondary endpoint. Also, if the results of the current on-going trial do not support the expectation that you will achieve transfusion-independence in this patient population, you might consider moving this secondary endpoint to a lower position in the order of testing.

(b) (4)

You propose to use a newly developed patient-reported outcome assessment, the TranQol (transfusion-dependent quality of life) questionnaire to assess change in quality of life (QoL). We have the following comments in regards to this new assessment:

Based on the information provided, we do not agree that the TranQol is an appropriate instrument to detect clinical benefit (b) (4) in clinical trials for your patient population.

- Broad QoL instruments such as the TranQol contain multiple questions that are often distal to the impact of treatment (e.g., “*I had trouble sleeping*,” “*I was hopeful about my future*,” “*Thalassemia negatively affected my family*”). The inclusion of these distal attributes of well-being that typify QoL questionnaires attenuate the overall ability of the measure to detect change.
- The assessment is not well-defined and reliable. Some of the domains combine disease-related symptoms, physical function, and impacts making it difficult to interpret or describe the clinical benefits of luspatercept (b) (4). For example, the Physical Health domain combines the concepts “*I was free of pain or discomfort*,” “*I was limited in my ability to do the kind of moderate/vigorous work I take part in*,” and “*My treatments prevent me from doing the things I want to do*” into one domain score. Additionally, no evidence has been provided documenting the measurement properties of this assessment.

While not regulatory requirements, the following advice is given to maximize the quality and interpretability of PRO data:

- (b) (4) we recommend you focus on the assessment of core patient-reported concepts that include the most important/bothersome disease-related symptoms, treatment-related symptoms, and/or physical function and assess these at appropriate intervals before and during the trial. Focusing on these core concepts may provide more meaningful, supportive information on the clinical benefit of luspatercept. Measures of disease related symptoms, treatment-related symptoms, and physical function should be analyzed as separate concepts or domains where feasible and a pre-specified plan for your PRO analyses should be provided.
- We encourage the use of the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to support characterization of treatment-related symptoms (i.e., toxicity). We believe the PRO-CTCAE has the potential to capture important information in collecting symptomatic adverse events (AEs) for descriptive safety/tolerability assessment.
- For any outcome assessment you propose as a key study endpoint to support labeling claims, we recommend that you provide a copy of the assessment, evidence of the assessment’s measurement properties, including validity and reliability, as well as the assessment’s conceptual framework and scoring for Agency review and comment.

We understand that flexibility is needed when applying the principles of the PRO Guidance for PRO measure development and selection. However, we suggest that the identification of the strengths and limitations of existing PRO measures using the principles of the PRO Guidance will ultimately facilitate your selection of the most appropriate PRO measure(s) for your clinical context.

MEETING DISCUSSION – Question 5:

None

Question 6 - Stratification Factors

Does the Agency agree with the proposed stratification factors for the transfusion dependent study?

FDA RESPONSE to Question 6: We have no objection to the stratification factors that you propose. We recommend that you explore the results from the on-going trials for other potential factors that might influence response. Please also include in your protocol submission a discussion of any other factors at baseline known to increase transfusion burden over time and how you protect against bias from an imbalance these factors.

MEETING DISCUSSION – Question 6:

None

Question 7 - Statistical Analysis Plan

Does the Agency agree with the statistical analysis plan for the proposed Phase 3 Transfusion Dependent study (ACE-536-B-THAL-001)?

FDA RESPONSE to Question 7: No. You propose to declare success if the response is 20 percentage points greater in the treatment arm than in the control arm. Whether this modest measure of success outweighs the toxicities of luspatercept is not clear.

MEETING DISCUSSION – Question 7:

None

Question 8 - Interim Statistical Analysis Plan

Does the Agency agree with on the proposal to submit the initial BLA based on the proposed Interim analysis from the Phase 3 Transfusion Dependent Study (ACE-536-B-THAL-001)?

FDA RESPONSE to Question 8: No. There is insufficient information in the briefing document to address this question. You will need to provide more detail regarding how you will determine if the results of the interim analysis are “overwhelmingly conclusive.” Please provide

the details such as the O'Brien-Fleming boundary and the alpha level that will be used to claim efficacy.

MEETING DISCUSSION – Question 8:

None

Question 9 - Patient Population

[REDACTED] (b) (4)

FDA RESPONSE to Question 9: No. We have the following comments on the eligibility criteria.

a) [REDACTED] (b) (4)

[REDACTED] (b) (4)

MEETING DISCUSSION – Question 9:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Question 10 - Stratification Factors

[REDACTED] (b) (4)

(b) (4)

MEETING DISCUSSION – Question 10:

None

Question 11 – Primary Endpoint

(b) (4)

FDA RESPONSE to Question 11: We agree that the meaningfulness of your primary endpoint will depend on the success of supporting key secondary endpoints with statistical rigor, and as such it will be a review issue. See also response 9c above.

MEETING DISCUSSION – Question 11:

None

Question 12 – Secondary Endpoints

(b) (4)

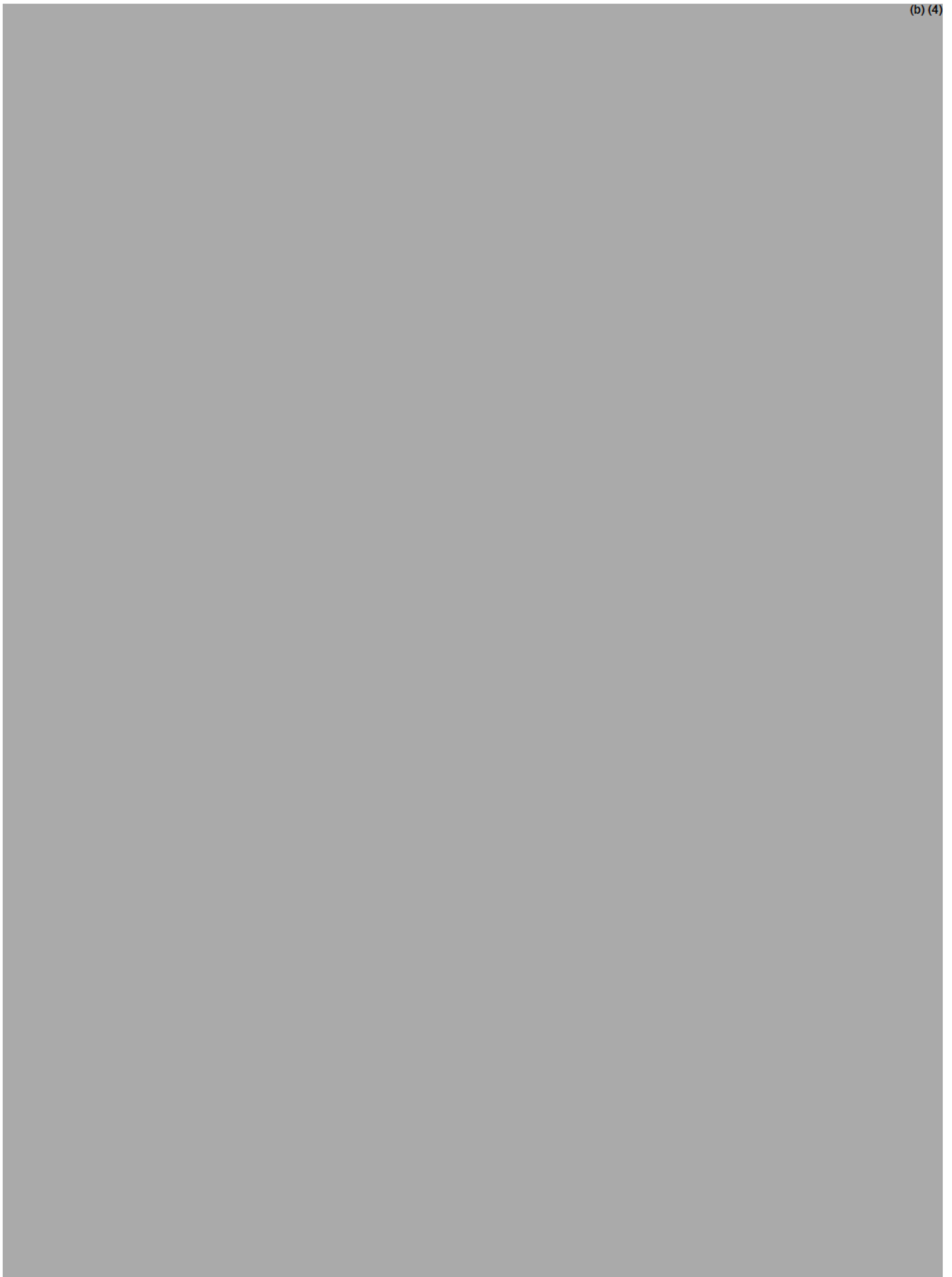
FDA RESPONSE to Question 12: We have no objection to the ranking of key secondary endpoints in the order that you have provided, but see also response 9c above.

(b) (4)

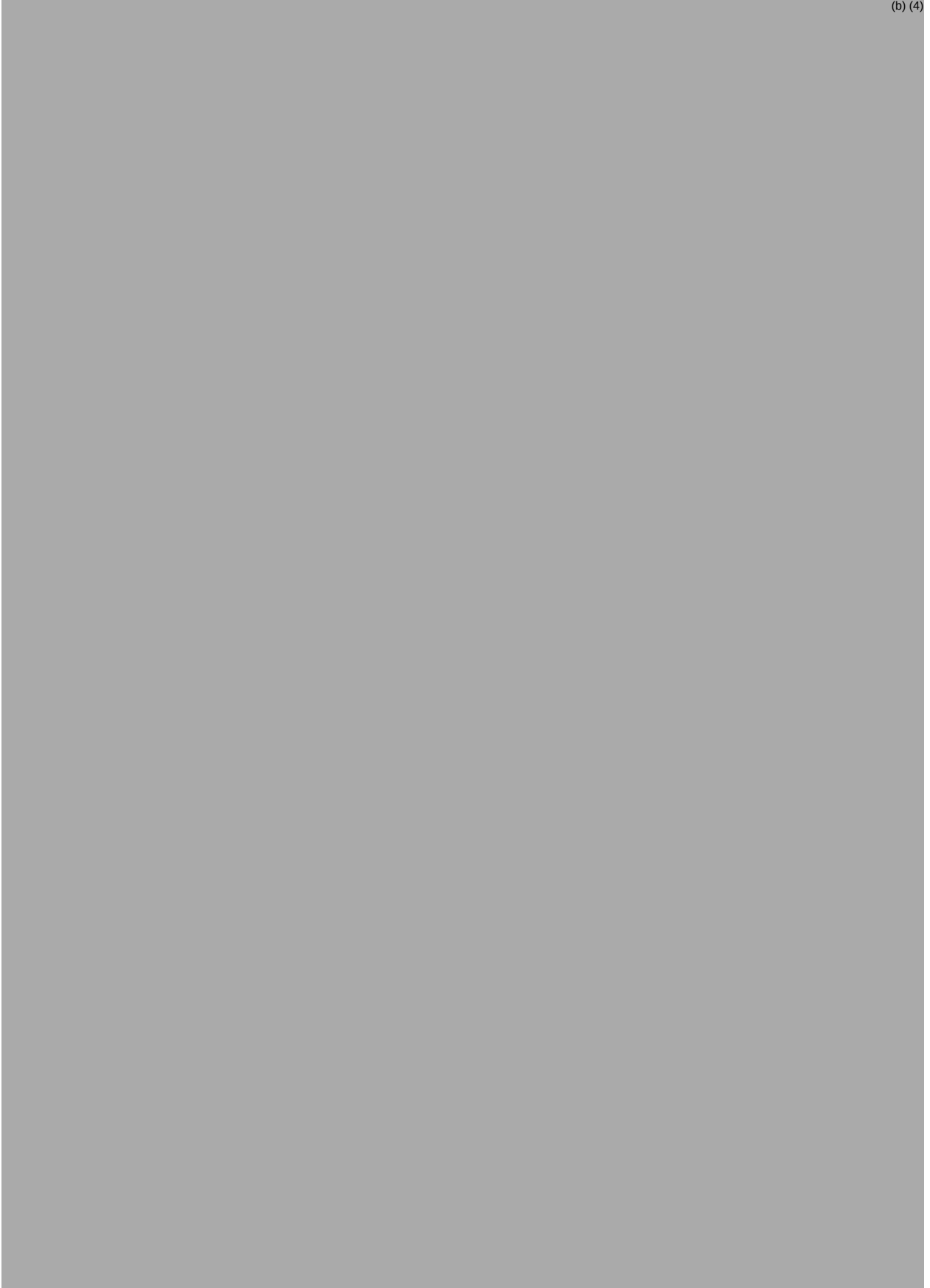
MEETING DISCUSSION – Question 12:

None

(b) (4)



(b) (4)



Question 17 – Starting Dose and Schedule

Does the Agency agree with the proposed starting dose and dosing schedule?

FDA RESPONSE to Question 17: No. There is not a sufficient number of subjects with either indication treated with the proposed dose-schedule to assure that you have developed the safety profile adequately to proceed to a pivotal trial.

The rationale for the proposed dosing schedule of every 3 weeks is also not clear.

MEETING DISCUSSION – Question 17:

The Sponsor will provide updated analysis to justify the dose and timing of the regimen.

Question 18 – Dose Titration Plan

Does the Agency agree with the proposed intra-subject dose titration plan?

FDA RESPONSE to Question 18: No. There is not a sufficient number of subjects with either indication treated with the proposed dose-schedule to assure that an inpatient dose escalation is warranted in the timeframe indicated.

MEETING DISCUSSION – Question 18:

None

Question 19 – Dose Modification Plan

Do the Agency agree with the proposed dose reduction modification plan to manage AEs and excessive hemoglobin increase?

FDA RESPONSE to Question 19: No. We have the following comments on the dose modification plan:

- a) The protocol should be clear that “related” is to mean possibly, probably or definitely related.
- b) When treatment is held for a grade 3 related toxicity, treatment should not be restarted until the toxicity resolves to no more than grade 1.
- c) The target hemoglobin for dose modification is too high. Subjects should interrupt therapy if the hemoglobin exceeds 11 g/dL or if the interim rise in hemoglobin is >1.5 g/dL in 3 weeks.
- d.) The rationale for only 25% dose reductions in response to changes in the Hgb is not clear. You have not provided information showing that the dose-reduction will not result in a further increase in hemoglobin.

MEETING DISCUSSION – Question 19:

The Agency and the Sponsor agreed that the Sponsor would submit a more extensive discussion of their plans for managing side effects and excursions of hemoglobin through delays and dose adjustments.

Question 20 – Proposed Long-Term Open-Label Extension Phase

Does the Agency agree with a proposed duration of (b) (4) years follow-up period for the open-label expansion study for safety and efficacy follow-up of the proposed Phase 3 studies?

FDA RESPONSE to Question 20: No. Since you propose treatment life-long, you will ultimately be expected to show at least 5 years of safety data.

MEETING DISCUSSION – Question 20:

None

Question 21 – Proposed Safety Database

Does the Agency agree that the proposed safety database is adequate to support the overall review of safety in the original BLA for the use of luspatercept in β -thalassemia patients?

FDA RESPONSE to Question 21: Your proposal to provide safety data on 308 subjects in total and 197 subjects treated with the proposed dose-schedule might be acceptable. It will depend on the robustness of your safety data at the time of submission of the BLA.

MEETING DISCUSSION – Question 21:

None

Question 22 – Proposed Safety Database with Interim Analysis Data from ACE-536-B-THAL-001

Does the Agency agree that the proposed safety database is adequate with interim data to support the overall review of safety in the initial BLA for luspatercept in β -thalassemia TD indication?

FDA RESPONSE to Question 22: For a new agent for life-long use, one year of safety data with the proposed dose-schedule in less than 100 subjects might not be sufficient to support a BLA, (b) (4). With such a small safety database, there might still be substantial uncertainty about whether the benefit outweighs the risks.

MEETING DISCUSSION – Question 22:

None

Question 23 – Clinical Pharmacology Program

Does the Agency agree that the proposed clinical pharmacology program (pharmacokinetics, exposure-response, and immunogenicity) is adequate to support the review of the original BLA for the use of luspatercept in β -thalassemia patients?

FDA RESPONSE to Question 23: No.

Your exposure-response analysis should also

1. Incorporate the impact of other covariates (such as baseline Hgb) in order to guide dose selection and dose-adjustments for your Phase 3 clinical study.
2. Evaluate if the rate of change in Hgb is exposure, concentration, or dose dependent.
3. Your final exposure-response/safety evaluation should also incorporate the results of your phase 3 study in order to support your recommended starting dose and subsequent dose-adjustments.

You should submit your currently available ECG data for FDA review to determine if additional ECG assessments are needed prior to the submission of your BLA (i.e., as part of, or incorporated into your proposed Phase 3 trials). You may need to conduct a thorough QT trial to capture large cardiac safety signals before the conduct of the planned registration trial(s). In some circumstances, alternative proposals to the thorough QT trial may be appropriate. Until a dedicated QT clinical trial is conducted or determined to be needed, include monitoring at baseline, the anticipated maximal plasma and steady-state concentrations, as clinically indicated and at the end of treatment in all clinical trials. For more information, refer to the Guidance for Industry entitled E14 Clinical Evaluation of QT/QTc Interval Prolongation.

From the information provided in tables describing the schedule of assessments for protocols ACE-536-B-Thal-001 (b) (4) for the proposed phase 3 studies, the latest sampling for anti-drug antibody (ADA) testing is 3 months after the last dose or study discontinuation. We recommend that patients that are still positive for ADA at the 3 month time point be monitored until the antibody levels return to baseline levels.

Ensure that the analytical methods used to determine the concentrations of luspatercept are validated. Refer to the Guidance for Industry Bioanalytical Method Validation. See the immunogenicity response to question 2.

MEETING DISCUSSION – Question 23:

None

2.0 IMPORTMENT MEETING INFORMATION:

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified requiring further discussion.

5.0 ACTION ITEMS

No issues identified requiring further actions.

6.0 ATTACHMENTS AND HANDOUTS

ATTACHMENT A – SPONSOR’S May 14, 2015, Responses to the FDA Preliminary Comments.

ATTACHMENT A - SPONSOR'S RESPONSE TO FDA COMMENTS

Product Name: Luspatercept (ACE-356)
Application Number: IND 112,562
Sponsor: Celgene Corporation (Celgene)

Provided below are Celgene responses to the FDA responses received on 06 May 2015, in reference to the questions included in the briefing package dated 08 Apr 2015 (SN0032). The briefing package was submitted in support of the Type B meeting scheduled for 15 May 2015 from 3:00 pm to 4:00 pm ET.

At the meeting on 15 May 2015, Celgene would like to focus on our additional responses and clarifications as provided below, and is seeking additional discussion on the following questions (in specified order):

- Question 4b (page 4 to 5)/Question 14 (page 13) (10 minutes)
- Question 9b and 9c (page 9 to 10) (10 minutes)
- Question 15 (page 14)/Question 16 (page 17 to 18) (10 minutes)
- Question 17 (page 18 to 19) (10 minutes)
- Question 19 (page 20 to 23) (10 minutes)

The Sponsor has also provided written responses to the Agency's comments to other questions (Questions 2, 5, 8, 12, 15 regarding PRO-CTCAE, and 20). These questions will not be discussed at the Type B face-to-face meeting due to time limitation; however, the Sponsor would appreciate if the Agency can provide written feedback to our responses.

Regarding the PREA Requirements noted in the FDA response document (page 12), orphan-drug designation of luspatercept (ACE-536) for "treatment of β -thalassemia" has been granted by the US FDA Office of Orphan Products Development (orphan drug designation #13-3898) on 11 Mar 2013. Because this drug product for this indication has an orphan drug designation, this application would be exempted from these requirements.

Non-Clinical

Question 1 – Non-Clinical Program for Phase 3 Initiation and Initial Registration

Does the Agency agree that the luspatercept nonclinical program supports the conduct of the proposed Phase 3 clinical studies in β -thalassemia and ultimately the initial registration of luspatercept in adults with β -thalassemia?

FDA Response Dated 06 May 2015:

The type of studies and nonclinical data available outlined in your meeting package appears to be sufficient to support the proposed clinical trial and BLA submission. A final decision regarding the adequacy of the nonclinical studies will be a review issue.

Celgene Response:

No further discussion is needed for this question.

Question 2 – Immunogenicity Testing Plan

Does the Agency agree that the proposed immunogenicity testing plan is adequate to support the conduct of the proposed Phase 3 clinical studies in β -thalassemia and initial registration of luspatercept in adults with β -thalassemia?

FDA Response Dated 06 May 2015:

Regarding the ADA and Neutralizing assays, insufficient information is provided to assess the adequacy of the assays. The adequacy of the assays will be a review issue upon submission of the validation studies to the IND.

Celgene Response:

The Sponsor agrees that review of the reports is required to accept the adequacy of analytical methods. The following validation reports have been submitted to IND 112,562 Sequence No. 0000:

1. (b) (4) for screening and confirmation of ADA positive samples
“Validation for the Detection of Anti-ACE536 Antibodies in Human Serum by an Electrochemiluminescent Assay (ECLA)”
2. (b) (4) for measurement of neutralizing activity to luspatercept
“Validation for the Detection of Neutralizing Antibodies to ACE-536 in Human Serum by ELISA”
3. (b) (4) for measurement of neutralizing activity to native ActRIIB-Extra Cellular Domain (IIB-ECD) “Detection of Neutralizing Antibodies to ACE-031 in Human Serum by ELISA”

However, the Sponsor is requesting the Agency to comment on the use of the tiered testing strategy to assess immunogenicity. The proposed plan is the same procedure as that currently in use in the ongoing clinical trials and would consist of the following assays:

- i. Screening
- ii. Confirmation/Titration
- iii. Neutralizing activity

As described in the Briefing Document, this plan follows the standard multi-tiered strategy outlined in the draft FDA guidance for “Assay Development for Immunogenicity Testing of Therapeutic Proteins” (FDA Draft Guidance, 2009) and is consistent with the guidance for “Immunogenicity Assessment for Therapeutic Protein Products” (FDA Guidance 2014), the EMEA guidance documents “Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins” (EMA 2007) and “Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use” (EMA 2012).

Initial screening, confirmation and titration of the ADA response will be done using a bridging immunoassay (b) (4) for anti-luspatercept antibodies with electrochemiluminescence based detection which was developed and validated (according to the guidelines in Mire-Sluis, 2004; Shankar, 2008) using a statistically derived cut determined and a

goat anti-hActRIIB antibody as positive control. Confirmation of specificity will be conducted using immunocompetition with (i) luspatercept, (ii) luspatercept extracellular domain (ECD), and (iii) native ActRIIB ECD.

Neutralizing activity will be determined for samples confirmed to have anti-luspatercept antibodies using two ligand-binding assays validated, in accordance with the guidance documents cited above. These assays determine NAB presence by their ability to bind immobilized luspatercept or native ActRIIB-Fc, thereby preventing the binding of labeled ligand (GDF11 or activin A, respectively) to the immobilized target.

Because the mechanism of action of luspatercept is to bind to soluble ligands and thus prevent the ligands from binding to their receptor (ligand trap), these ligand binding assays provide a direct measurement of the neutralizing activity and are therefore appropriate to detect the presence neutralizing anti- luspatercept antibodies present in patient samples.

Follow-up Discussion with the Agency:

Does the Agency agree that the multi-tiered analytical plan is adequate to support the conduct of the proposed Phase 3 clinical studies in β -thalassemia and initial registration of luspatercept in adults with β -thalassemia?

This will not be a discussion item for the 15 May Type B meeting but the Sponsor would appreciate a written confirmation from the Agency on this question.

Clinical

Question 3 – Clinical Development Program

Does the Agency agree that the proposed clinical development program is adequate to support the initial registration of luspatercept for the treatment of adult subjects with β -thalassemia?

FDA Response Dated 06 May 2015:

No. You propose to conduct one randomized trial for each indication. In order for a single trial to support registration for an indication, the trial must be well conducted, and the results of the trial must be internally consistent, clinically meaningful, and statistically very persuasive. See also the comments below regarding the design of the individual trials.

Celgene Response:

No further discussion is needed for this question.

Clinical - Proposed Phase 3 Study Design in Transfusion-Dependent β-Thalassemia Adults (ACE-536-B-THAL-001); Questions 4 to 8

Question 4 – Key Study Design Elements Agreed to (b) (4) EOP 1 Meeting

Does the Agency agree that the agreements reached at the (b) (4) EOP1 meeting (b) (4) on the following key study design elements of the proposed Phase 3 study in (b) (4) subjects are applicable to the proposed luspatercept Phase 3 study in TD subjects?

FDA Response Dated 06 May 2015:

No. Our comments will reflect review of your proposal for clinical trials of luspatercept.

Celgene Response:

No further discussion is needed for this question.

Question (4a)

Definition of Patient Population

FDA Response Dated 06 May 2015:

The key enrollment criteria that you identified are acceptable for this protocol.

Celgene Response:

No further discussion is needed for this question.

Question (4b)

Control Arm

FDA Response Dated 06 May 2015:

We agree that a placebo control would be of value, but there is a concern about dropouts in the control arm when subjects do not see a quick response despite repeated injections. Please provide a plan for mitigating this bias.

Celgene Response:

To mitigate the potential bias should subjects in the control arm drop-outs early due to lack of a quick response, the Sponsor proposes that the primary efficacy analysis be measured at 6 months. The response evaluation will be a rolling 12-week period weighted toward the end of the 6 months (ie, after a minimum of 2 months of treatment). Patients will continue to be followed on assigned treatment for a total of 12 months to generate longer-term efficacy and intermediate term safety information.

In the ongoing Phase 2 study, relatively rapid responses (reduction in transfusion burden) to luspatercept have been observed in TD subjects. This is likely due to the mechanism of action of luspatercept, affecting late-stage erythropoiesis. Therefore, an efficacy assessment at 6 months should be adequate to measure clinical effect in this placebo-controlled study.

<u>Question for Type B Meeting Discussion:</u>

Does the Agency agree the proposed primary efficacy measurement at 6 months may mitigate the potential bias of early drop-outs, with patients continue to be followed on treatment for a total of 12 months for longer-term efficacy and intermediate term safety information?

Question (4c)

Primary Endpoint

FDA Response Dated 06 May 2015:

No. The clinical benefit of a 33% reduction in transfusion burden is not clear, especially with the limited treatment effect that you are targeting. We recommend that you modify the definition to require 50% reduction in transfusion burden AND a reduction of at least 2 units over a 12-week period.

Celgene Response:

Please see response to Question 5.

Question (4d)

2:1 Randomization

FDA Response Dated 06 May 2015:

Yes.

Celgene Response:

No further discussion is needed for this question.

Question 5 – Secondary Endpoints

Does the Agency agree with the proposed secondary efficacy endpoints and their ranking to support clinical benefit in subjects with transfusion dependent β -thalassemia?

FDA Response Dated 06 May 2015:

We have no objection to the ranking of key secondary endpoints in the order that you have provided. We do recommend that if you choose to use 33% reduction in transfusion burden as the primary endpoint, you should consider using 50% reduction in transfusion burden AND a reduction of at least 2 units over a 12-week period as the first key secondary endpoint. Also, if the results of the current on-going trial do not support the expectation that you will achieve transfusion-independence in this patient population, you might consider moving this secondary endpoint to a lower position in the order of testing.

(b) (4)

You propose to use a newly developed patient-reported outcome assessment, the TranQol (transfusion-dependent quality of life) questionnaire to assess change in quality of life (QoL). We have the following comments in regards to this new assessment:

Based on the information provided, we do not agree that the TranQol is an appropriate instrument to detect clinical benefit (b) (4) in clinical trials for your patient population.

- Broad QoL instruments such as the TranQol contain multiple questions that are often distal to the impact of treatment (e.g., *"I had trouble sleeping," "I was hopeful about my future," "Thalassemia negatively affected my family"*). The inclusion of these distal attributes of well-being that typify QoL questionnaires attenuate the overall ability of the measure to detect change.
- The assessment is not well-defined and reliable. Some of the domains combine disease-related symptoms, physical function, and impacts making it difficult to interpret or describe the clinical benefits of luspatercept (b) (4). For example, the Physical Health domain combines the concepts *"I was free of pain or discomfort," "I was limited in my ability to do the kind of moderate/vigorous work I take part in,"* and *"My treatments prevent me from doing the things I want to do"* into one domain score. Additionally, no evidence has been provided documenting the measurement properties of this assessment.

While not regulatory requirements, the following advice is given to maximize the quality and interpretability of PRO data:

- (b) (4), we recommend you focus on the assessment of core patient-reported concepts that include the most important/bothersome disease-related symptoms, treatment-related symptoms, and/or physical function and assess these at appropriate intervals before and during the trial. Focusing on these core concepts may provide more meaningful, supportive information on the clinical benefit of luspatercept. Measures of disease related symptoms, treatment-related symptoms, and physical function should be analyzed as separate concepts or domains where feasible and a pre-specified plan for your PRO analyses should be provided.
- We encourage the use of the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to support characterization of treatment-related symptoms (i.e., toxicity). We believe the PRO-CTCAE has the potential to capture important information in collecting symptomatic adverse events (AEs) for descriptive safety/tolerability assessment.
- For any outcome assessment you propose as a key study endpoint to support labeling claims, we recommend that you provide a copy of the assessment, evidence of the assessment's measurement properties, including validity and reliability, as well as the assessment's conceptual framework and scoring for Agency review and comment. We understand that flexibility is needed when

applying the principles of the PRO Guidance for PRO measure development and selection. However, we suggest that the identification of the strengths and limitations of existing PRO measures using the principles of the PRO Guidance will ultimately facilitate your selection of the most appropriate PRO measure(s) for your clinical context.

Celgene Response:

The Sponsor agrees with the Agency's recommendation to use $\geq 33\%$ reduction in transfusion burden with a reduction of at least 2 units over a continuous 12-week period as the primary endpoint, and to include as the first key secondary endpoint, a $\geq 50\%$ reduction in transfusion burden with a reduction of at least 2 units over a continuous 12-week period. The key secondary endpoints will be measured at 6 months and 12 months from randomization.

(b) (4)
We understand that the Agency/SEALD does not agree that the TranQoL is an appropriate instrument to detect clinical benefit (b) (4). Based on the Agency's feedback, the Sponsor has revised the ranking of the secondary endpoint accordingly.

In summary, the Sponsor proposes the following revision to the primary and secondary efficacy endpoints:

Primary endpoint:

Proportion of subjects with hematological improvement, defined as $\geq 33\%$ reduction in RBC transfusion burden with a reduction of at least 2 units over a continuous 12-week period

Key secondary endpoints:

1. Proportion of subjects with hematological improvement, defined as $\geq 50\%$ reduction in RBC transfusion burden with a reduction of at least 2 units over a continuous 12-week period
2. Mean change in liver iron concentration (LIC) by MRI
3. Mean change in daily dose of iron chelation therapy (ICT) use
4. Change in serum ferritin

Other secondary endpoints:

5. Change in bone mineral density by DXA
6. Change in myocardial iron overload by MRI
7. Change in Quality of Life
8. Healthcare resource utilization
9. Duration of the reduction in transfusion burden
10. Duration of transfusion independence
11. Time to erythroid response
12. Proportion of subjects who are transfusion-free for at least 8 weeks during treatment

Please see response to Question 15 regarding the use and value of the PRO-CTCAE in β -thalassemia patients.

Follow-up Discussion with the Agency:

Does the Agency agree with the revised secondary efficacy endpoints and their ranking to support clinical benefit in subjects with transfusion dependent β -thalassemia?

This will not be a discussion item for the 15 May Type B meeting but the Sponsor would appreciate a written confirmation from the Agency on this question.

Question 6 – Stratification Factors

Does the Agency agree with the proposed stratification factors for the transfusion dependent study?

FDA Response Dated 06 May 2015:

We have no objection to the stratification factors that you propose. We recommend that you explore the results from the on-going trials for other potential factors that might influence response. Please also include in your protocol submission a discussion of any other factors at baseline known to increase transfusion burden over time and how you protect against bias from an imbalance these factors.

Celgene Response:

No further discussion is needed for this question.

Question 7 – Statistical Analysis Plan

Does the Agency agree with the statistical analysis plan for the proposed Phase 3 Transfusion Dependent study (ACE-536-B-THAL-001)?

FDA Response Dated 06 May 2015:

No. You propose to declare success if the response is 20 percentage points greater in the treatment arm than in the control arm. Whether this modest measure of success outweighs the toxicities of luspatercept is not clear.

Celgene Response:

No further discussion is needed for this question.

Question 8 – Interim Statistical Analysis Plan

Does the Agency agree with on the proposal to submit the initial BLA based on the proposed Interim analysis from the Phase 3 Transfusion Dependent Study (ACE-536-B-THAL-001)?

FDA Response Dated 06 May 2015:

No. There is insufficient information in the briefing document to address this question. You will need to provide more detail regarding how you will determine if the results of the interim analysis are “overwhelmingly conclusive.” Please provide the details such as the O’Brien-Fleming boundary and the alpha level that will be used to claim efficacy.

Celgene Response:

The Sponsor proposes one planned interim analysis when the primary endpoint data available for approximately 50% of the total 297 patients. In order to control the overall type 1 error rate, the O’Brien-Fleming implementation of the Lan-Demets alpha spending function will be used to

establish the statistical comparison boundary. If the interim analysis is performed with exactly 50% of the data, the nominal alpha will be 2-sided 0.003 (calculated from EAST software).

An independent DMC will review the unblinded interim efficacy and safety data. If the p-value for primary endpoint comparison crosses the O'Brien-Fleming boundary, with supportive other efficacy and safety data, the DMC may recommend stopping of the further randomization. The Sponsor will then discuss the interim results in the context of the totality of the data package with the Agency for next steps. Meanwhile, the study will continue as planned until the Sponsor and the Agency have reviewed the information and reached an agreement on the path forward.

Follow-up Discussion with the Agency:

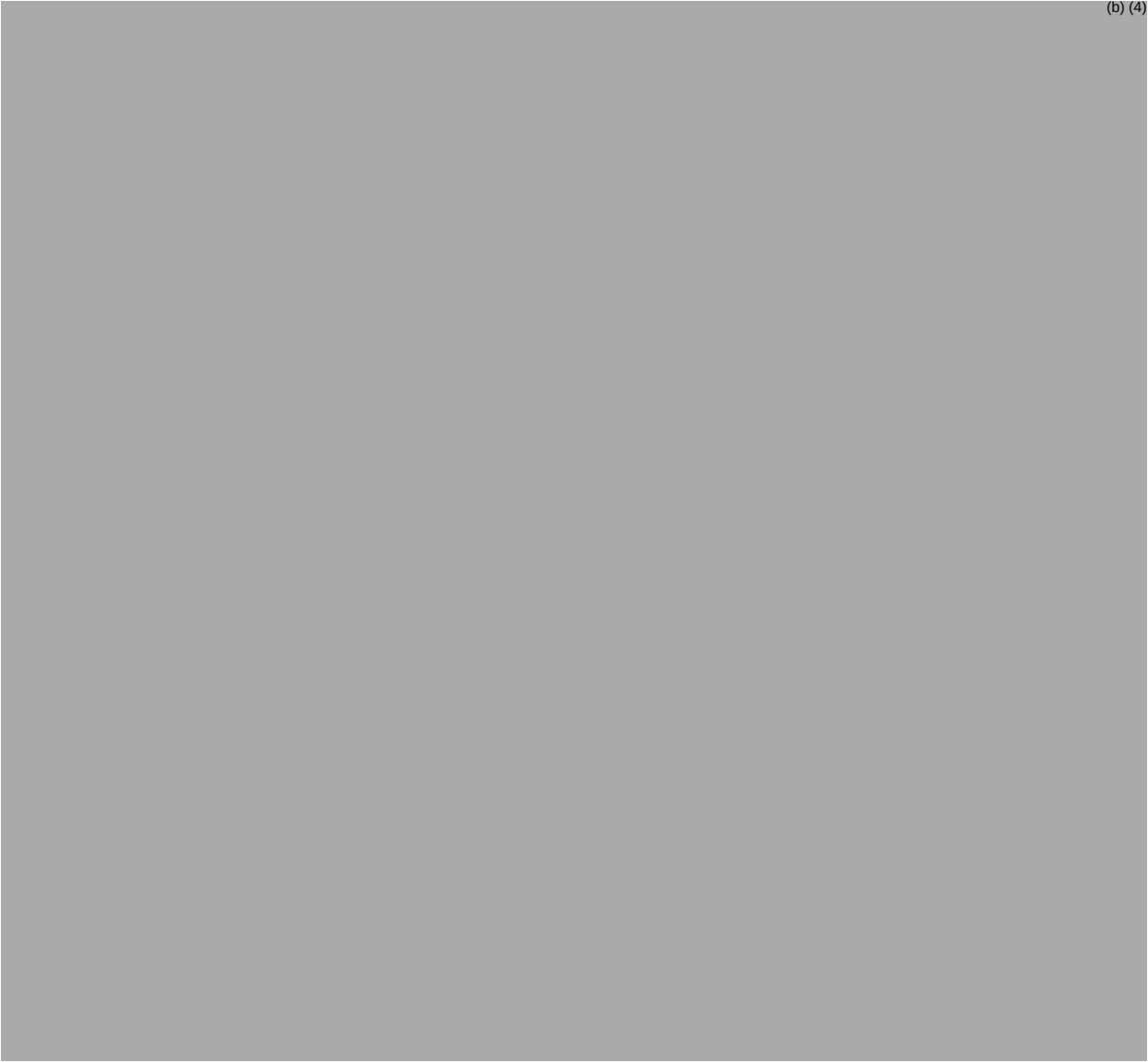
Does the Agency agree with the details provided above regarding the interim analysis plan?

This will not be a discussion item for the 15 May Type B meeting but the Sponsor would appreciate a written feedback from the Agency on this response.

(b) (4)



(b) (4)



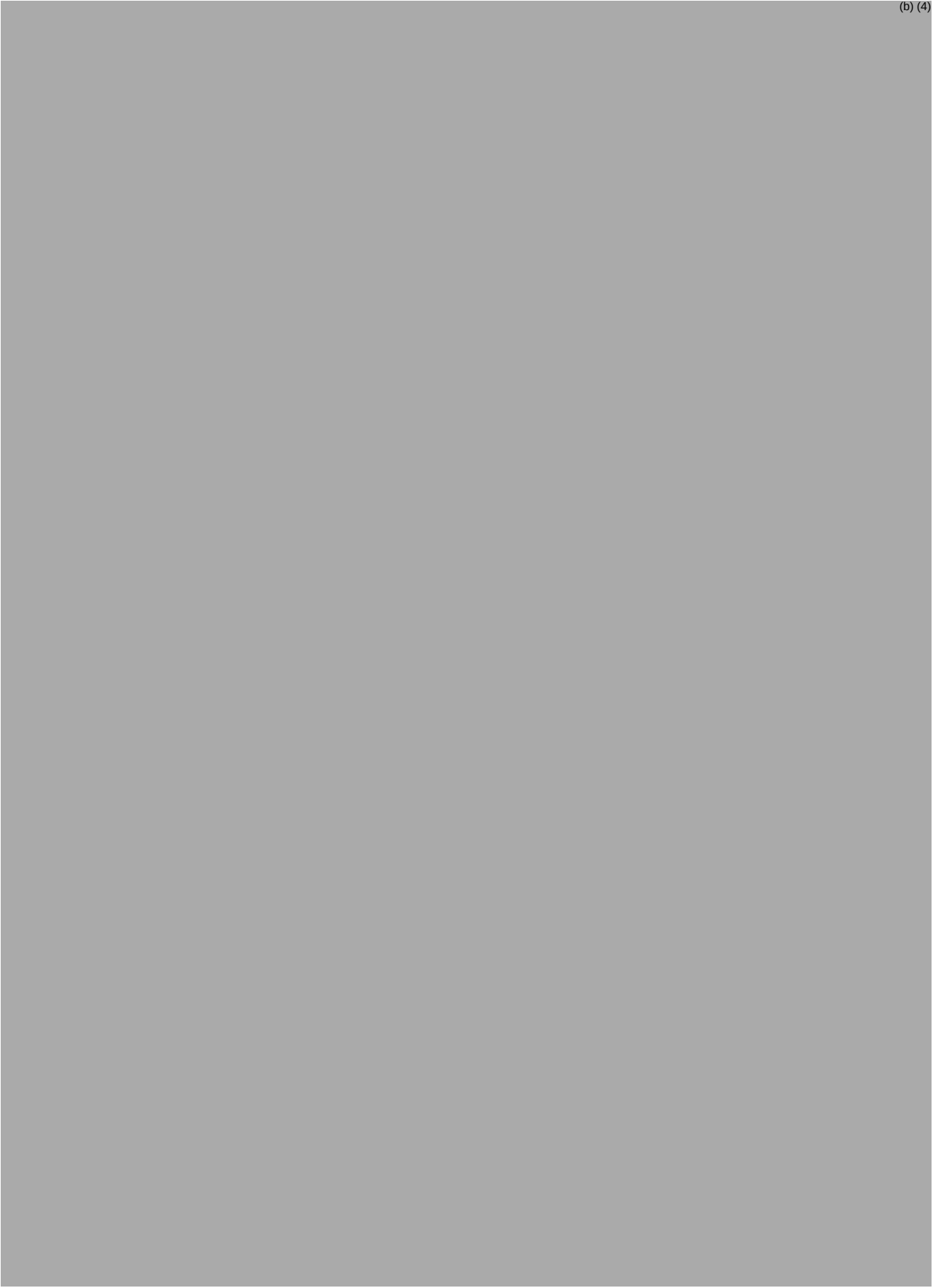
(b) (4)



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(b) (4)



Question for Type B Meeting Discussion:

Would the Agency agree to further discuss the proposed strategy prior to the initiation of the observational study?

Clinical - Recommended Phase 3 Starting Dose and Dose Modification Plan for the Proposed Phase 3 Studies, ACE-536-B-THAL-001 (b) (4) (Question 17 to 19)

Question 17 – Starting Dose and Schedule

Does the Agency agree with the proposed starting dose and dosing schedule?

FDA Response Dated 06 May 2015:

No. There is not a sufficient number of subjects with either indication treated with the proposed dose-schedule to assure that you have developed the safety profile adequately to proceed to a pivotal trial.

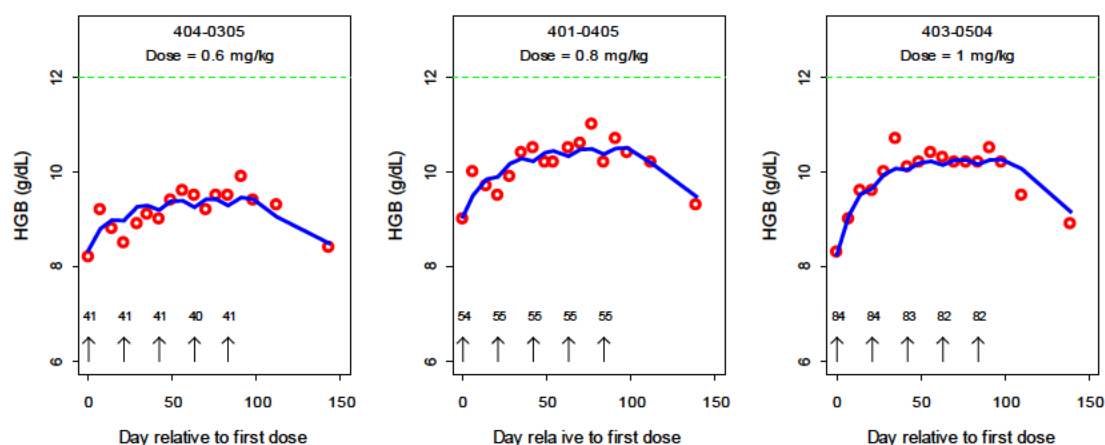
The rationale for the proposed dosing schedule of every 3 weeks is also not clear.

Celgene Response:

The rationale for the proposed dosing schedule of every 3 weeks

Although its PK half-life in patient populations is approximately 10 days, the biologic half-life of luspatercept (ie, effect on hemoglobin) is significantly longer. Increases in hemoglobin remained detectable through Day 57 postdose after a single low SC dose of luspatercept (0.25 mg/kg) in healthy postmenopausal women (See Figure 10 in Briefing Document) (Study A536-02). Sustained hemoglobin increase for at least 3 weeks was consistently observed in subjects with NTD β -thalassemia, as illustrated in Figure 1 below. These data support the proposed Q3W dosing schedule.

Figure 1: Representative Hemoglobin-Time Profiles in Subjects with β -Thalassemia and Treated with Luspatercept Once Every Three Weeks



Note: Red circles represent observed data. Blue lines represent the hemoglobin level predicted by a population PK/PD model. Arrows indicate the dosing time and the number above the arrow indicates the administered dose.

Regarding the number of patients treated with luspatercept, as of 10 Apr 2015, 50 subjects with β -thalassemia have been exposed to luspatercept in Study A536-04 and the extension study A536-06, including 22 TD subjects and 28 NTD subjects. Of the 50 subjects, a total of 37 subjects have been treated with the recommended Phase 3 dose of ≥ 0.8 mg/kg SC every 3 weeks. Of these 37 patients, 19 have received ≥ 5 cycles (15 weeks) and 9 have received ≥ 7 cycles (21 weeks). The majority of these patients are still being treated in the ongoing studies.

As of 10 Apr 2015, in the safety analyses for the 50 subjects who received at least one dose of the study drug of which 1 subject (2%) reported serious TEAEs and there were no reports of serious TEAEs considered related to study drug as assessed by investigators. The updated data are comparable with preliminary data presented in the Briefing Document (SAEs in 1 subject, 2.9%, with 12 Jan 2015 data-cut).

It is expected that data from approximately a total of 65 subjects from the ongoing Phase 2 studies will be available later this year prior to the initiation of the Phase 3 studies.

In addition, the integrated exposure-response analysis will be updated to further support the selection of the Phase 3 dose range. These results will be submitted for the Agency's review prior to or as part of the submission of Phase 3 protocol.

Question for Type B Meeting Discussion:

Does the Agency agree with the plan to confirm the Phase 3 dose range as part of the submission of the Phase 3 protocol?

Question 18 – Dose Titration Plan

Does the Agency agree with the proposed intra-subject dose titration plan?

FDA Response Dated 06 May 2015:

No. There is not a sufficient number of subjects with either indication treated with the proposed dose-schedule to assure that an inpatient dose escalation is warranted in the timeframe indicated.

Celgene Response:

As shared in the Briefing Document (Section 5.3.3.5.2 Preliminary Exposure-Response Relationship), the mean increase in hemoglobin was significantly correlated with the increased luspaterecept AUC in serum. A higher dose may be needed to achieve or maintain the target hemoglobin level for subjects with low hemoglobin level at baseline.

As of 10 Apr 2015, a total of 23 subjects treated with the proposed dosing regimen (0.8 mg/kg every 3 weeks) in the ongoing Phase 2 studies (A536-04 and A536-06) were eligible to dose escalate per protocol. Among them, 7 (30%) subjects (n=6 for NTD, n=1 for TD) have experienced dose escalation from the starting dose of 0.8 mg/kg, including 3 subjects escalated to 1 mg/kg and 4 subjects escalated to 1.25 mg/kg. Maintenance of target hemoglobin level was achieved in 5 (n=4 for NTD and n=1 for TD) of the 7 subjects who had a dose escalation. A review of the safety data from subjects with dose escalation upto 1.25 mg/kg has shown no change in safety profile across dose cohorts.

The exposure-response analysis will be performed to evaluate the proposed dose titration plan.

No further discussion needed at this time.

Question 19 – Dose Modification Plan

Do the Agency agree with the proposed dose reduction modification plan to manage AEs and excessive hemoglobin increase?

FDA Response Dated 06 May 2015:

No. We have the following comments on the dose modification plan:

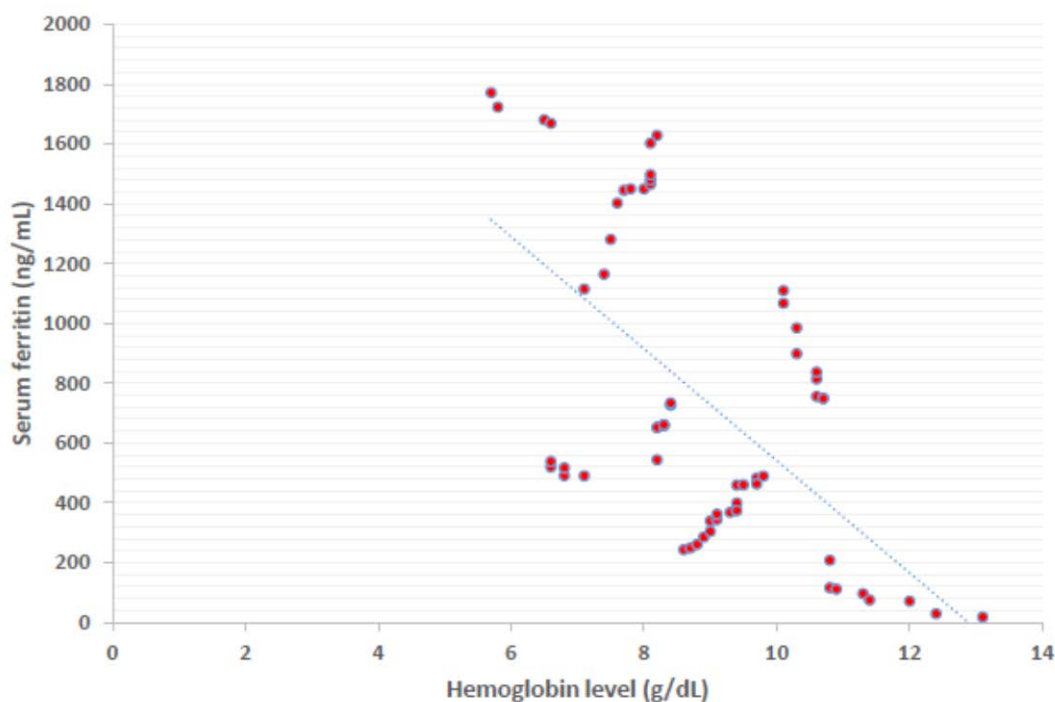
- a) The protocol should be clear that “related” is to mean possibly, probably or definitely related.**
- b) When treatment is held for a grade 3 related toxicity, treatment should not be restarted until the toxicity resolves to no more than grade 1.**
- c) The target hemoglobin for dose modification is too high. Subjects should interrupt therapy if the hemoglobin exceeds 11 g/dL or if the interim rise in hemoglobin is >1.5 g/dL in 3 weeks.**
- d.) The rationale for only 25% dose reductions in response to changes in the Hgb is not clear. You have not provided information showing that the dose-reduction will not result in a further increase in hemoglobin.**

Celgene Response:

- a) The Sponsor will update the protocol to note clearly that that “related” is to mean possibly, probably or definitely related.
- b) The Sponsor will update the dose modification table to indicate that when treatment is held for a grade 3 related toxicity, treatment should not be restarted until the toxicity resolves to no more than grade 1 (see [Table 1](#)).
- c) The Sponsor proposes to revise the dose modification table to include instruction to reduce the dose if the interim rise in hemoglobin is > 1.5 g/dL in 3 weeks and interrupt the therapy if the hemoglobin level is > 11.5 g/dL (see [Table 1](#)) with the following rationale:

The rate of hemoglobin rise is related to the systemic drug level and bone marrow reserve at the baseline. Based on a PK/PD simulation, if the interim rise in hemoglobin is > 1.5 g/dL in 3 weeks, such rapid rise of hemoglobin can be more efficiently controlled by reducing the dose, rather than by interrupting the therapy ([Figure 2](#)). Interruption of the therapy would not lower the rate of the drug-induced hemoglobin rise and thus subjects would experience a rapid hemoglobin increase again upon resuming the dose. In addition, subjects can still be anemic even after a rapid rise of hemoglobin (eg, hemoglobin is 8 g/dL at baseline and 9.5 g/dL after the initial dose). In this situation, interruption of the therapy is not warranted.

Regarding the Agency’s comment to interrupt therapy if the hemoglobin exceeds 11 g/dL, Celgene proposes to interrupt therapy if hemoglobin exceeds 11.5 g/dL to maximize the potential of luspatercept in reducing transfusion burden and associated secondary iron overload. For the treatment of NTD patients, a recent cross-sectional study of 63 β -thalassemia intermedia patients not receiving iron chelating agents demonstrated that decreased serum ferritin level is significantly correlated with higher hemoglobin level (see figure below).



(Taher, 2015, submitted and not yet published).

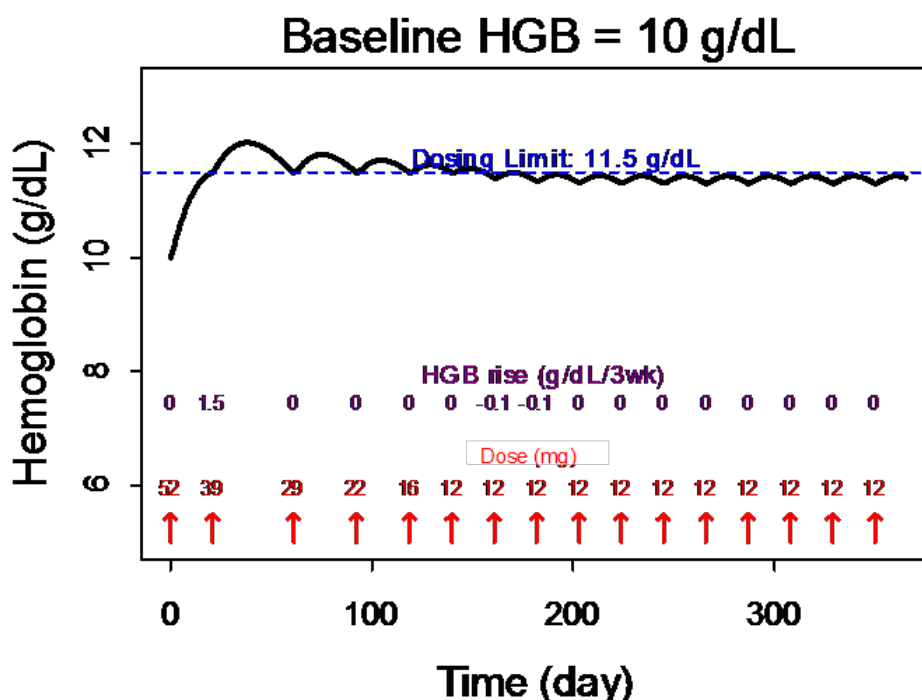
Unlike ESAs which may increase hemoglobin through expansion of early erythroid precursors in the marrow and others sites, our therapeutic intent with luspatercept in β -thalassemia is to improve anemia by correcting the underlying ineffective erythropoiesis. Therefore, we do not believe luspatercept shares the same safety issues as ESAs with respect to targeting a higher hemoglobin level.

In addressing the Agency's concern with a hemoglobin level > 11 g/dL, Celgene has included safety data from the ongoing Phase 2 study (in which the hemoglobin limit is 13 g/dL) in the Briefing Document (Table 5 in the Briefing Document), for which a total of 8 subjects of the 35 treated subjects (as of 20 Jan 2015) reached a hemoglobin level of > 11.9 g/dL during treatment. There were no AEs of hypertension or thromboembolic events reported associated with higher hemoglobin.

- d) The Sponsor has conducted PK/PD simulation to evaluate the needed magnitude of a dose reduction in response to changes in hemoglobin. By using population values of PK and PD parameters, the simulation results suggest that majority of NTD subjects would not experience any hemoglobin overshoots at the proposed dose regiments even after dose escalations which is consistent with the observation in phase 2 studies. However, there might be individuals who have unexpected high response to treatment. Therefore, additional simulations were performed by assuming extreme conditions. As such, the minimum value of CL/F (total clearance), V/F (volume of distribution), k_{out} (rate constant for hemoglobin loss in blood), and EC_{50} (drug concentration at 50% of the maximum hemoglobin response) estimated for subjects in study A536-04 and the highest baseline hemoglobin level (10 g/dL) were used to simulate the hemoglobin response as strong as possible for the proposed starting dose (0.8 mg/kg). Small CL/F and V/F values lead to

high drug concentration in serum while small values of k_{out} and EC_{50} , combined with the highest baseline hemoglobin value, lead to rapid and large hemoglobin increase. As shown in Figure 2 and Table 1, a 25% to 50% dose-reduction, along with dose delay, adequately prevents further increase in hemoglobin even under the assumed extreme condition.

Figure 2: Evaluation of the Adequacy of Dose Modification Rules under Extreme Conditions by PK/PD Simulation



Solid lines represent the mean hemoglobin level in response to dose reduction/delay, as predicted by a population PK/PD model. Arrows indicate the dosing time and the number above the arrow indicates the administered dose (assuming a body weight of 65 kg). The rate of hemoglobin rise (difference between the predose hemoglobin values over a dosing interval) is indicated by the value in purple.

The minimum value of CL/F (0.43 L/day), V/F (7.1 L), k_{out} (0.06/day), and EC_{50} (1.9 $\mu\text{g/mL}$) and the highest baseline hemoglobin level (10 g/dL) were used to simulate the hemoglobin response as strong as possible for the starting dose of 0.8 mg/kg. The population E_{max} value (0.337) was used in simulation because the inter-individual variability was near zero.

Summary

Taking into consideration the Agency's comments, the unique MoA of luspatercept, the clinical experience in phase 2 studies, and the PK/PD simulation results, the Sponsor proposes the following revised dose reduction/delay rules in response to AEs or a change in hemoglobin:

Table 1: Dose Delay, Dose Reduction and Discontinuation Guidelines:

Event at the day of dosing	Action
Any related AE $\geq$ Grade 2 ^a	Dose delay ^c until resolved to < Grade 1 or baseline
Any related AE $\geq$ Grade 3 ^a	Dose delay ^c until resolved to < Grade 1 or baseline, and then reduce dose by 25%
≥ 2 dose reductions due to related AE ^a	Discontinue treatment
Hgb <11.5 g/dL and Δ Hgb $\geq$ 1.5 g/dL at Day 21 from last dose ^b	Reduce dose by 25%
Hgb $\geq$ 11.5 g/dL and Δ Hgb <1.5 g/dL at Day 21 from last dose ^b	Dose delay until Hgb < 11.0 g/dL
Hgb $\geq$ 11.5 g/dL and Δ Hgb $\geq$ 1.5 g/dL at Day 21 from last dose ^b	Dose delay until Hgb < 11.0 g/dL and then reduce dose by 25%
^a Possibly, probably or definitely related ^b Based on the pre-treatment Hgb value not influenced by transfusion; Hgb should be rechecked weekly during dose delay ^c If dose delay is >12 consecutive weeks, treatment should be discontinued.	

Question for Type B Meeting Discussion:

Does the Agency agree with the revised dose modification plan?

Clinical - Proposed Long-Term Open-Label Extension Phase of the Phase 3 Studies

Question 20 – Proposed Long-Term Open-Label Extension Phase

Does the Agency agree with a proposed duration of (b) (4) years follow-up period for the open-label expansion study for safety and efficacy follow-up of the proposed Phase 3 studies?

FDA Response Dated 06 May 2015:

No. Since you propose treatment life-long, you will ultimately be expected to show at least 5 years of safety data.

Celgene Response:

Celgene plans to follow-up for safety of subjects exposed to luspatercept for 5 years, which include a one-year Phase 3 study and a 4-year open-label extension study.

Follow-up Discussion with the Agency:

Does the Agency agree with this proposal for the long-term follow-up?

This will not be a discussion item for the 15 May Type B meeting but the Sponsor would appreciate a written confirmation from the Agency on this question.

Clinical - Proposed Safety Database

Question 21 – Proposed Safety Database

Does the Agency agree that the proposed safety database is adequate to support the overall review of safety in the original BLA for the use of luspatercept in β -thalassemia patients?

FDA Response Dated 06 May 2015:

Your proposal to provide safety data on 308 subjects in total and 197 subjects treated with the proposed dose-schedule might be acceptable. It will depend on the robustness of your safety data at the time of submission of the BLA.

Celgene Response:

No further discussion is needed for this question.

Question 22 – Proposed Safety Database with Interim Analysis Data from ACE-536-B-THAL-001

Does the Agency agree that the proposed safety database is adequate with interim data to support the overall review of safety in the initial BLA for luspatercept in β -thalassemia TD indication?

FDA Response Dated 06 May 2015:

For a new agent for life-long use, one year of safety data with the proposed dose-schedule in less than 100 subjects might not be sufficient to support a BLA, (b) (4). With such a small safety database, there might still be substantial uncertainty about whether the benefit outweighs the risks.

Celgene Response:

No further discussion is needed for this question.

Clinical Pharmacology Program

Question 23 – Clinical Pharmacology Program

Does the Agency agree that the proposed clinical pharmacology program (pharmacokinetics, exposure-response, and immunogenicity) is adequate to support the review of the original BLA for the use of luspatercept in β -thalassemia patients?

FDA Response Dated 06 May 2015:

No.

Your exposure-response analysis should also

4. Incorporate the impact of other covariates (such as baseline Hgb) in order to guide dose selection and dose-adjustments for your Phase 3 clinical study.
5. Evaluate if the rate of change in Hgb is exposure, concentration, or dose dependent.
6. Your final exposure-response/safety evaluation should also incorporate the results of your phase 3 study in order to support your recommended starting dose and subsequent dose-adjustments.

You should submit your currently available ECG data for FDA review to determine if additional ECG assessments are needed prior to the submission of your BLA (i.e., as part of, or incorporated into your proposed Phase 3 trials). You may need to conduct a thorough QT trial to capture large cardiac safety signals before the conduct of the planned registration trial(s). In some circumstances, alternative proposals to the thorough QT trial may be appropriate. Until a dedicated QT clinical trial is conducted or determined to be needed, include monitoring at baseline, the anticipated maximal plasma and steady-state concentrations, as clinically indicated and at the end of treatment in all clinical trials. For more information, refer to the Guidance for Industry entitled [E14 Clinical Evaluation of QT/QTc Interval Prolongation](#).

From the information provided in tables describing the schedule of assessments for protocols ACE-536-B-Thal-001 (b) (4) for the proposed phase 3 studies, the latest sampling for anti-drug antibody (ADA) testing is 3 months after the last dose or study discontinuation. We recommend that patients that are still positive for ADA at the 3 month time point be monitored until the antibody levels return to baseline levels.

Ensure that the analytical methods used to determine the concentrations of luspatercept are validated. Refer to the Guidance for Industry [Bioanalytical Method Validation](#). See the immunogenicity response to question 2.

Celgene Response:

The Sponsor appreciates the Agency's recommendations on the exposure-response analysis and will incorporate them into the future analyses.

Available ECG data from the ongoing Phase 2 studies will be submitted for the Agency's review prior to or as part of the submission of Phase 3 protocol before initiation of the study.

The Sponsor acknowledges the Agency's comment regarding ADA monitoring in the proposed Phase 3 studies. ACE-536-B-Thal-001 [REDACTED] (b) (4) will include monitoring of patients who are still positive for ADA at the 3 month time point after the last dose until the antibody levels return to baseline levels or for one year, whichever occurs first.

The analytical methods used to determine the concentrations of luspatercept are validated per FDA Guidance for Industry Bioanalytical Method Validation.

No further discussion is needed for this question.

New References Previously Not Included/Listed in the Briefing Document

Taher AT, Musallam KM, Saliba AN, Garziadei G, Cappellini MD. Hemoglobin Level and Morbidity in Non-Transfusion-Dependent Thalassemia. Publication submitted but not yet published. A copy is encl

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISSEROTH
05/22/2015