

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761125Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



IND 112023

**MEETING MINUTES**

Novartis Pharmaceuticals Corp.  
Attention: Franklin Akomeah, PhD  
Sr. Global Program Regulatory Manager  
6201 South Freeway  
TC-45  
Fort Worth, TX 76134.

Dear Dr. Akomeah:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RTH258 (brolucizumab).

We also refer to the meeting between representatives of your firm and the FDA on August 27, 2018. The purpose of the meeting was to discuss regulatory questions as well as the presentation of the clinical and patient reported outcomes sections of the upcoming BLA submission.

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 Judit Milstein at 301-796-0763.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, MD  
Deputy Director  
Division of Transplant and Ophthalmology Products  
Office of New Drugs  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** pre-NDA

**Meeting Date and Time:** August 27, 2018, 12:00-1:00 PM  
**Meeting Location:** 10903 New Hampshire Avenue, Building 22, Room 1415  
Silver Spring, MD 20993

**Application Number:** IND 112023  
**Product Name:** Brolocizumab (RTH258)

**Indication:** Neovascular Age-Related Macular Degeneration (nAMD)  
**Sponsor/Applicant Name:** Novartis Pharmaceuticals Corp.

**Meeting Chair:** Wiley A. Chambers, MD  
**Meeting Recorder:** Judit Milstein

**FDA ATTENDEES**

Wiley A. Chambers, Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)  
William M. Boyd, Clinical Team Leader, DTOP  
Rhea Lloyd, Clinical Reviewer, DTOP  
Martin Nevitt, Clinical Reviewer, DTOP  
Wonyul Lee, Biometrics Reviewer, Division of Biometrics IV (DBIV)  
Yan Wang, Biometrics Team Leader, DBIV  
Philip Colangelo, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV  
Bruce Huang, Product Quality Reviewer, Division of Biotechnology Review and Research II (DBRRII)  
William Hallett, Product Quality Team Leader, DBRRII  
Maria Jose Lopez-Barragan, Microbiology Reviewer, Division of Microbiology Assessment Branch IV  
Michelle Campbell, Social Scientist, Clinical Outcomes Assessment Staff  
Eithu Lwin, Project Manager, DTOP  
Jacquelyn Smith, Regulatory Project Manager, DTOP  
Wendy Streight, Regulatory Project Manager, DTOP (on the phone)

## SPONSOR ATTENDEES

Cheryl Elder	Global Program Head
Georges Weissgerber	Global Program Clinical Head
Andreas Weischselberger	Global Program Biostatistics Head
Meghan Brown	Dir. Regulatory Affairs, CMC
Nancy Landzert	Franchise Head, Regulatory, CMC Biologics
Andrew Craddock	Technical Project Leader
Arthur Ciociola	VP, Franchise Head, Regulatory Affairs
Vera Berchten	Global Program Regulatory Director
Franklin Akomeah	Senior Global Program Regulatory Manager
Dhaval Desai	VP, Medical Unit Head, Ophthalmology
Julie Clark	Medical Director, US CDMA

(b) (4)

## BACKGROUND

Novartis Pharmaceuticals Corp. (the Sponsor) has developed Brolucizumab solution for intravitreal injection for the treatment of neovascular age-related macular degeneration (nAMD) and plans to submit a BLA in December 2018.

The Sponsor requested this meeting to discuss the presentation of the BLA submission as well as questions regarding the need for Advisory Committee, REMS, and compliance with PREA.

Preliminary responses to the questions posted by the Sponsor in their briefing document dated July 26, 2018, were sent on August 22, 2018. In response to these comments, the Sponsor requested further discussion on Question 4.

## DISCUSSION

For the purposes of these minutes, the questions posted by the Sponsor in their briefing document are in bold format, the preliminary responses are in italics, the Sponsor's response is in bold italics and the meeting discussion is in normal font.

### **Question 1 – Clinical data package**

**Does the agency agree that the proposed clinical data package and available results are sufficient for the assessment of the brolucizumab efficacy and safety profile to support registration of the nAMD indication?**

*FDA Comments: The proposed clinical data package and available results are sufficient to support filing of brolucizumab for the nAMD indication. Potential approval can only be determined following review of the application.*

Meeting Discussion: None

**Question 2 – Patient reported outcomes  
Novartis is seeking to include**

(b) (4)

[Redacted]

**Specifically, Novartis requests the  
opinion of the Agency with regards to the following:**

**a. Does the Agency agree that**

(b) (4)

[Redacted]

Meeting Discussion: None

**b. Does the Agency agree that**

(b) (4)

[Redacted]

*FDA Comments: No,*

(b) (4)

[Redacted]

[Redacted]

(b) (4)



Meeting Discussion: None

c. **Does the Agency agree**

(b) (4)



*FDA Comments: Labeling is a review issue requiring submission and review of a complete application.*

(b) (4)



Meeting Discussion: None

**Question 3 – Table of contents (TOC)**

**Does the Agency agree that the proposed content, format and outline of the BLA is adequate for filing this submission (TOC provided in Appendix 3)?**

*FDA Comments:* The proposed content, format and outline of the TOC for this BLA appears adequate for filing. In addition to the case report forms for deaths and serious adverse events, we also request the case report forms for all discontinued subjects, regardless of cause.

Meeting Discussion: None

**Question 4 – US PI clinical studies section**

 (b) (4)  
**Novartis proposes to include this information in the clinical studies section of the prescribing information. Beyond the current Guidance for Industry on labeling, does the Agency have any additional feedback on this approach?**

*FDA Comments:* We have no additional feedback at this time. Labeling is a review issue requiring submission and review of a complete application.

***Sponsor's Response:*** The Sponsor would like to discuss the inclusion of  (b) (4)  
  
. See Sponsor's response as an attachment to this document.

Meeting Discussion: The Sponsor indicated  (b) (4)  
  
The information contained in the Package Insert is intended to be a reflection of how the product should be used which may or may not be the way the studies were conducted. Assessments of labeling are made after review of the complete application and excludes promotional language and potentially includes negative results.

**Question 5 – US PI dosage and administration section**

**In the dosage and administration section of the prescribing information, Novartis is proposing the following text:**

**“The recommended dose for TRADENAME is 6 mg** (b) (4)

**Does the Agency agree that for brolocizumab,** (b) (4)

*FDA Comments: No. Labeling is a review issue requiring submission and review of a complete application.*

*We would not agree that* (b) (4)  
*without a complete review of the submitted application.* (b) (4)

Meeting Discussion: None

**Question 6 – Risk Evaluation and Mitigation Strategy (REMS)**

**Does the Agency agree that a risk evaluation and mitigation strategy (REMS) is not necessary for this product?**

*FDA Comments: Although it is not likely that a REMS will be necessary for this product, the final determination will be made during the application review cycle.*

Meeting Discussion: None

**Question 7 – Advisory Committee Meeting**

**Does the Agency agree that an Advisory Committee Meeting is not likely needed?**

*FDA Comments: Preliminary plans on whether an Advisory Committee Meeting will be needed will be communicated if the application is filed.*

Meeting Discussion: None

## **Question 8 – Pediatric research equity act (PREA)**

### **Does the Agency agree that the application is compliant with PREA?**

*FDA Comments: We acknowledge the Agreed Initial Pediatric Plan (Agreed iPSP) correspondence issued on April 27, 2015. The final determination on the PREA compliance will be made at the time of the BLA approval.*

Meeting Discussion: None

### **ADDITIONAL COMMENTS**

As this BLA will be reviewed under “The Program” [PDUFA VI], the Sponsor confirmed that all major components of the application will be included in the original submission and that no late submissions are being currently planned.

The Division reminded the Sponsor to include in the BLA submission a comprehensive list of all clinical sites and manufacturing facilities.

### **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.

## **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

## **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

#### **ISSUES REQUIRING FURTHER DISCUSSION**

None

#### **ACTION ITEMS**

The Division will issue the Minutes of the Meeting within 30 days.

#### **ATTACHMENTS AND HANDOUTS**

Sponsor's position to discuss under Question 4

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/s/  
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WILEY A CHAMBERS  
09/16/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 112023

**MEETING MINUTES**

Novartis Pharmaceutical Corporation  
Attention: Meghan Brown, PhD  
Regulatory CMC Director  
One Health Plaza  
East Hannover, NJ 07936-1080

Dear Dr. Brown:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RTH258 (brolucizumab).

We also refer to the meeting between representatives of your firm and the FDA on August 27, 2018. The purpose of the meeting was to discuss [REDACTED] (b) (4)

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 Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, MD  
Deputy Director  
Division of Transplant and Ophthalmology Products  
Office of New Drugs  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

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/s/  
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WILEY A CHAMBERS  
09/12/2018

**Meeting Preliminary Comments**  
Division of Transplant and Ophthalmology Products

**Meeting Date:** May 17, 2018

**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1313  
Silver Spring, Maryland 20903

**Meeting Type:** Guidance

**Application:** IND 112023

**Drug Name:** RTH258 (brolocizumab intraocular solution)

**Sponsor:** Novartis Pharmaceutical Corporation

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion for the meeting scheduled for May 17, 2018, between Novartis Pharmaceutical Corporation (the Sponsor) and the Division of Transplant and Ophthalmology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible.

For the purposes of these responses, the questions submitted in your briefing document dated March 29, 2018, are in **bold** font and FDA preliminary responses are in *italics* font.

## Clinical Questions

1. **Novartis proposes to assess clinical efficacy for the Phase III studies RTH258C001 (HAWK) and RTH258-C002 (HARRIER) separately (not pooled) in the summary of clinical efficacy (SCE), and to assess safety in two study pools (related to the monthly loading regimen and to the targeted loading and maintenance regimen) in the summary of clinical safety (SCS). Does the Agency agree with the proposed non-pooled analysis for clinical efficacy and the pooling strategy for safety topics?**

*FDA Comments: Yes, we agree.*

2. **Does the Agency agree with the proposed plan for the submission of datasets and SAS-programs?**

*FDA Comments: For studies RTH258-C001 and RTH258-C002, please submit all SAS programs used to create the ADaM datasets, and to generate tables, figures, listings for all efficacy and safety analyses in the clinical study reports.*

3. **Novartis plans to submit the narrative portion of the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS) in Modules 2.7.3 SCE and 2.7.4 SCS, respectively. Novartis proposes to submit the appendices of safety data analysis and integrated analyses in Module 5.3.5.3, and appendices of efficacy data in the SCE and/or in Module 5.3.5.3. Does the Agency agree with this proposal?**

*FDA Comments: Yes, we agree. Please also submit the datasets and SAS programs used to generate the efficacy and safety analysis results reported in Modules 2.7 and 5.3.5.3.*

4. **For the Phase III studies RTH258-C001 (HAWK) and RTH258-C002 (HARRIER), Novartis will provide patient narratives for all cases of death, all ocular SAEs in the study eye, SAEs suspected to be related to the injection procedure, AEs leading to permanent study drug discontinuation and AEs of special interest in the study eye. Does the Agency agree with this proposal?**

*FDA Comments: Yes, we agree.*

5. **Does the Agency agree with Novartis proposal on the submission of Summary Level Clinical Site Data to the Office of Scientific Investigation in support of the Agency's inspection of clinical sites?**

*FDA Comments: Acceptable.*

## Chemistry, Manufacturing and Controls Questions

6. **The original BLA for brolocizumab solution for injection in vial will introduce a slightly modified drug product formulation (formulation B) compared to the one (formulation A) used in the two Phase 3 studies RTH258-C001 and RTH258-C002, and presented as commercial drug product formulation in the briefing book for the Type C**

meeting held on September 20, 2017. Formulation B (intended commercial formulation)

(b) (4)

and is used in the extension to study RTH258-C001(CRTH258A2301E1) to complement the comprehensive analytical drug product comparability assessment.

Does the Agency agree with:

- a. the Novartis proposed strategy to demonstrate comparability between the Phase 3 (formulation A) and intended commercial formulation (formulation B)?

*FDA Comments: We agree with your proposal to demonstrate comparability between the Phase 3 formulation and the commercial formulation. In addition, please see our comments from the Type C meeting on September 20, 2017.*

- b. the Novartis proposed strategy to use stability data from pilot scale batches of formulation B (considered fully representative of the commercial process) to assign the commercial shelf-life? This strategy was previously agreed by FDA for formulation A (assuming comparability to the commercial batches is demonstrated).

*FDA Comments: We agree if analytical comparability of the pilot lots to phase 3 and commercial lots are demonstrated.*

7. Novartis plans to submit (b) (4) months registration stability data from pilot scale batches and (b) (4) months confirmatory stability data from process validation batches in the initial application to support a proposed shelf life of (b) (4) months. During the review of the application, Novartis would be able to submit 18 months data from pilot scale and 9 months data from process validation batches 90 days after the original submission date to support an 18 months shelf life. Does the Agency agree that updated stability data could be provided during the review to support a proposed shelf life of 18 months and that this would not trigger a new review cycle or extend the initial review cycle?

*FDA Comments: We agree that this proposed update to the stability data may be submitted to the Agency within 90 days of the original submission date. The determination of the shelf life will be a review issue based on our review of the data.*

8. Novartis has observed a low endotoxin recovery effect in the brolocizumab drug substance and drug product. Does the agency agree that the Novartis endotoxin control and testing strategy for brolocizumab is acceptable and rabbit pyrogen testing can be waived for commercial brolocizumab release testing?

*FDA Comments: The proposed drug product endotoxin specification of (b) (4) EU/mL appears to be acceptable. You may use an in-vitro method which provides consistent and reliable endotoxin detection in lieu of the Limulus Amoebocyte Lysate bacterial endotoxin test. In addition, endotoxin contamination may be mitigated with a robust microbial control and sterility assurance strategy.. The Agency will waive the rabbit pyrogen testing for commercial brolocizumab release testing.*

9. In the original BLA for brolocizumab, Novartis intends to replace the ELISA potency method with the cell based HUVEC potency method and remove the (b) (4) parameter from the specifications.

Does the Agency agree that:

- a. The data presented in this briefing book demonstrate the equivalence of the ELISA and the cell-based (HUVEC) methods to adequately control the potency of brolocizumab and thus support the use of the HUVEC method as the only potency method for release and stability testing of drug substance and drug product.

*FDA Comments: We agree.*

- b. The strategy presented in the briefing book does support the removal of the (b) (4) parameter for drug substance release testing.

*FDA Comments: We agree with your proposal to include data on (b) (4) in your upcoming BLA submission. The removal of the (b) (4) will be a review decision.*

#### Regulatory/Other Questions

10. Does the Agency agree with the proposed plan regarding the safety update report?

- a. Does the Agency agree with the proposed timing and content of the safety update?

*FDA Comments: Yes. Submission of the Safety Update at 90 days is acceptable.*

- b. Does the Agency agree that this would not trigger a new review cycle or extend the initial review cycle?

*FDA Comments: Submission of the required safety update does not in itself trigger the extension of the initial review cycle.*

11. Does the Agency agree with the proposal for the submission of financial disclosure?

*FDA Comments: Yes, it is acceptable.*

12. Does Agency agree there is no need to conduct an environmental risk assessment (ERA) for brolocizumab?

*FDA Comments: We agree.*

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/s/  
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MICHAEL J PUGLISI  
05/15/2018



IND 112023

**MEETING MINUTES**

Alcon Research, Ltd.  
Attention: Paul Nitschmann, MD  
Head, Regulatory Affairs Pharmaceuticals  
6201 South Freeway  
Fort Worth, TX 76134-2099

Dear Dr. Nitschmann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ESBA1008.

We also refer to the meeting between representatives of your firm and the FDA on May 8, 2013. The purpose of the meeting was to discuss the development program for ESBA1008.

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 Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, MD  
Deputy Director  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure: Minutes of the meeting



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** End-of-Phase 2

**Meeting Date and Time:** May 8, 2013, 1:00-2:00 PM  
**Meeting Location:** FDA, White Oak Campus  
10903 New Hampshire Avenue  
Building 22, Conference Room # 1309  
Silver Spring, MD 20993

**Application Number:** IND 112023  
**Product Name:** ESBA1008  
**Indication:** Treatment of exudative age-related macular degeneration (AMD)  
**Sponsor/Applicant Name:** Alcon Research, Ltd.

**Meeting Chair:** Wiley A. Chambers, MD  
**Meeting Recorder:** Judit Milstein

**FDA ATTENDEES**

Renata Albrecht, Director, Division of Transplant and Ophthalmology Products  
Wiley A. Chambers, Deputy Director  
William M. Boyd, Clinical Team Leader  
Rhea Lloyd, Clinical Reviewer  
Lucious Lim, Clinical Reviewer  
Jennifer Harris, Clinical Reviewer  
Martin Nevitt, Clinical Reviewer  
Sonal Wadhwa, Clinical Reviewer  
Dongliang Zhuang, Biometrics Reviewer (on the phone)  
Yan Wang, Biometrics Team Leader  
Chikako Torigoe, Product Quality Reviewer  
Laurie Graham, Product Quality Team Leader  
Yoriko Harigaya, Clinical Pharmacology Reviewer  
Philip Colangelo, Clinical Pharmacology Team Leader  
Andrew McDougal, Pharmacology/Toxicology Reviewer  
Kassa Ayalew, Reviewer, Office of Scientific Investigations

**SPONSOR ATTENDEES**

Robert Kim, Head, R&D Pharmaceutical, Alcon Research, Ltd.  
Kerry Markwardt, Project Head  
Paul Nitschmann, Regulatory Affairs

Andreas Wenzel, Clinical (on the phone)  
Andreas Weischelberger, Statistics (on the phone)

## BACKGROUND

ESBA-1008, a humanized single-chain antibody fragment inhibiting vascular endothelia growth factor-A (VEGF-A0 is being developed for the treatment of choroidal neovascularization associated with exudative (wet) age-related macular degeneration (AMD).

The sponsor conducted Clinical Study C-10-083 to investigate the safety and tolerability of ESBA-1008 in patients with exudative AMD in 4 ascending clinical doses of 0.5mg, 3 mg, 4.5 mg and 6 mg with a planned expansion of the cohorts with the highest tolerated dose to compare the efficacy and duration of action of ESBA1008 versus Lucentis.

Data from preliminary interim analysis indicate that the study met its primary efficacy endpoint of non-inferiority vs. Lucentis in the change from baseline to Month 6 in central subfield (CSF) thickness of the retina. The sponsor believes that ESBA1008, 6 mg may have the potential to demonstrate superiority efficacy and extended duration of effect in comparison to Lucentis.

The sponsor submitted a briefing document on April 4, 2013. Preliminary responses to the questions posted in the briefing document were sent on April 30, 2013.

## DISCUSSION

For the purpose of these minutes, the questions posted by the sponsor in their briefing document are in **bold** format, the preliminary responses are in *italics* and the discussion during the meeting are in normal font.

## Quality Questions

### Question 1:

**All Phase III clinical trials will be carried out using drug product manufactured with drug substance produced by (b) (4), which is the same as that intended for commercial distribution. Alcon plans to conduct a CMC comparability assessment of drug product manufactured from (b) (4) and (b) (4) drug substance. Alcon plans to provide the CMC comparability assessment with the IND amendment for Phase III clinical studies. Therefore, Alcon will not be submitting a CMC comparability assessment protocol to the agency prior to the IND amendment for Phase III. Does the Agency agree?**

*Agency Response: No. Insufficient information has been provided in the meeting package to make an assessment of the comparability of DS manufactured by (b) (4) and (b) (4). The comparability results should be submitted prior to clinical use of DP manufactured with DS from (b) (4). The comparability assessment should be performed per ICH Q5E. It is recommended that the assessment include release, in-process, characterization and stability testing. Stability testing should include accelerated and stressed conditions with a comparison of the degradation profiles of the materials manufactured by different processes. It is recommended that comparability assessments be performed for both DS and DP.*

Meeting Discussion: The Sponsor stated that they understood the drug substance and drug product testing as recommended by the Division and asked if it was acceptable to submit the results in the IND amendment for the Phase 3 studies. The Division agreed but recommended that the sponsor submit the information with sufficient time for the Agency to review the data.

**Question 2:**

**Are the proposed test and specifications for ESBA1008 Drug Substance (ESBA1008 Drug Substance Solution, 127 mg/mL) acceptable for Phase III clinical studies?**

Agency Response: *No, we have the following recommendations with regard to drug substance specifications:*

- a. *The current potency specification (b) (4) is too broad and should be narrowed. Revise the specification or provide a justification to support the current range.*
- b. *A non-reduced SDS assay should be included in both release and stability testing.*
- c. *It is recommended that consideration be given to using release and stability acceptance criteria in SDS assays that can control the presence of new size variants, such as 'conforms to reference'.*
- d. *The levels of charge variants (percentage of main, acidic, basic forms) should be reported in release tests and stability studies. For licensure, the activity of charge variants will need to be determined and variants with activity different from that of the main isoform will need to be controlled with quantitative acceptance criteria. Until these quantitative acceptance criteria can be established, it is recommended that consideration be given to using release and stability acceptance criteria that can control the presence of new charge variants, such as 'conforms to reference'.*
- e. *Release and stability testing will need to include acceptance criteria for product related impurities such as the percentage of higher and lower molecular weight species, if applicable. Until acceptance criteria are established, impurity levels for the SEC-HPLC and/or the SDS assays should be included on the certificate of analysis.*
- f. *There are different SDS-based and charge assays being used for release and stability testing. Provide clarification. It is recommended that release and stability specifications use the same methods. If methodologies are being updated, it is recommended that current and proposed methods be used concurrently to generate sufficient data to support the proposed methods.*
- g. *A visible particulate test with appropriate acceptance criteria should be incorporated into release and stability programs. Updated specifications should be submitted to the IND.*

Meeting Discussion: None

**Question 3:**

**Are the proposed test and specifications for the Drug Product (ESBA1008 Solution for Intravitreal Injection, 120 mg/mL) acceptable for Phase III clinical studies?**

Agency Response: No. See a-f under Question 2. In addition, the following should be addressed:

- a. For licensure, sub-visible particle levels will need to meet USP <789> recommended limits at release and during the proposed shelf-life of the product.
- b. It is noted that DS release and stability testing includes SEC-HPLC purity criteria of (b)(4)% monomer while the release and stability criteria of DP are (b)(4)% monomer. Provide clarification. It is recommended that the SEC-HPLC monomer criteria for DP release and stability testing be tightened.
- c. Provide clarification on when sterility testing is being performed in the drug product stability protocol. It is recommended that sterility be monitored at regular time intervals (i.e., on an annual basis). Alternatively, container/closure integrity can be monitored at regular intervals and sterility testing performed at the end of the shelf-life.
- d. Provide information that indicates that the intended fill volume meets USP <1151> expectations in regard to overfill volumes. With small volume presentations, fill volumes generally do not exceed (b)(4)% of the labeled product size.
- e. DS and DP specifications do not include the use of the same charge and size based assays. Provide clarification. It is recommended that DS and DP specifications include the use of the same assays.

Meeting Discussion: None

**Preclinical Questions**

**Question 4:**

**In accordance with the ICH S6(R1) guidance, ocular and systemic toxicity of ESBA1008 will be evaluated following intravitreal (IVT) delivery, the intended clinical route of administration, for up to 6 months in duration. Separate intravenous (IV) studies will not be conducted since the systemic exposure following IVT delivery is at least 20 fold lower in humans than the exposure observed in monkeys and the systemic effects of VEGF inhibitors are well known. Additionally, only a single species, cynomolgus monkeys, will be used since monkeys are the most relevant species in which IVT tolerability can be accurately assessed. Does the Agency agree?**

Agency Response: Based on the systemic concentrations reported for trial C-10-083, the Agency concurs that IV toxicology studies are not warranted to support the dose and formulation tested in trial C-10-083.

*FDA concurs that the use of a single relevant non-rodent animal model is acceptable. The scientific basis for considering the cynomolgus monkey to be a pharmacologically relevant model for ESBA1008 however was not located (e.g. comparative binding/functional data, VEGF sequence homology). Please indicate where in the IND this information is located or provide the justification to the IND.*

Meeting Discussion: None

**Question 5:**

**In scaling up for the Confirmatory clinical trials and commercialization, Alcon is optimizing the manufacturing process and transferring it from (b) (4) to (b) (4). All Phase III clinical trials will be carried out with the (b) (4) product, which will be the commercial product. Alcon proposes to conduct a 3 month toxicology study in cynomolgus monkeys to bridge the safety of the (b) (4) product to the previously generated safety data with the (b) (4) product. Does the agency agree?**

Agency Response: *Yes, presuming that Phase 3 dose will be tested.*

Meeting Discussion: None

**Question 6:**

**In accordance with the ICH S6(R1) guidance, standard carcinogenicity, fertility and reproductive/developmental toxicity studies may not be necessary for biotechnology-derived pharmaceuticals. The effects of VEGF inhibitors on carcinogenicity, fertility and reproductive/developmental toxicity are well-known, the systemic exposure of ESBA1008 following intravitreal administration is extremely low, and the intended patient population affected by Age-Related Macular Degeneration (AMD) is  $\geq 50$  years old. Therefore, Alcon is seeking agreement not to conduct these studies. Does the agency agree?**

Agency Response: *Testing for mutagenicity and carcinogenicity are not required for ESBA1008. For the range of systemic exposures reported for trial C-10-083, nonclinical studies to investigate reproductive and developmental toxicity would not be warranted. Please be aware that FDA may require testing to support higher systemic exposure.*

Meeting Discussion: None

**Question 7:**

**Alcon proposes to provide pharmacokinetic estimates of systemic exposure to ESBA1008 but proposes not to assess metabolism, excretion, or systemic tissue distribution. Does the Agency agree?**

Agency Response: *FDA concurs that additional testing is not needed to address these topics. In the BLA, provide evaluations of ESBA1008 metabolism, excretion, and systemic distribution based on available information (e.g. original studies, public information about VEGF).*

Meeting Discussion: None

## Clinical Questions

### Question 8:

**Based upon results from C-10-083 and nonclinical data, Alcon's position is that the most effective dose of ESBA1008 has been identified, and data presented in this briefing packet will justify administration of a 6 mg dose in the confirmatory clinical trials. Alcon does not plan to test additional doses, but will test multiple regimens using ESBA1008 in patients with wet AMD. Does the Agency agree?**

*Agency Response: Disagree. Since changes in macular thickness have not been demonstrated to correlate with changes in visual function (i.e., visual acuity), the Agency is uncertain if the most effective dose has been identified. Additionally, the clinical significance of a given magnitude change in macular thickness has not been established. The Agency recommends that demonstration of efficacy include evidence of statistical significance and clinical relevance. Statistically significant differences in visual function (e.g., visual acuity, visual field, etc.) at more than one time point are recommended. In order to determine the most effective dose, it is recommended that dose-ranging studies be conducted using a more appropriate endpoint.*

Meeting Discussion: The sponsor stated that they have selected the 6 mg dose, primarily based on VA outcomes in trial C-10-083. It was noted that ESBA1008 can not be formulated at a higher concentration than 6 mg/mL.

The Division clarified that the primary concern with regard to the dose selection is the time point at which efficacy endpoint was assessed, Day 28. Prior studies in AMD suggest that VA data prior to 9 months is not always predictive of the response after 9 months. For this reason, the Division stated that the presented data were insufficient to select a dose moving forward. The recommendation was to study at least two doses (i.e., 6 mg/mL and < 6mg/mL) for at least 9-months in order to select a dose to study in Phase 3.

### Question 9:

**In Ph 3 trials, Alcon is planning to evaluate an individualized regimen (Treat and Extend) in order to optimize the benefit/risk ratio of anti-VEGF treatments. In addition, Alcon wants to evaluate a fixed q8 week regimen. Therefore, Alcon proposes to conduct two confirmatory clinical trials in wet AMD patients, one comparing ESBA1008 given bi-monthly versus EYLEA given bi-monthly, and one comparing ESBA1008 Treat and Extend versus LUCENTIS given monthly. Does the Agency agree that these two studies will support an indication for "the treatment of patients with neovascular (wet) age-related macular degeneration"?**

*Agency Response: Only protocol design overviews are presented in the briefing package for review. The design concept of Study 1 is acceptable. The design concept of Study 2 is potentially acceptable if specific, pre-specified criteria to confirm stability and to recommend re-treatment are agreed upon. Both studies could support an BLA submission for the treatment of*

*patients with neovascular (wet) age-related macular degeneration, but due to potential variability among patients, the treat and extend regimen is not recommended at this time.*

Meeting Discussion: The sponsor stated that they agree with the Division that variability among patients regarding treatment need is a critical element in the identification of adequate treatment regimens. The sponsor's opinion was that a Treat and Extend regimen as proposed in the briefing document, with specific stability and retreatment criteria (BP, page 17) is adequate. The sponsor further stated that due to its prophylactic / pro-active treatment schedule, they consider this approach superior to a PRN approach and therefore, questioned why the Agency recommends not pursuing this approach at this time.

The Division stated that no non-fixed regimen has been shown to be more efficacious than a fixed dosing regimen. The Division agreed that fixed regimens are not a guarantee of optimal dosing. The Division noted that current diagnostic tools do not appear to have the required sensitivity and do not track with disease progression well enough to adequately guide retreatment decisions. The Division, however, stated that non-fixed regimens might be approved if the data were supportive. Post-Marketing Studies would likely be required to answer open questions if data fails to demonstrate that the non-fixed regimen is at least noninferior to the fixed regimen.

**Question 10:**

**For the primary endpoint analysis in support of efficacy, Alcon proposes to** (b) (4)

**Does the Agency agree?**

Agency Response: Disagree. (b) (4) is unlikely to support an application. We recommend the change from baseline in distance BCVA at Month 12 as the primary efficacy endpoint.

Meeting Discussion: Alcon stated that they understood the Agency's concern with (b) (4)

They then asked if the Division would be willing to consider (b) (4)

The Division stated that (b) (4)

Therefore, the Sponsor's proposal (b) (4) is not acceptable as primary efficacy endpoint.

The Division stated that while the sponsor might chose (b) (4) for their analysis, the Agency would not use that primary endpoint its analysis. The determination of efficacy and, therefore, approvability would be based on the Agency's analysis of the data and not the sponsor's one.

**Question 11:**

**Alcon is proposing to assess noninferiority regarding the BCVA outcome with a noninferiority margin of (b) (4) when comparing against monthly LUCENTIS. Does the Agency agree?**

*Agency Response: Disagree. The proposed clinical study design in the protocol synopsis submitted is not acceptable. The studies should include at least 9 months of treatment and should be powered to demonstrate that the 95% confidence interval (two sided) of the treatment difference in mean visual acuity is within 3-4 letters. Additional comments may be forthcoming when the final protocol is submitted.*

Meeting Discussion: The sponsor inquired as to why the decision of the 3-4 letters difference in mean visual acuity is necessary for the non-inferiority determination. The Division responded that these numbers were based on external feedback from the clinical community, as (b) (4), the Division selected 3-4 letters as an acceptable non-inferiority margin.

The sponsor requested clarification that the NDA could be submitted with 9-months data. The Division stated that they would accept 9 months safety and efficacy data but that data on 2 years treatment would be eventually expected in follow-up on the safety of the product. This longer term data could be submitted post-approval.

**Question 12:**

**Alcon is proposing that (b) (4) would be included in the package insert. Does the Agency agree?**

*Agency Response: Disagree. (b) (4)*

Meeting Discussion: The sponsor stated that (b) (4)

The Division responded that statistical significance was essential and that a change  $\geq 15$  letters would be considered clinically meaningful. The Division further clarified that a risk/benefit assessment on the totality of the data is taken into consideration on the changes  $< 15$  letters, and that this determination cannot be made before running the trial.

The Division also stated that treatment burden, e.g. intravitreal injection frequency is not in itself a factor considered in the risk/benefit analysis, but rather that the incidence of adverse events associated with these injections could be taken in to consideration for that analysis.

The sponsor also inquired as to whether two trials of different design and control arms are acceptable for demonstrating non-inferiority. The Division responded that for the demonstration of non-inferiority and even superiority, the study designs do not need to be identical but rather need to lead to the same conclusion. The Division also clarified that class statements may be considered when at least 3 or more members of a class have been compared with the test article with the same outcomes.

**Question 13:**

**Alcon believes that assessor masking is sufficient to ensure integrity of the primary efficacy endpoint and that sham injections are not needed. Does the Agency agree?**

*Agency Response: Disagree. Adequate and well controlled studies are expected to include adequate measures to minimize bias on the part of the subjects, observers, and analysts of the data. We agree that sham injections are not the best method to minimize bias.*

Meeting Discussion: The sponsor inquired as to whether sham injections, as done in other studies (i.e., only an anesthetic injection), was adequate. The Division responded that sham injections do not provide optimal masking, but if an anesthetic is given and the sham procedure includes pressure on the eye with the hub of a needle, then the masking might be adequate.

**Question 14:**

**Alcon proposes to submit the NDA with 12 months clinical data from 2 Ph 3 studies and submit longer term (24 month) safety data from 1 study during the review period. Does the Agency agree?**

*Agency Response: Agree. The proposed timeline is acceptable, only 12 month data is necessary for the review of the initial application. Twenty-four month data from both trials should be submitted when available however, unless the 24 month data is part of the initial submission it is unlikely to be included in the initial review.*

Meeting Discussion: See response to Question 11. The Division confirmed that at least 9 month data (12-months data preferred) are necessary for filing, and that the 24-month data can be submitted post approval.

The Sponsor also requested clarification as to the required number of patients for measuring anti-drug antibodies during the Phase 3 studies. The Division stated that all patients in all trials should be included and that this information can be obtained from Phase 2 or Phase 3 studies. The Division also recommended that in the first year this measurement be performed quarterly and afterwards every 6 months.

**Question 15:**

**Alcon's position is that the data from the Ph 2 clinical trial C-10-083 is adequate to describe the pharmacokinetics of ESBA 1008. Does the Agency agree?**

*Agency Response: Yes, we agree as long as the PK data generated from this study is with the final clinical dose (6 mg) to be taken into Phase 3 trials and is with the final to-be-marketed formulation of ESBA 1008.*

Meeting Discussion: None

## **Regulatory Questions**

### **Question 16:**

**Based on the indication being pursued, the target population, and other class approved drugs, Alcon plans to request a pediatric waiver. Does the Agency agree?**

*Agency Response: Agree that a pediatric waiver is appropriate for this indication. A Pediatric Study Plan should be submitted within 60 days of this meeting.*

Meeting Discussion: None

## **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 a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).

## **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>

## **ISSUES REQUIRING FURTHER DISCUSSION**

None

## **ACTION ITEMS**

Minutes will be issued within 30 days.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WILEY A CHAMBERS  
06/07/2013