# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761125Orig1s000

# PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

# LABELS AND LABELING ASSESSMENT

| | |
|---|---|
| Date of Assessment: | September 27, 2019 |
| Assessor: | Vicky Borders-Hemphill, PharmD<br>Labeling Assessor<br>Office of Biotechnology Products (OBP) |
| Through: | Brian Roelofs, PhD, Product Quality Assessor<br>OBP/Division of Biotechnology Review and Research II |
| Application: | BLA 761125 |
| Applicant: | Novartis Pharmaceuticals Corporation |
| Submission Date: | February 7, 2019 |
| Product: | Beovu (brolucizumab-dbll) |
| Dosage form(s): | Injection |
| Strength and Container-Closure: | 6 mg/0.05 mL in a single-dose vial |
| Purpose of assessment: | The Applicant submitted a biologics license application for Agency review |
| **Recommendations:** | The prescribing information (submitted on September 25, 2019), and container labels and carton labeling (submitted on September 18, 2019) are acceptable from an OBP labeling perspective. |

| Materials Considered for this Label and Labeling Assessment | |
|---|---|
| **Materials Assessed** | **Appendix Section** |
| Proposed Labels and Labeling | A |
| Evaluation Tables | B |
| Acceptable Labels and Labeling | C |

n/a = not applicable for this review

## DISCUSSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B).

## CONCLUSION

The prescribing information (submitted on September 25, 2019), and container labels and carton labeling (submitted on September 18, 2019) are acceptable from an OBP labeling perspective. (see Appendix C)

## APPENDICES

**Appendix A**: Proposed Labeling

Prescribing Information (submitted on February 7, 2019
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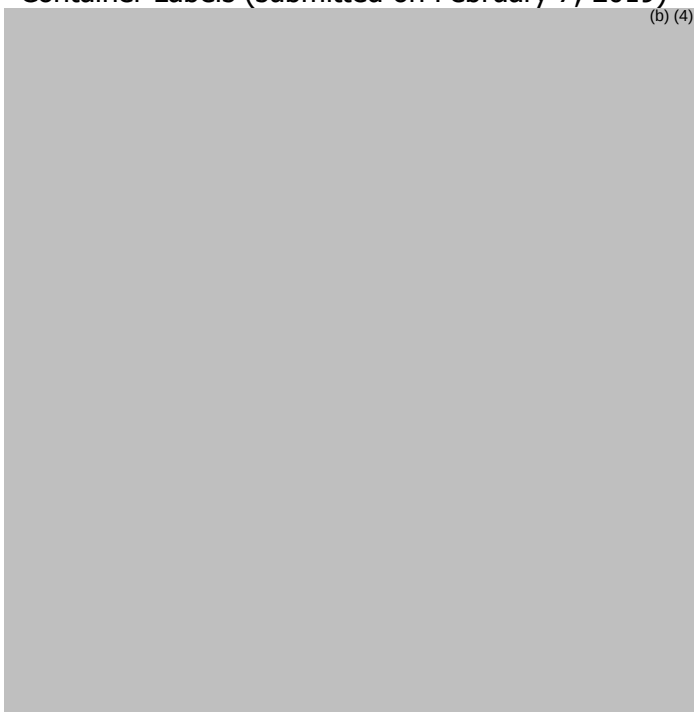
Container Labels (submitted on February 7, 2019)

(b) (4)





2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

**Appendix B**: Evaluation Tables
**Evaluation Tables:** Label[1,2] and Labeling[3] Standards

**Container[4] Label Evaluation**

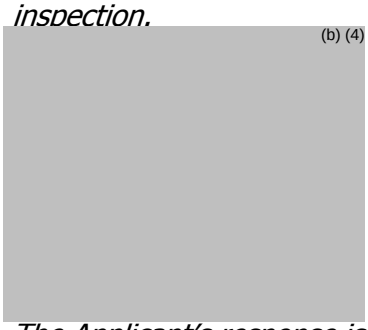
| **Proper Name** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (placement of dosage form below the proper name)* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Manufacturer name, address, and license number** | **Acceptable** |
| Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (using the qualifying phrase "Manufactured by:")* | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (U.S license number for container bearing a partial label)* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Lot number or other lot identification** | **Acceptable** |
| Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii) | ✓ Yes<br>☐ No<br>☐ N/A |
| **Expiration date** | **Acceptable** |
| Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: USP General Chapters <7> Labeling*<br>*Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Beyond Use Date (Multiple-dose containers)** | **Acceptable** |
| *Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling* | ☐ Yes |

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

| | |
|---|---|
| | ☐ No<br>☒ N/A |
| **Product Strength** | **Acceptable** |
| Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Multiple-dose containers** *(recommended individual dose)* | **Acceptable** |
| Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 | ☐ Yes<br>☐ No<br>☒ N/A |
| **Statement: "Rx only"** | **Acceptable** |
| Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Medication Guide** | **Acceptable** |
| Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d) | ☐ Yes<br>☐ No<br>☒ N/A |
| **No Package for container** | **Acceptable** |
| Regulation: 21 CFR 610.60(b) | ☐ Yes<br>☐ No<br>☒ N/A |
| **No container label** | **Acceptable** |
| Regulation: 21 CFR 610.60(d) | ☐ Yes<br>☐ No<br>☒ N/A |
| **Ferrule and cap overseal** *(for vials only)* | **Acceptable** |
| *Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Comment/Recommendation:** Confirm there is no text on the ferrule and cap overseal of the vials.<br>*Applicant's response: Confirmed. There is no text on the ferrule and cap overseal of the vials. The Applicant's response is acceptable* | |
| **Visual inspection** | **Acceptable** |
| Regulation: 21 CFR 610.60(e) | ✓ Yes |

| | |
|---|---|
| | ☐ No<br>☐ N/A |

**Comment/Recommendation:** Confirm that sufficient area of the container remains uncovered for its full length to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located
*Applicant's response: Confirmed. There is sufficient space on the vial to conduct a visual inspection of the product after the label is affixed.* (b) (4) *Below is a photo that shows there is sufficient space for a visual inspection.*




*The Applicant's response is acceptable*

| ***NDC numbers*** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 201.2, 21 CFR 207.35 | ✓ Yes<br>☐ No<br>☐ N/A |
| **Route of administration** | **Acceptable** |
| Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Preparation instructions** | **Acceptable** |
| Regulation: 21 CFR 201.5(g) | ☐ Yes<br>☐ No<br>☒ N/A |
| *Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic* | ☐ Yes<br>☐ No<br>☒ N/A |
| **Package type term** | **Acceptable** |
| *Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)*<br>*USP chapter <659> Packaging and Storage Requirements* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Misleading statements** | **Acceptable** |
| Regulation: 21 CFR 201.6 | ☐ Yes<br>☐ No |

| | |
|---|---|
| | ☒ N/A |
| **Prominence of required label statements** | **Acceptable** |
| Regulation: 21 CFR 201.15 | ✓ Yes<br>☐ No<br>☐ N/A |
| **Spanish-language (Drugs)** | **Acceptable** |
| Regulation: 21 CFR 201.16 | ☐ Yes<br>☐ No<br>☒ N/A |
| **FD&C Yellow No. 5 and/or FD&C Yellow No. 6** | **Acceptable** |
| Regulation: 21 CFR 201.20 | ☐ Yes<br>☐ No<br>☒ N/A |
| **Bar code label requirements** | **Acceptable** |
| Regulations: 21 CFR 201.25, 21 CFR 610.67 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011*<br>*Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)** | **Acceptable** |
| Regulations: 21 CFR 610.68, 21 CFR 201.26 | ☐ Yes<br>☐ No<br>☒ N/A |
| **Net quantity** | **Acceptable** |
| Regulation: 21 CFR 201.51 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic*<br>*Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)*<br>*USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Statement of Dosage** | **Acceptable** |
| Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2) | ☐ Yes<br>☐ No<br>☒ N/A |
| **Comment/Recommendation:** *see carton* | |

| **Inactive ingredients** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.100 | ☐ Yes<br>☐ No<br>☒ N/A |
| **Comment/Recommendation:** *see carton* | |
| *Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling* | ☐ Yes<br>☐ No<br>☒ N/A |
| **Storage requirements** | **Acceptable** |
| *Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements* | ☐ Yes<br>☐ No<br>☒ N/A |
| **Comment/Recommendation:** *see carton* | |
| **Dispensing container** | **Acceptable** |
| Regulation: 21 CFR 201.100(b)(7) | ☐ Yes<br>☐ No<br>☒ N/A |

## Package[5] Label Evaluation

| **Proper name** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2) | ✓ Yes<br>☐ No<br>☐ N/A |
| **Manufacturer name, address, and license number** | **Acceptable** |
| Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (using the qualifying phrase "Manufactured by:")* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Lot number or other lot identification** | **Acceptable** |
| Regulation: 21 CFR 610.61(c) | ✓ Yes<br>☐ No<br>☐ N/A |
| **Expiration date** | **Acceptable** |
| Regulations: 21 CFR 610.61(d), 21 CFR 201.17 | ✓ Yes<br>☐ No<br>☐ N/A |
| **Beyond Use Date (Multiple-dose containers)** | **Acceptable** |

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

| | |
|---|---|
| *Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling* | ☐ Yes<br>☐ No<br>☒ N/A |
| **Preservative** | **Acceptable** |
| Regulation: 21 CFR 610.61(e) | ✓ Yes<br>☐ No<br>☐ N/A |
| **Number of containers** | **Acceptable** |
| Regulation: 21 CFR 610.61(f) | ✓ Yes<br>☐ No<br>☐ N/A |
| **Product Strength** | **Acceptable** |
| Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Storage temperature/requirements** | **Acceptable** |
| Regulation: 21 CFR 610.61(h) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Consider adding the alternative storage information to the carton labeling: "Prior to use, the unopened TRADENAME vial may be kept at room temperature below 25°C (77°F) for up to 24 hours."
*Applicant's response: Sponsor agrees to add to carton and the language has been aligned with the same sentence is now in the carton: "Prior to use, the unopened glass vial of BEOVU may be kept at room temperature, 20°C to 25°C (68°F to 77°F) for up to 24 hours."*
*The Applicant's response is acceptable*

| | |
|---|---|
| **Handling: "Do Not Shake", "Do not Freeze" or equivalent** | **Acceptable** |
| Regulation: 21 CFR 610.61(i) | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Add additional handling instructions of "Do Not Shake" to the carton labeling
*Applicant's response: As noted for the Prescribing Information, all of the product storage and handling instructions have been included based on our drug product stability data and the results are summarized in section 3.2.P.8.1. Based on the product stability data, there are no concerns specifically noted or as a result of shaking the final drug product. Therefore, the Sponsor proposes to not include the phrase "Do not Shake".*

*FDA response: Per the product quality reviewer, Based on OBP's assessment of the total data provided in the submission and the IR response (received September 26, 2019), we believe the risk to product quality is minimal. The sponsor's proposal to keep "Do not Shake" off of the carton container and PI labels is acceptable.*

| **Multiple dose containers (recommended individual dose)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.61(j) | ☐ Yes<br>☐ No<br>☒ N/A |

| **Route of administration** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Consider adding the route of administration to appear after the strength statement wherever the names, dosage forms, and strength appear together.
*The Applicant revised as requested*

| **Known sensitizing substances** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber) | ☐ Yes<br>☐ No<br>☒ N/A |

| **Inactive ingredients** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61, 21 CFR 201.100 | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Revise the presentation of the inactive ingredient to appear in alphabetical order, to differentiate the active ingredient from the inactive ingredients, and to be consistent with the prescribing information from (b) (4) to read as follows: "Each vial is designed to deliver 0.05 mL of solution containing 6 mg brolucizumab-xxxx, polysorbate 80 (0.02%), sodium citrate (10 mM), sucrose (5.8%), and Water for Injection, USP"
*The Applicant revised as requested adding the four-letter suffix*

| | |
|---|---|
| *Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

| **Source of the product** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.61(p) | ☐ Yes<br>☐ No<br>☒ N/A |

| **Minimum potency of product** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.61(r) | ✓ Yes<br>☐ No |

| | |
|---|---|
| | ☐ N/A |
| **Rx only** | **Acceptable** |
| Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Divided manufacturing** | **Acceptable** |
| Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) | ☐ Yes<br>☐ No<br>☒ N/A |
| **Distributor** | **Acceptable** |
| Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5) | ✓ Yes<br>☐ No<br>☐ N/A |
| **Bar code** | **Acceptable** |
| Regulations: 21 CFR 610.67, 21 CFR 201.25 | ✓ Yes<br>☐ No<br>☐ N/A |
| Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011*<br>*Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)** | **Acceptable** |
| Regulations: 21 CFR 610.68, 21 CFR 201.26 | ☐ Yes<br>☐ No<br>☒ N/A |
| **NDC numbers** | **Acceptable** |
| Regulations: 21 CFR 201.2, 21 CFR 207.35 | ✓ Yes<br>☐ No<br>☐ N/A |
| **Preparation instructions** | **Acceptable** |
| Regulation: 21 CFR 201.5(g) | ☐ Yes<br>☐ No<br>☒ N/A |
| *Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic*<br>*USP General Chapters <7> Labeling* | ☐ Yes<br>☐ No<br>☒ N/A |
| **Package type term** | **Acceptable** |

| | |
|---|---|
| *Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)*<br>*USP chapter <659> Packaging and Storage Requirements* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Comment/Recommendation:** Add the statement "Discard unused portion." to appear after the package type term "single dose vial;"<br>*Applicant's response: This statement is already on back panel and the Sponsor agrees to add to main display panel with increased prominence. Side and top panels would be cluttered and possibly be illegible with this additional text.*<br>*The Applicant's response is acceptable* | |
| **Misleading statements** | **Acceptable** |
| Regulation: 21 CFR 201.6 | ☐ Yes<br>☐ No<br>☒ N/A |
| **Prominence of required label statements** | **Acceptable** |
| Regulation: 21 CFR 201.15 | ✓ Yes<br>☐ No<br>☐ N/A |
| **Spanish-language (Drugs)** | **Acceptable** |
| Regulation: 21 CFR 201.16 | ☐ Yes<br>☐ No<br>☒ N/A |
| **FD&C Yellow No. 5 and/or FD&C Yellow No. 6** | **Acceptable** |
| Regulation: 21 CFR 201.20 | ☐ Yes<br>☐ No<br>☒ N/A |
| **Phenylalanine as a component of aspartame** | **Acceptable** |
| Regulation: 21 CFR 201.21(c) | ☐ Yes<br>☐ No<br>☒ N/A |
| **Sulfites; required warning statements** | **Acceptable** |
| Regulation: 21 CFR 201.22(b) | ☐ Yes<br>☐ No<br>☒ N/A |
| **Net quantity** | **Acceptable** |
| Regulation: 21 CFR 201.51 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic*<br>*Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* | ✓ Yes<br>☐ No<br>☐ N/A |

| | |
|---|---|
| *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).* | |
| **Statement of Dosage** | **Acceptable** |
| Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2) | ✓ Yes<br>☐ No<br>☐ N/A |
| **Comment/Recommendation:** Consider revising the statement of dosage from (b) (4) to read as follows: "Dosage: See Prescribing Information"<br>*The Applicant revised as requested* | |
| **Dispensing container** | **Acceptable** |
| Regulation: 21 CFR 201.100(b)(7) | ☐ Yes<br>☐ No<br>☒ N/A |
| **Medication Guide** | **Acceptable** |
| Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d) | ☐ Yes<br>☐ No<br>☒ N/A |

## Prescribing Information and Patient Labeling Evaluation

**PRESCRIBING INFORMATION**

| **Highlights of Prescribing Information** | |
|---|---|
| **PRODUCT TITLE** | **Acceptable** |
| Regulation: 21 CFR 201.57(a)(2) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic* | ✓ Yes<br>☐ No<br>☐ N/A |
| **Comment/Recommendation:**<br>The proper names of biological products typically do not include a route of administration or dosage form. Therefore, the route of administration and/or dosage form should not be located inside the parentheses. Thus, the dosage form was relocated to appear outside of the parenthesis<br>*The Applicant revised as requested*<br><br>The route of administration (ROA) in the product title, "for intravitreal injection", was revised to "for intravitreal use" for consistent approach to labeling across FDA approved products. When the ROA does not precede the dosage form, the ROA is presented as "for [insert ROA] use" at the end of the product title, preceded by a comma (see Draft Guidance for Industry: Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products – Content and Format). | |

*This recommendation was not implemented because this proposed revision was not provided to the applicant by DTOP because the term "use" is too vague and "injection" is a better term. OBP labeling defers to the division although this is not a consistent approach to labeling of products in the class or most FDA approved products.*

Once the four-letter suffix has been approved, apply to the four-letter suffix to the proper name throughout all labels and labeling
*The Applicant revised as requested*

| **DOSAGE AND ADMINISTRATION** | **Acceptable** |
|---|---|
| *Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions* | ☐ Yes<br>☐ No<br>☒ N/A |

| **DOSAGE FORMS AND STRENGTHS** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100 | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Dosage form was added per 21 CFR 201.57(a)(8)
*The Applicant revised as requested*

| | |
|---|---|
| *Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)*<br>*USP chapter <659> Packaging and Storage Requirements*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:**

The strength presentation was revised. For single-dose and multiple-dose injectable drug products with containers that supply a volume of drug less than 1 mL: The only expression of strength should be strength per fraction of mL. For example: 6 mg/0.05 mL. (See USP General Chapters: <7> Labeling).
*The Applicant revised as requested*

**Full Prescribing Information**

| **2 DOSAGE AND ADMINISTRATION** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.57(c)(3)(iv) | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Deleted the redundant information ("TRADENAME kit includes…vial and filter needle") already provided in section 2.3 and added to section 16.
*The Applicant revised as requested*

OBP labeling recommends that the storage requirements and alternative storage information for the supplied product be only included in the required section 16 (How Supplied Storage and Handling)
*This recommendation was not implemented because this proposed revision was not provided to the applicant by DTOP because of the division's preference to maintain this information in this*

*section of labeling. OBP labeling defers to DTOP and this section of the labeling meets the requirements set forth in 21 CFR 201.57(c)(3)(iv).*

OBP labeling recommends that the identifying characteristics of the supplied product be only included in required section 3 (dosage forms and strengths)
*This recommendation was not implemented because this proposed revision was not provided to the applicant by DTOP because of the division's preference to maintain this information in this section of labeling. OBP labeling defers to DTOP.*

OBP labeling notes that this instruction to visually inspect is also provided in section 2.4 and recommends to delete from section 2.3 to reduce redundancy. *The redundant statement was removed from section 2.4 and maintained in section 2.3. OBP labeling finds this acceptable.*

| | |
|---|---|
| *Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products* | ☐ Yes<br>☐ No<br>☒ N/A |
| **3 DOSAGE FORMS AND STRENGTHS** | **Acceptable** |
| Regulation: 21 CFR 201.57(c)(4) | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** the dosage form and identifying characteristics of the dosage form have been added per 21 CFR 201.57(c)(4).
*The Applicant has applied a dosage form and the identifying characteristics, and this conforms to the regulatory requirement.*

| | |
|---|---|
| *Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)*<br>*USP chapter <659> Packaging and Storage Requirements*<br>*USP General Chapters: <7> Labeling*<br><br>*USP General Chapters <771> which refers to <1151> which then refers to <1121> for the dosage form nomenclature* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** *DTOP preferred that the dosage form for section 3 be "Intravitreal injection" because DTOP determined that it is critically important to identify this as an intravitreal injection. At the internal labeling meeting, OBP Labeling recommended to DTOP that the dosage form remain "Injection" as this is standard nomenclature for FDA approved labeling of products in solution that will be injected (See the labeling review tool (http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/UCM622163.pdf). We briefly discussed USP General Chapters <771> which refers to <1151> which then refers to <1121> for the nomenclature which follows what is outlined in the labeling review tool. This drug product does not have a USP monograph so the USP chapters are preferential but highly recommended for applicants to follow. OBP labeling defers to DTOP for this labeling preference.*

| | |
|---|---|
| **11 DESCRIPTION** | **Acceptable** |

| | |
|---|---|
| Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q) | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:**
The pharmacological class was added per 21 CFR 201.57(c)(12)
*The Applicant revised as requested*

The dosage form was added per 21 CFR 201.57(c)(12)
*The Applicant revised as requested*

The route of administration was added per 21 CFR 201.57(c)(12)
*The Applicant revised as requested*

The inactive ingredient list was revised to appear in alphabetical order and the quantitative amounts of the inactive ingredients were relocated to differentiate the active ingredient from the inactive ingredients.
*The Applicant revised as requested*

| | |
|---|---|
| *Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>* | ✓ Yes<br>☐ No<br>☐ N/A |
| **16 HOW SUPPLIED/ STORAGE AND HANDLING** | **Acceptable** |
| Regulation: 21 CFR 201.57(c)(17) | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:**
The dosage form and identifying characteristics of the dosage form were added per 21 CFR 201.57(c)(17)
*The Applicant revised as requested*

The filter needle has been added to the carton contents
*The Applicant revised as requested*

Additional handling instructions of "do not shake" have been added
*Applicant's response: As noted for the Prescribing Information, all of the product storage and handling instructions have been included based on our drug product stability data and the results are summarized in section 3.2.P.8.1. Based on the product stability data, there are no concerns specifically noted or as a result of shaking the final drug product. Therefore, the Sponsor proposes to not include the phrase "Do not Shake".*
*FDA response: Per the product quality reviewer, Based on OBP's assessment of the total data provided in the submission and the IR response (received September 26, 2019), we believe the risk to product quality is minimal. The sponsor's proposal to keep "Do not Shake" off of the carton container and PI labels is acceptable.*

| | |
|---|---|
| *Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:**

| | |
|---|---|
| [redacted] (b) (4) has been deleted to avoid the inclusion of statements that are not applicable to special handling and storage conditions for the health care practitioner.<br>*The Applicant revised as requested* | |
| **MANUFACTURER INFORMATION** | **Acceptable** |
| Regulations: 21 CFR 201.100(e), 21 CFR 201.1 | ✓ Yes<br>☐ No<br>☐ N/A |
| **Comment/Recommendation:** the name and full address of the manufacturer, and placeholder for the US License number were added (see 21 CFR 201.1 and 21 CFR 610.61(b))<br>*The Applicant revised as requested but did not include "One Health Plaza" which is acceptable* | |
| *Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)* | ✓ Yes<br>☐ No<br>☐ N/A |

**APPENDIX C. Acceptable Labels and Labeling**

Prescribing Information (submitted on September 25, 2019 \\cdsesub1\evsprod\bla761125\0032\m1\us\proposed-clean.pdf)

Container Labels (submitted on September 18, 2019)

[redacted] (b) (4)

Carton Labeling (submitted on September 18, 2019)

(b) (4)

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 9/27/2019 03:01:00PM
GUID: 50814c7000007a3d59329f660d8ddf02

Brian Roelofs

Digitally signed by Brian Roelofs
Date: 9/27/2019 03:30:21PM
GUID: 57f29d150070ca84f102970a51133e31

First Approval for Indication

Recommendation: BLA Approval

BLA Number: 761125
Review Number: 1
Review Date: July 31, 2019

| | |
|---|---|
| Drug Name/Dosage Form | Beovu (brolucizumab) injection (solution) |
| Strength/Potency | 6 mg/0.05 mL |
| Route of Administration | Intravitreal |
| Rx/OTC dispensed | Rx |
| Indication | Treatment of neovascular age-related macular degeneration (nAMD) |
| Applicant/Sponsor | Novartis Pharmaceuticals Corporation |

## Product Overview

Brolucizumab is a humanized monoclonal single-chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa, produced in *Escherichia coli* (E. coli) (b) (4) by recombinant DNA technology. Brolucizumab binds to the vascular endothelial growth factor A (VEGF-A), thereby preventing the interaction of the three major isoforms of VEGF-A (i.e., VEGF110, VEGF121, and VEGF165) with receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A, brolucizumab can suppress endothelial cell proliferation, thereby reducing pathologic neovascularization and decreasing vascular permeability. Brolucizumab drug product is a sterile, clear to slightly opalescent, colorless to slightly brownish-yellow and preservative-free aqueous solution. Each vial of brolucizumab drug product contains (b) (4) designed to deliver a single dose of 0.05 mL containing 6 mg brolucizumab (120 mg/mL in 10 mM sodium citrate, 5.8% sucrose, 0.02% polysorbate 80, and water for injection at pH 7.2). The recommended dose is 6 mg (0.05 mL) administered by intravitreal injection (b) (4) for the first three doses, (b) (4)

## Quality Review Team

| Discipline | Reviewer | Branch/Division |
|---|---|---|
| Drug Substance (DS) | Brian Roelofs | OPQ/OBP/DBRRII |
| Drug Product (DP) | Brian Roelofs | OPQ/OBP/DBRRII |
| Immunogenicity | Brian Roelofs | OPQ/OBP/DBRRII |
| Labeling | Vicky Borders Hemphill<br>Brian Roelofs | OPQ/OBP<br>OPQ/OBP/DBRRII |
| Facility | Zhong Li | OPQ/OPF/DIA |
| Microbiology | Bo Chi (DS)<br>Anita Khatiwara (DP) | OPQ/OPF/DMA-IV<br>OPQ/OPF/DMA-IV |
| RBPM | Leeza Rahimi | OPQ/OPRO |
| Team Lead | Yan Wang<br>Reyes Candau-Chacon<br>Peter Qiu | OPQ/OBP/DBRRII<br>OPQ/OPF/DMA-IV<br>OPQ/OPF/DIA |
| Application Technical Lead | Yan Wang | OPQ/OBP/DBRRII |

Mutidisciplinary Review Team:

| Discipline | Reviewer | Office/Division |
|---|---|---|
| RPM | Judit Milstein and Dheera Semiday | OND/OAP/DTOP |
| Cross-disciplinary Team Lead | William Boyd | OND/OAP/DTOP |
| Medical Officer | Rhea Lloyd | OND/OAP/DTOP |
| Pharm/Tox | Andrew McDougal | OND/OAP/DTOP |
| Clinical Pharmacology | Abhay Joshi | OTS/OCP/DCPIV |
| Statistics | Wonyul Lee | OTS/OB/DBIV |

1. Names:
   a. Proprietary Name: Beovu
   b. Trade Name: Beovu
   c. Non-Proprietary Name/USAN: Brolucizumab
   d. CAS Registry Number: 1531589-13-5
   e. Common Name: Humanized monoclonal single-chain Fv (scFv) antibody fragment
   f. INN Name: Brolucizumab
   g. OBP systematic name: MABFRAG HUMANIZED ANTI P15692 (VEGFA_HUMAN) [RTH258] (parent IND: 112023)
   h. Other name(s): ESBA1008, RTH258, AL-86810 and (b) (4)

Submissions Reviewed:

| **Submission(s) Reviewed** | **Document Date** (disciplines affected) |
|---|---|
| STN 761125/SN0001 (BLA submission) | February 7, 2019 (OBP, DMA, DIA) |
| STN 761125/SN0007 (Response to IR 1) | April 23, 2019 (DMA, OBP) |
| STN 761125/SN0008 (Amendment of Response to IR 1) | May 8, 2019 (DMA) |
| STN 761125/SN0011 (Response to IR 2) | May 24, 2019 (DMA) |
| STN 761125/SN0012 (Response to IR 3) | June 4, 2019 (DMA) |
| STN 761125/SN0014 (Response to IR 4) | June 17, 2019 (DMA, OBP) |
| STN 761125/SN0015 (Response to IR 5) | June 28, 2019 (DMA) |
| STN 761125/SN0016 (Response to IR 6) | June 28, 2019 (OBP) |
| STN 761125/SN0017 (Response to IR 7) | July 5, 2019 (OBP) |
| STN 761125/SN0018 (Response to IR 8 and IR9) | July 11, 2019 (OBP) |
| STN 761125/SN0019 (Response to IR 10) | July 17, 2019 (DMA) |
| STN 761125/SN0022 (Response to IR 11) | July 22, 2019 (DMA) |
| STN 761125/SN0023 (Response to IR 12) | July 24, 2019 (DMA) |
| STN 761125/SN0024 (Response to IR 10) | July 26, 2019 (DMA) |

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

| DMF # | DMF Type | DMF Holder | Item referenced | Code[1] | Status[2] | Date Review Completed |
|---|---|---|---|---|---|---|
| (b) (4) | III | | (b) (4) | 3 | Adequate | N/A |
| | III | | | 3 | Adequate | N/A |
| | III | | | 3 | Adequate | N/A |
| | III | | | 3 | Adequate | N/A |
| | III | | | 3 | Adequate | N/A |
| | IV | | | 3 | Adequate | 7/22/2019 |

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

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

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

| Document | Application Number | Description |
|---|---|---|
| IND | 112023 | Parent IND |

3. Consults: None

Executive Summary

I. Recommendations:

## A. Recommendation and Conclusion on Approvability:

Recommendation:
The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761125 for Beovu (brolucizumab) manufactured by Novartis Pharmaceuticals Corporation. The data submitted in this application are adequate to support the conclusion that the manufacture of Beovu (brolucizumab) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

## B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance: (b) (4)
  - Drug Product:
    Novartis Pharma Stein AG, Schaffhauserstrasse, 4332 Stein AG Switzerland (FEI: 3002653483)

- Fill size and dosage form: 6 mg/0.05 mL solution

- Dating period:
  - Drug Product: 18 months at 2-8°C
  - Drug Substance: (b) (4)
  - For packaged products:
    - Filter needle: same as drug product
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the process performance qualification drug substance batches and drug product lots.
    - For stability protocols: We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release in accordance with 21 CFR 601.2a. Brolucizumab is a specified product.

## C. Benefit/Risk Considerations:

Brolucizumab is a humanized single-chain Fv antibody fragment directly against human VEGF-A, preventing binding to its receptors VEGFR-1 and VEGFR-2, for the treatment of nAMD, with a molecular weight of ~26 kDa. VEGF-A is elevated in patients with nAMD and plays a key role in the neovascularization process. While a few VEGF-A inhibitors are currently on the market for

treatment of nAMD, there is still high unmet medical need for new treatments for nAMD that are more specific and efficacious.

Review of manufacturing has identified that the methodologies used for DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of brolucizumab DS at (b) (4) and of brolucizumab DP at Novartis Pharma Stein AG, Schaffhauserstrasse, Switzerland. The OBP (Office of Biotechnology Products) product quality and immunogenicity assay, DMA (Division of Microbiology Assessment) microbiological DS and DP, DIA (Division of Inspectional Assessment) facility, and OBP labeling technical assessments are located as separate documents in Panorama.

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

1. Complete method development and implement a method (b) (4) for a drug substance in-process control.

   Final Report Submission: 31-Dec-2019 (method development completed)
   30-Apr-2020 (evidence of implementation of testing)
   First annual report (b) (4) test results)

2. Complete an accelerated leachables study using the final container closure system with both brolucizumab drug product and the most appropriate representative buffer.

   Final Report Submission: 30-September-2020

3. Qualify the drug substance in-process and release samples for the bioburden test and drug substance in-process samples for the endotoxin test using samples from three drug substance batches manufactured using the commercial process at (b) (4)

   Final Report Submission: 31-Jan-2020

4. Develop an endotoxin detection method adequate to detect endotoxin from the drug product release samples.

   Final Report Submission: 31-Dec-2019
   Test Method Implementation: 30-Apr-2020

II. Summary of Quality Assessments:

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

| CQA (Type) | Risk | Origin | Control Strategy | Other |
|---|---|---|---|---|
| Binding to VEGF-A and prevention of binding to its receptors VEGFR-1 and VEGFR-2 | Efficacy | Intrinsic to the molecule impacted by oxidation, aggregation and fragmentation | (b) (4) | Brolucizumab is a single-chain Fv antibody fragment manufactured from E. coli. (b) (4) |
| Identity | Efficacy and Safety | Intrinsic to the molecule | | N/A |
| High Molecular Weight (HMW) species/Aggregates (Product related impurity) | Efficacy, Pharmaco kinetics (PK)/ Pharmaco dynamics (PD), and Safety (Immunog enicity) | Manufacturing process, storage and exposure to high pH, heat, and light | | (b) (4) |
| Low Molecular Weight (LMW) species/Fragments (Product related impurity) | Efficacy | Manufacturing process and exposure to low pH, high pH and heat | | |
| Charge variant profile (Basic variants) | Efficacy | Manufacturing process and exposure to low pH, high pH, heat and light | | |
| Charge variant profile (Acidic variants) | Efficacy, PK/PD, and Safety | Manufacturing process and exposure to low | | |

| | | | |
|---|---|---|---|
| | (Immunogenicity) | pH, high pH, heat, oxidation reagent stress and light | (b) (4) |
| (b) (4) | Efficacy | Manufacturing process and exposure to low pH, high pH and heat | |
| (b) (4) | Safety (Immunogenicity) | Manufacturing process | |
| (b) (4) | Safety (Immunogenicity) | Manufacturing process | |

B. Drug Substance [Brolucizumab] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

| CQA (Type) | Risk | Origin | Control Strategy | Other |
|---|---|---|---|---|
| Endotoxin (contaminant) | Safety and Purity | Endotoxin can be introduced by raw materials and throughout the manufacturing process | (b) (4) | N/A |
| Bioburden (contaminant) | Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms) | Bioburden can be introduced by raw materials and throughout the manufacturing process. | | N/A |
| (b) (4) | Efficacy, Safety and Stability | Formulation component | | N/A |

| | | | | |
|---|---|---|---|---|
| Quantity | Efficacy | Manufacturing process | (b) (4) | N/A |
| pH (General) | Efficacy and Stability | Formulation components and stability | | N/A |
| Osmolality (General) | Stability | Composition of the DS | | N/A |
| Color of solution (General) | Stability | Formulation components and stability | | N/A |
| Appearance of the solution and turbidity | Stability | Formulation components and stability | | N/A |
| Host cell DNA (Process related impurity) | Safety | (b) (4) | | (b) (4) |
| Host cell protein (Process related impurity) | Immunogenicity | (b) (4) | | N/A |
| (b) (4) (Process related impurity) | Safety | Cell banks, raw materials | | PMC to establish control strategy at (b) (4) |
| Leachables (Process-related impurity) | Safety and Stability | from manufacturing contact material and the DS container closure system (CCS) | | Risk for leachables from CCS is low (b) (4) |
| Culture medium (b) (4) | Safety | Cell bank (b) (4) | | Levels are below toxicological concern based on the risk assessment |
| Elemental impurities | Safety | Cell culture medium, product- | | The levels are tested for characterization |

| | | | | |
|---|---|---|---|---|
| | | contact surfaces, raw materials, excipients, and (b) (4) | | purposes (b) (4), and the levels are consistently below safety concern limit (SCT) of (b) (4) |

- Description:
  Brolucizumab is a humanized monoclonal single-chain Fv (scFv) antibody fragment containing the variable regions of the light (VL) (111 amino acids) and heavy chains (VH) (120 amino acids) of an immunoglobulin, connected with a short linker peptide of 21 amino acids in rich with glycine and serine. It is not glycosylated and does not contain the Fc region of immunoglobulins. The theoretical average molecular mass of brolucizumab based on the amino acid composition as deduced from DNA sequence is 26313 Da.

- Mechanism of Action (MoA):
  Brolucizumab binds to VEGF-A, thereby preventing the interaction of the three major isoforms of VEGF-A (i.e., VEGF110, VEGF121, and VEGF165) with receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A, brolucizumab can suppress endothelial cell proliferation, thereby reducing pathologic neovascularization and decreasing vascular permeability.

- Potency Assay:
  A cell-based assay is used to determine the potency of brolucizumab based on its ability to inhibit VEGF-A dependent proliferation of human umbilical vein endothelial cells (HUVEC). Specifically, after incubation of HUEVC with rhVEGF165 (recombinant human VEGF165 isoform) and brolucizumab, the cells are lysed and exposed to a luciferase reagent that produces a chemiluminescent product when exposed to ATP. Decrease in ATP levels indicates successful brolucizumab inhibition of VEGF-A mediated HUVEC proliferation. The resulting chemiluminescence is then determined with a luminometer. The chemiluminescence is measured and it is inversely proportional to brolucizumab inhibition. The potency of brolucizumab test samples is determined in comparison to a reference standard.

- Reference Materials:
  (b) (4)
  (b) (4) The protocols contain adequate testing and acceptance criteria (AC). The procedures to monitor the stability of the PRS and WRS are appropriate.

- Critical Starting Materials or Intermediates:
  The MCB is derived from E. coli (b) (4)

- Manufacturing Process Summary:
  (b) (4)

- Container Closure:
  Brolucizumab (b) (4) . The CCS is suitable for brolucizumab, based on stability data and maintenance of closure integrity.

- Dating Period and Storage Conditions:
  The dating period for the DS is (b) (4)

C. Drug Product [Beovu] Quality Summary:

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

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

| CQA (Type) | Risk | Origin | Control Strategy | Other |
|---|---|---|---|---|
| Sterility (contaminant) | Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms) | Contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity | (b) (4) | N/A |
| Endotoxin (contaminant) | Safety, Purity, and Immunogenicity | Raw materials, contamination may be introduced throughout the DP manufacturing process | | Low endotoxin recovery from the DP (b) (4) . PMC to develop a method that can adequately detect endotoxin at DP release |
| Container closure integrity (contaminant) | Safety (maintenance of sterility during shelf-life) | Container closure breaches during storage | | N/A |
| Quantity | Efficacy | Manufacturing process | | N/A |
| Color of solution (General) | Stability | Formulation components and stability | | N/A |
| Appearance of the solution and turbidity | Stability | Formulation components and stability | | N/A |
| pH (General) | Efficacy and Stability | Formulation components and stability | | N/A |
| Osmolality (General) | Stability | Composition of the DP | | N/A |
| Volume in container (General) | Efficacy/Dosing | Fill process | | N/A |
| Particulate matter for subvisible particles (Product or process related impurities) | Safety and Immunogenicity | Manufacturing process and CCS, subvisible particles could be product or foreign particles | | N/A |
| Foreign matter for visible particles | Safety and Immunogenicity | Manufacturing material and CCS | | N/A |

| | | | | |
|---|---|---|---|---|
| (Product and process related impurities) | | | | |
| Polysorbate 80 concentration | Efficacy, Safety and Stability | Formulation component | (b) (4) | N/A |
| Leachables (Process-related impurities) | Safety | Manufacturing equipment and CCS | | PMC to complete an accelerated leachables study using the final CCS with both brolucizumab DP and the most appropriate representative buffer |

- Potency and Strength:
  The strength of brolucizumab is 6 mg/0.05 mL solution (Each brolucizumab single-dose vial is designed to deliver 0.05 mL of 120 mg/mL brolucizumab solution). Potency is defined as the percent activity relative to the current brolucizumab WRS. The potency assay is the same as described in the DS section of this memo.

- Summary of Product Design:
  Brolucizumab is supplied as (b) (4) solution (b) (4) in single-dose 2 mL glass vials for intravitreal injection.

- List of Excipients:
  10 mM sodium citrate, 0.02% polysorbate 80, 5.8% sucrose, water for injection, pH 7.2.

- Reference Materials:
  The same reference standards are used for DS and DP

- Manufacturing Process Summary:
  (b) (4)

- Container Closure:
  The primary container closure system for brolucizumab consists of a 2 mL (b) (4) glass vial closed with a gray, (b) (4) rubber stopper. The rubber stopper is sealed with a colored aluminum cap with a flip-off (b) (4)

  Appropriate compatibility studies were performed for the primary CCS.

- Dating Period and Storage Conditions:
  The dating period for the DP is 18 months when stored at 2-8°C. The data included in the BLA support storage for up to 24 hours when stored at temperatures (b) (4) once removed from refrigerator, as described in the labeling. Appropriate in-use stability of the brolucizumab DP for injection was performed with the representative commercially available intravitreal device delivery system combinations.

- List of Co-Package Components:
  The intended commercial presentation will be a vial kit which will include one vial of brolucizumab 6 mg/0.05 mL solution for injection co-packaged with a 5-µm blunt filter needle (b) (4)

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:
- Store in a refrigerator at 2°C to 8°C
- Prior to use, the unopened vial may be kept at room temperature (b) (4) for up to 24 hours
- Do not freeze
- Protect from light

F. Establishment Information:

| Overall Recommendation: Approve | | | | | |
|---|---|---|---|---|---|
| DRUG SUBSTANCE | | | | | |
| Function | Site Information | DUNS/FEI Number | Preliminary Assessment | Inspectional Observations | Final Recommendation |
| Drug Substance - Manufacturing (All manufacturing steps). IPC testing (All tests). Storage (Drug substance). Quality control Stability Testing | (b) (4) | | Pre-license inspection requested | VAI | Approve |
| Drug Substance - Quality control (All tests except (b) (4) | | | Acceptable based on file review | N/A | Approve |

| | | | | | |
|---|---|---|---|---|---|
| (b) (4) | | | | | |
| Manufacturing site(s) of MCB & Manufacturing site(s) of WCB. | (b) (4) | | Acceptable based on file review | N/A | Approve |
| Storage site of MCB & Storage site of WCB | | | Acceptable based on file review | N/A | Approve |
| DRUG PRODUCT | | | | | |
| Function | Site Information | DUNS/FEI Number | Preliminary Assessment | Inspectional Observations | Final Recommendation |
| Drug Product - Manufacturing, primary packaging and storage. Quality control and Stability Testing. | Novartis Pharma Stein AG<br><br>Schaffhauserstrasse, Stein, Switzerland, 4332 | 3002653483 | Acceptable based on file review | PLI waived | Approve |
| DP- Quality Control & Stability Testing. (b) (4) Quality control. Stability testing. Storage site of MCB & WCB. | Novartis Pharma AG Lichtstrasse 35, Basel, Switzerland, 4056 | 300280777 | Acceptable based on file review | N/A | Approve |
| Drug Product - Alternate site for Secondary packaging | (b) (4) | | No evaluation necessary | N/A | N/A |
| Drug Product - Alternate site for Secondary packaging | | | No evaluation necessary | N/A | N/A |

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) and Novartis Pharma Stein AG (FEI 3002653483), proposed for brolucizumab DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

| eCTD Section | Protocol | Brief Summary | Reporting Category |
|---|---|---|---|
| 3.2.S.2.3 | (b) (4) | | (b) (4) will be submitted in the **Annual Report.** |
| 3.2.S.2.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.2.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.2.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.2.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.7.2 | | | (b) (4) |

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

| eCTD Section | Protocol | Brief Summary | Reporting Category |
|---|---|---|---|
| 3.2.P.8.2 | Annual stability protocol for DP with shelf-life extension | At 5°C ± 3°C at least one bath per year at 0, 3, 6, 12, 18, 24 and 36 month, according to the tests and AC listed in 3.2.P.8.3 Stability Data and 3.2.P.5.1 Specification, respectively | Stability updates will be provided annually as part of the **Annual Report** |

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

## Quality Assessment Summary Tables

### Table 1: Noteworthy Elements of the Application

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

Yan Wang (OPQ/OBP)

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Reyes Candau-Chacon

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Zhihao Peter Qiu

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Xianghong Jing

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbial Assessment (IV)

# PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

**Primary Reviewer:** Anita Khatiwara, Ph.D.
**Quality Assessment Lead:** Reyes Candau-Chacon, Ph.D.

| | |
|---|---|
| **BLA:** | STN761125/0 |
| **Applicant:** | Novartis Pharmaceuticals Corporation |
| **US License:** | 1244 |
| **Subject:** | Original Biologics License Application (BLA) |
| **Product:** | Beovu (brolucizumab) |
| **Dosage:** | 120 mg/mL (6mg/0.05mL), sterile solution for intravitreal injection |
| **Indication:** | Treatment of neovascular age-related macular degeneration (AMD) |
| **Manufacturing Site**: | Novartis Pharma Stein AG, Schaffhauserstrasse, Stein, Switzerland 4332 (FEI: 3002653483) |
| **FDA Receipt Date:** | February 7, 2019 |
| **Goal date:** | August 7, 2019 |

**Recommendation for Approvability:** BLA 761125 as amended is recommended for approval from a sterility assurance and microbiology product quality perspective with the following post-marketing commitment:

> Develop an endotoxin detection method capable of detecting endotoxin from the DP release samples.

## Review Summary

Novartis Pharmaceuticals Corporation has submitted BLA 761125 in eCTD format for the approval of brolucizumab. The drug product is manufactured at Novartis Pharma Stein AG, Schaffhauserstrasse, Stein, Switzerland 4332 (FEI: 3002653483).

### Product Quality Microbiology Information Reviewed

| Submission Type | Sequence number | Sequence date |
|---|---|---|
| Original BLA | 0001 | 02/07/2019 |
| Amendment | 0009 | 05/08/2019 |
| Amendment | 0011 | 05/24/2019 |
| Amendment | 0014 | 06/17/2019 |
| Amendment | 0023 | 7/24/2019 |
| Amendment | 0024 | 7/26/2019 |

# Product Quality Microbiology Assessment

## 1.14 LABELING

Brolucizumab is packaged in a kit that includes a single-dose vial containing the DP solution co-packaged with a sterile 5-µm blunt filter needle. The DP is withdrawn from the vial using the filter needle attached to a syringe; the filter needle is then detached from the syringe and a 30G1/2" injection needle us attached to the syringe for the injection. The injection needle and the syringe are not included in the kit. Any DP remaining after injection should be discarded.

*Secondary reviewer's comment: Information of* (b) (4) *of the filter needle is reviewed in section P.3.5 of this memo.*

*Satisfactory*

## 3.2. P DRUG PRODUCT (DP)

## P.1 Description and Composition of the Drug Product

Brolucizumab DP is a sterile, single use, preservative free, colorless to slightly brownish yellow, solution for injection filled in a (b) (4) glass vial closed with a rubber stopper and sealed with an aluminum cap with a flip-off disk. The detailed composition of the DP is provided in Table 2-1 in the submission.

*The description is adequate.*

## P.2 Pharmaceutical Development

(b) (4)



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Anita Khatiwara

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Reyes Candau-Chacon

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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

**Date:** **7/24/2019**
**To:** Administrative File, **STN 761125/0**
**From**: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
**Endorsement**: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV
**Subject**: New Biologic License Applications (BLA)
**Applicant:** Novartis Pharmaceuticals Corporation
**US License:** **1244**
**Facility:** (b) (4)
**Product:** brolucizumab (RTH258)
**Dosage:** Solution for injection, Intravitreal injection, 120 mg/mL
**Indications:** Treatment of neovascular age-related macular degeneration (AMD)
**PDUFA date**: October 7, 2019

**Recommendation:** The drug substance part of this BLA is recommended for approval from a quality microbiology perspective with the following post-marketing commitment (PMC):

Qualify the DS in process and release samples for the bioburden test and DS in-process samples for the endotoxin test using samples from three drug substance lots manufactured using the commercial process at (b) (4)

## Review Summary

Novartis has submitted this Biologics License Application (BLA) for brolucizumab for the treatment of neovascular age-related macular degeneration (AMD). The drug substance (DS) is manufactured at (b) (4) The drug product (DP) is manufactured at Novartis Pharma at Stein AG, Switzerland. The application contains CMC information in an eCTD format.

This review contains an assessment of the brolucizumab drug substance section of the BLA from microbiology perspective. The amendments reviewed are provided in the table below:

| Sequence number | Date | Description |
|---|---|---|
| 0001 | 2/7/2019 | Original BLA submission |
| 0012 | 6/4/2019 | Response to IR |
| 0014 | 6/17/2019 | Response to IR |

| | | |
|---|---|---|
| 0015 | 6/28/2019 | Response to IR |
| 0019 | 7/17/2019 | Response to IR |
| 0022 | 7/22/2019 | Response to IR |
| 0023 | 7/24/2019 | Response to IR |

**Assessment**

**Drug Substance (3.2.S)**

**General Information (3.2.S.1)**

Brolucizumab is a humanized monoclonal single-chain Fv (scFv) antibody fragment directed against human vascular endothelial growth factor (hVEGF), thereby preventing the interaction of VEGF with its receptors on the surface of endothelial cells. Brolucizumab is manufactured using *E. coli* (b) (4) strain. The DS formulation contains (b) (4)

**Manufacture (3.2.S.2)**

**Manufacturer(s) (3.2.S.2.1)**

**Drug substance manufacturing and testing**

(b) (4)

**Description of Manufacturing Process and Process Controls (3.2.S.2.2) and Controls of Critical Steps (3.2.S.2.4)**

Brolucizumab is manufactured in a (b) (4)

(b) (4)

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Reyes Candau-Chacon

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

U.S. FOOD & DRUG ADMINISTRATION

# BLA STN 761125

**Product: Brolucizumab**

**Manufacturer: Novartis Pharmaceuticals Corporation**

**Brian Roelofs, Ph.D., Primary Reviewer**
**Yan Wang, Ph.D., Team Leader**

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OBP CMC Review Data Sheet

1. BLA#: 761125

2. Review Date: June 19th, 2019

3. Primary Review Team:
   a. Medical Officer: Rhea Lloyd and William Boyd (Cross Disciplinary Team Lead)
   b. Pharm/Tox: Andrew McDougal
   c. Product Quality Team
      OPQ/OBP: Brian Roelofs (Product Quality(PQ)), Yan Wang (Application Technical Lead) and Xianghong Jing (Review Chief)
      OPQ/OPF/DMA: Maria (Reyes) Candau-Chacon (Quality Application Lead (QAL)), Anita Khatiwara (Drug Product (DP)), Bo Chi (Drug Substance (DS))
      OPQ/OPB/DIA: Zhong Li and Peter Zhihao Qiu (QAL)
      OPQ/OBP (Labeling): Vicky Borders-Hemphill
      OPQ RBPM: Leeza Rahimi
   d. Clinical Pharmacology: Abhay Joshi
   e. Statistics: Wonyul Lee
   f. OND RPM: Judit Milstein & Dheera Semidey (OND/OAP/DTOP)

4. Major GRMP Deadlines:

| | |
|---|---|
| a. Filing Meeting | March 26th, 2019 |
| b. Mid-cycle meeting | June 7th, 2019 |
| c. Wrap-up meeting | August 12th, 2019 |
| d. Primary review due | July 22nd, 2019 |
| e. Secondary review due. | July 22nd, 2019 |
| f. PDUFA action date. | October 7th, 2019 |

5. Communications with Sponsor and OND:

| Communication/Document: | Date: | Submission | Review Status |
|---|---|---|---|
| Original Submission | February 7th, 2019 | (STN 761125/SN 0001) | Complete |
| Filing Review Memo | March 28th, 2019 | | Complete |
| PQ Information Request #1 | April 23rd, 2019 | (STN 761125/SN 0007) | Complete |
| PQ Information Request #2 | June 17th, 2019 | (STN 761125/SN 0014) | Complete |
| PQ Information Request #3 | June 28th, 2019 | (STN 761125/SN 0016) | Complete |
| PQ Information Request #4 | July 5th, 2019 | (STN 761125/SN 0017) | Complete |
| PQ Information Request #5 | July 11th, 2019 | (STN 761125/SN 0018) | Complete |
| PQ Information Request #6 | July 11th, 2019 | (STN 761125/SN 0018) | Complete |

6. Drug Product Name/Code/Type:
   a. Proprietary Name: BEOVU
   b. Trade Name: BEOVU™
   c. Non-Proprietary Name/USAN: Brolucizumab
   d. CAS Registry Number: 1531589-13-5

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e. Common Name: Humanized monoclonal single-chain Fv (scFv) antibody fragment directed against human vascular endothelial growth factor A (hVEGF-A).
f. INN Name: Brolucizumab
g. OBP systematic name (refer to OPQ-SOP-OBP-3006): MABFRAG HUMANIZED ANTI P15692 (VEGFA_HUMAN)[RTH258]
h. Other names: ESBA1008, RTH258, AL-86810 and (b) (4)

7. Pharmacological Category: Therapeutic scFv antibody fragment inhibitor of hVEGF-A / treatment of neovascular age-related macular degeneration (nAMD)

8. Dosage Form: Solution for injection in a single dose glass vial

9. Strength/Potency:
(i): The concentration/strength of the Drug Product: 6 mg/0.05 mL
(ii): Type of potency assay(s): The potency assay assesses the ability of brolucizumab to bind to exogenous human VEGF-A and inhibit the interaction of hVEGF-A with VEGF-receptors (VEGFR) on the surface of human umbilical vein endothelial cells (HUVEC). Signaling through VEGF-receptors normally stimulates HUVEC proliferation, the potency of brolucizumab is determined by the ability of increasing concentrations of the drug to inhibit proliferation relative to an internal reference standard.

10. Route of Administration: Intravitreal injection

11. Referenced Drug Master Files (DMF):

| DMF# | DMF Holder | Item Referenced | Letter of Cross-Reference | Comments (status) |
|---|---|---|---|---|
| (b) (4) | | | Yes | Active. No review was required as all information related to safety and compatibility with the DS was provide in the BLA. |
| | | | Yes | Active. No review was required as all information related to safety and compatibility with the DS was provide in the BLA. |
| | | | Yes | Active. No review was required as all information related to safety and compatibility with the |

| | | | | |
|---|---|---|---|---|
| | | | | DS was provide in the BLA. |
| (b) (4) | | | Yes | Active. No review was required as all information related to safety and compatibility with the DP was provide in the BLA. |
| | | | Yes | Active. No review was required as all information related to safety and compatibility with the DP was provide in the BLA. |
| | | | Yes | Active. Review was complete by DMA. |

12. Inspectional Activities: The pre-licensure inspection of the DS manufacturing facility at (b) (4) (b) (4) was conducted from (b) (4) by Zhong Li (OPQ/DIA), William Hallett (OPQ/OBP) and Brian Roelofs (OPQ/OBP). The inspection covered the manufacture of DS from (b) (4) From FDA 483 was issued with seven observations:

1) Deficient laboratory records in that they do not include a complete record of all data obtained during testing, specifically with regards to audit trail generation and storage of testing data.
2) Failure to establish adequate procedural controls to protect the electronic data acquisition systems.
3) Failure to establish adequate QC laboratory procedures with regards to out of specification retesting and repeat testing.
4) Failure to provide adequate assurance that the cleaning procedures are effective to prevent cross-contamination for shared product-contact process equipment.
5) Control of laboratory samples in an unsecured back-up freezer.
6) Qualification of the process gas distribution systems
7) Document control of the forms that are used for GMP activities.

Novartis responded to the Form 483 on June 11th, 2019. It was recommended that the inspection be classified as voluntary action indicated.

The pre-license inspection on the DP manufacturing facility at Novartis Pharma Stein AG (Shaffhauserstrasse, Stein, Switzerland 4332, FEI# 3002653483) was waived.

13. Consults Requested by OBP:
N/A

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

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

15. Precedents: None

16. Administrative:
Signature Block

| Name and Title | Signature and Date |
|---|---|
| Yan Wang, Ph.D.<br>Application Technical Lead, DBRRII/OBP/OPQ/CDER | See electronic signature and date |
| Brian Roelofs, Ph.D.<br>Primary Reviewer, DBRRII/OBP/OPQ/CDER | See electronic signature and date |

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation
The data submitted in this Biologics License Application (BLA) (STN 761125) support the conclusion that the manufacture of BEOVU™ (brolucizumab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious agents and meets the standards recommended by the FDA. The conditions used in the commercial manufacturing process have been adequately validated, and the product has been consistently manufactured from multiple production runs. It is recommended that BEOVO™ (brolucizumab) be approved for human use under the conditions specified in the package insert.

II. List of Deficiencies to be Communicated: None.

III. List of Post-Marketing Commitments/Requirements:

1. Complete method development and implement a method (b) (4) for a drug substance in-process control.

   Final Report Submission: 31-Dec-2019 (method development completed)
   30-Apr-2020 (evidence of implementation of testing)
   First annual report ((b) (4) test results)

2. Complete an accelerated leachables study using the final container closure system with both brolucizumab drug product and the most appropriate representative buffer.

   Final Report Submission: 30-September-2020

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List of protocols approved with this BLA:

| eCTD Section | Protocol | Brief Summary | Reporting Category |
|---|---|---|---|
| 3.2.S.2.3 | (b) (4) | | (b) (4) will be submitted in **Annual Report** |
| 3.2.S.2.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.2.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.2.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.2.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.5 | | | Results will be reported in **Annual Report** following study completion |
| 3.2.S.7.2 | | | (b) (4) |
| 3.2.P.8.2 | Annual stability protocol for DP with shelf-life extension | At 5°C ± 3°C at least one bath per year at 0, 3, 6, 12, 18, 24 and 36 months, according to the tests and AC listed in 3.2.P.8.3 Stability Data and 3.2.P.5.1 Specification, respectively | Stability updates will be provided annually as part of the **Annual Report** |

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

A. Environmental Assessment of Claim of Categorical Exclusion:

Novartis Pharmaceuticals Corporation claims a categorical exclusion from an Environmental Assessment on the basis of 21 CFR 25.31(c) as the production of BEOVU™ (brolucizumab) is not anticipated to significantly alter the concentration or distribution of substances which occur naturally in the environment, their metabolites, or degradation products in the environment (BLA section 1.12.14).

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Novartis Pharmaceuticals Corporation also states that to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment. Categorical exclusion is appropriate for this product and should be granted.

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

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

VII. Review of Immunogenicity Assays – Module 5.3.1.4:
The current immunogenicity assay used for screening for anti-drug antibodies (ADA) in human serum utilizes a homogeneous bridging ligand binding electrochemiluminescence (ECL) format. The assay sensitivity was determined to be 39.1 ng/mL and can detect 125 ng/mL ADA in the presence of 10.0 μg/mL brolucizumab which is well above the maximum concentration range observed in the phase 3 clinical trials (2.7-117 ng/mL). The neutralizing antibody (nAb) assay utilized a competitive ligand binding ECL format to detect the presence of nAb to brolucizumab in serum. The assay sensitivity was determined to be 487.8 ng/mL and the assay tolerated 100 ng/mL brolucizumab at a concentration of 5000 ng/mL positive control (PC) antibody and 50.0 ng/mL brolucizumab at 1250 ng/mL of PC antibody. The immunogenicity assays were adequately validated, and the assessment of the assays is provided in this memorandum.

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**Contents**

## 2.3 QUALITY OVERALL SUMMARY (QOS)

*Assessment of the QOS did not identify anything that was not included in Module 3. Therefore, all information will be covered in Module 3. It should be noted that as of finalization of this review, although many updates have occurred to Module 3, the matching updates have not yet been implemented in Module 2.3.*

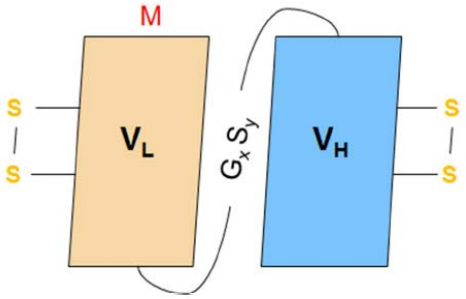
The Figures and Tables in the assessment were directly copied from the original BLA submission and subsequent BLA amendments during the review cycle unless otherwise noted. The assessor's comments are provided in *italics*.

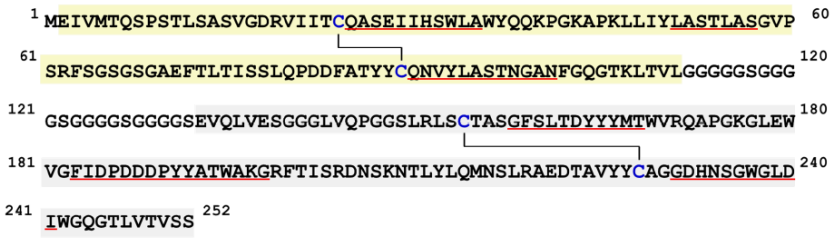
## S. DRUG SUBSTANCE

Brolucizumab is a humanized monoclonal scFv antibody fragment that inhibits hVEGF-A by binding to the receptor binding site on VEGF-A. This prevents the interaction of VEGF-A with VEGFR 1 and 2 on the endothelial cell surface. Brolucizumab is not glycosylated and does not contain the Fc region of immunoglobulins. The biological activity of brolucizumab is determined by measuring the ability of brolucizumab to reduce the proliferation of HUVEC after sequestration of VEGF-A.
The VEGF family consists of five related glycoproteins, VEGF-A, -B, -C, -D, and PIGF. VEGF-A has eight exons and creates isoforms of differing lengths ($VEGF_{121}$, $VEGF_{145}$, $VEGF_{148}$, $VEGF_{162}$, $VEGF_{165}$, $VEGF_{183}$, $VEGF_{189}$, and $VEGF_{206}$). The isoforms are present as a result of alternative splicing and proteolytic cleavage.

### 3.2.S.1.2 Structure

Brolucizumab is a fusion protein and consists of a light chain variable region ($V_L$) fragment and a heavy chain variable region fragment ($V_H$), which belong to the human kappa and VH3 subtypes respectively. The chains are connected via a flexible glycine/serine linker containing 21 amino acids.




Note: CDRs of the light chain (yellow background) and heavy chain (grey background) variable regions are underlined. The disulfide bridges within the light and heavy chain are shown.

The molecular weight of brolucizumab is 26,313 daltons. Due to the expression of brolucizumab in *E. coli*, there is an extra N-terminal methionine residue on the light chain compared to the consensus human immunoglobulin light chain. Brolucizumab has two disulfide bridges (Cys24-Cys89 and Cys154-Cys228).

### 3.2.S.1.3 General Properties

Brolucizumab DS is a clear to slightly opalescent, colorless to slightly brown-yellow aqueous solution. The pH of the aqueous solution is in the range of (b) (4), the isoelectric point (pI) of the main brolucizumab peak is approximately 5.4 as determined by capillary isoelectric focusing (cIEF). The theoretically calculated extinction coefficient of brolucizumab based on the amino acid composition is 2.209 x $10^3$ mL/(g cm) at 280 nm.

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## 3.2.S.2 Manufacture

### 3.2.S.2.1 Manufacturer(s)

(b) (4)

[redacted]

### 3.2.S.2.2 Description of Manufacturing Process and Process Controls & 3.2.S.2.4 Control of Critical Steps and Intermediates

(b) (4)

[redacted]



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(b) (4)

**P: DRUG PRODUCT**

**3.2.P.1 Description and Composition of the Drug Product**

The following table describes the composition of the DP:

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**Table 2-1 Composition of the drug product**

| Ingredient | Concentration (mg/mL) | Nominal amount (mg/vial) | Amount including overfill (mg/vial) | Function | Reference to standards |
|---|---|---|---|---|---|
| Brolucizumab (RTH258) | 120 | 6 | (b) (4) | Active ingredient | Novartis monograph |
| Sucrose | 58 | 2.9 | | (b) (4) | Ph. Eur; USP/NF |
| Sodium citrate [1)] | 2.58 | 0.13 | | | Ph. Eur; USP/NF |
| Polysorbate 80 [2)] | 0.20 | 0.01 | | | Ph. Eur; USP/NF |
| (b) (4) | pH 7.2 | pH 7.2 | | | Ph. Eur; USP/NF |
| | --- | --- | | | Ph. Eur; USP/NF |
| Water for injections [4)] | ad 1 mL, | ad 0.050 mL, (b) (4) | | | Ph. Eur; USP/NF |
| 1) | (b) (4) | | | | |
| 2) | | | | | |
| 3) | | | | | |

4) USP/NF name: Water for injection

The CCS for DP consist of a (b) (4) glass vial closed with a rubber stopper and sealed with an aluminum cap with a flip-off disk (assessed below in 3.2.P.2.6). The commercial presentation will be a vial kit which will include one vial of brolucizumab 6 mg/0.05 mL solution for injection co-packaged with a filter needle (b) (4)

## 3.2.P.2 Pharmaceutical Development

(b) (4)



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*The sponsor also included technical drawings for the vial, rubber stopper and flip off cap and specifications for the components of the CCS. The information provided for the DP CCS is adequate.*

## 3.2.P.8 Stability

### 3.2.P.8.1 Stability Summary and Conclusion

The proposed shelf-life for brolucizumab DP is 18 months at a storage condition of 2-8˚C in the designated CCS.

To support the storage conditions for brolucizumab DP, the sponsor provided the results of two stability studies using long term (2-8˚C), accelerated (25±2˚C/60±5% relative humidity) and stressed (30±2˚C/75±5% relative humidity) storage conditions:

- Registration stability study conducted on three lots produced with the commercial process except for a difference in scale (i.e, (b) (4) L) at the Novartis Pharma Stein site (lots 2019250, 2020588 and 2020589) out to 18 months at the long-term and 6 months at the accelerated and stressed conditions. The registration study also included the following studies:
    - 12 months of upper tolerance limit data after shaking (150 rpm) for 14 days at accelerated conditions or 7 days at long term conditions for lot 2020589.
    - 12 months of lower tolerance limit data after 2 freeze/thaw (f/t) cycles each consisting of 6 days at -20˚C and 1 day at 25˚C/60%RH, 7 days shaking (150 rpm) at long term conditions inverted and a stability study at long term conditions for lot 2020588.
    - Photostability study (24,000 lux hours, 1.2 million lux hours through primary and secondary packaging) for lot 2019250.
- Confirmatory stability study started on the three PV lots (S0004, S0005 and S0006) out to the available 6 months for the long-term, accelerated conditions and stressed condition.

The stability studies tested the same methods provided in the DP specification (section 3.2.P.5.1). As noted in section 3.2.P.5.1, some of the criteria are adjusted for the stability study.

The sponsor also provided a statistical assessment of the long-term trending of DS attributes to calculate a full shelf-life based on the available data from the registration study. All tested attributes are projected to be stable to (b) (4) in the chosen long-term storage condition.

***Assessor comment:*** *The data from the registration stability use lots with the same formulation and manufacturing process with difference in scale (i.e., (b) (4) L) compared to the proposed commercial process ((b) (4) L). Therefore, the registration lots can be considered as pilot-plant scale lots according to DP manufacturing process comparison and the comparability data provided n section 3.2.P.2.2 as well as ICH Q5C. All time points met acceptance criteria and only very minor trends were displayed at the proposed storage condition (< 5±3˚C). I agree with the sponsor's proposal for a shelf-life of 18 months based on the currently available data from the real time real condition representative lots. Since the DP shelf life is based on the pilot-plant scale lots, the sponsor needs to comment to provide the long-term stability data from at least three commercial DP lots. As noted below, the sponsor comments to do so by completing the long-term stability study of three PV DP lots. This approach is acceptable.*

*The statistical assessment is informative for the potential for long-term storage of DP and likely informs the sponsor's decision to continue shelf-life testing out to 36 months, but we do not grant shelf-life based on statistical modeling for biological molecules. Additionally, the sponsor is only requesting 18 months of shelf-life for brolucizumab DP at this time, though the stability protocol allows for extension in the future (reviewed below).*

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### 3.2.P.8.2 Post-Approval Stability Commitment

The sponsor has three proposals with regards to the DP stability program:

- Registration stability study: The sponsor commits to complete the study outlined above "through the product shelf life". The proposal includes testing at the long-term condition through 36 months.
- Commitment stability study: The sponsor commits to complete the study outlined above "through the product shelf life". This also includes testing through 36 months should product continue to meet acceptance criteria.
- Annual stability studies: The sponsor commits to put one lot of brolucizumab 6 mg/0.05 mL Solution for injection on stability annually and test according to the following protocol through the product shelf life:

**Table 1-1 Stability program – Annual stability studies**

(b) (4)

[redacted]

***Assessor comment:*** *The plans to complete the registration and commitment stability programs are acceptable and will provide 6 total lots of commercial presentation data at long term storage condition and 6 months for accelerated and stressed conditions respectively.*
*The proposed annual stability protocol was determined to be inadequate. ICH Q5C "Stability Testing of Biotechnological/Biological Products" includes language indicating that products with proposed shelf lives of greater than 1 year should have stability studies conducted every three months during the first year, every 6 months during the second year and annually thereafter.* (b) (4) [redacted] *s assessed below, use of the long-term condition (5±3˚C) will be sufficient to assess any unexpected changes in product quality. Additionally, the annual stability program for the DS, which is considered comparable to the DP in formulation,* (b) (4) *In an IR sent to the sponsor on June 28th, 2019 we recommended that the sponsor* (b) (4) [redacted] (b) (4) *The sponsor responded on July 5th, 2019 (eCTD #0017) agreeing* (b) (4) *and updated 3.2.P.8.2 accordingly with the following table:*

**Table 1-1 Stability program – Annual stability studies**

| Storage condition | Storage time (months) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0[1] | 3 | 6 | 12 | 18[2] | 24[2] | 36[2] |
| 5 ± 3°C | - | X | X | X | X | X | X |

X: Test point
- Not to be tested
1 Results taken from release analysis
2 Optional end of shelf-life testing depending on approved commercial shelf-life

*This response is acceptable.*

### 3.2.P.8.3 Stability Data

The following table prepared by the assessor summarizes the available primary stability data for DP:

| Available Stability Data for DP | | | | | |
|---|---|---|---|---|---|
| **Lot Number** | **Manufacturing Process Formulation** | **Batch Use** | **Storage Condition** | **Study Duration (Months)** | **Data Available (Months)** |
| 2019250 | B | Registration Stability Study | 5±3°C, ambient RH, inverted | 36 | 18 |
| | | | 25±2°C/65±5% RH, inverted | 6 | 6 |
| | | | 30±2°C/75±5% RH, inverted | 6 | 6 |
| 2020588 | B | Clinical/Registration Stability Study | 5±3°C, ambient RH, inverted | 36 | 18 |
| | | | 25±2°C/65±5% RH, inverted | 6 | 6 |
| | | | 30±2°C/75±5% RH, inverted | 6 | 6 |
| 2020589 | B | Registration Stability Study | 5±3°C, ambient RH, inverted | 36 | 18 |
| | | | 25±2°C/65±5% RH, inverted | 6 | 6 |
| | | | 30±2°C/75±5% RH, inverted | 6 | 6 |
| S0004 | B | PV/Confirmatory Stability Study | 5±3°C, ambient RH, inverted | 36 | 18 |
| | | | 25±2°C/65±5% RH, inverted | 6 | 6 |
| | | | 30±2°C/75±5% RH, inverted | 6 | 6 |
| S0005 | B | PV/Confirmatory Stability Study | 5±3°C, ambient RH, inverted | 36 | 18 |
| | | | 25±2°C/65±5% RH, inverted | 6 | 6 |
| | | | 30±2°C/75±5% RH, inverted | 6 | 6 |
| S0006 | B | PV/Confirmatory Stability Study | 5±3°C, ambient RH, inverted | 36 | 18 |
| | | | 25±2°C/65±5% RH, inverted | 6 | 6 |
| | | | 30±2°C/75±5% RH, inverted | 6 | 6 |

***Assessor comment:*** *In the initial submission, the sponsor indicated that all three lots used in the registration study were used in clinical trials. This was not consistent with the information provided in the "Clinical Trial Formulae" document in section 3.2.P.3.5. Clarification was requested in the IR sent on June 14th, 2019. The response received July 11th, 2019 (eCTD #0018) indicated that lots 2019520 and 2020588 were not used in a clinical trial. The above table has been adjusted to reflect that only lot 2020588 has been used in clinical trial, specifically the "CRTH258A2301E1 HAWK extension" trial.*
*All provided stability data were assessed and used to evaluate the appropriateness of the criteria. All stability data for the registration batches through the proposed shelf-life met acceptable criteria, and*

*the criteria are set based on the sponsor's statistical modeling out to 36 months.* (b) (4)

(b) (4)

*Interestingly brolucizumab concentration by UV and potency were preserved through the 6 months of testing at accelerated and stressed conditions for DP. However, the purity data clearly show a thermal sensitivity for brolucizuma* (b) (4)

*In totality, the provided stability data support the sponsor's proposed shelf-life of 18 months for brolucizumab DP when stored in the indicated CCS at 5±3°C.*

*Photostability Study*

The sponsor provided the results of a photostability study in which the registration batches were exposed to either 24,000 lux hours or 1.2 million lux hours irradiated through the primary package, 1.2 million lux hours through the primary package and the cardboard box along with a dark control. All samples were stored inverted.

***Assessor comment:*** *No differences were noted in the sample exposed to 24,000 lux hours, 1.2 million lux hours in the primary package and cardboard box or the dark control. [(b) (4)%] A very minor reduction in* ***purity by CE-SDS (reducing*** *[(b) (4)%]* ***and non-reducing)*** *is also noted. Overall, brolucizumab demonstrated a small loss of purity in response to the most extreme light-stress condition and should be kept protected from light.*

*In Use Stability*

The sponsor provided in-use stability data from pre-validation batch 2022748 after 12 hours, 24 hours and 48 hours of ambient light and temperature exposure (25-30°C/ambient RH, not more than 1000 lux). Based on the results the sponsor considers up to 24 hours exposure to ambient conditions (not more than 30°C) and not more than 1000 lux to be acceptable.

***Assessor comment:*** *The provided data show very slight decreases in purity by AEX and purity by SEC over the 48 hours tested, but all results are still well within the acceptable specification. The sponsor also provided compatibility data in the delivery instrument reviewed above in section 3.2.P.2.6 with 1 hour of exposure. This is considered more relevant as the study provided here is in the CCS and not the delivery device.*

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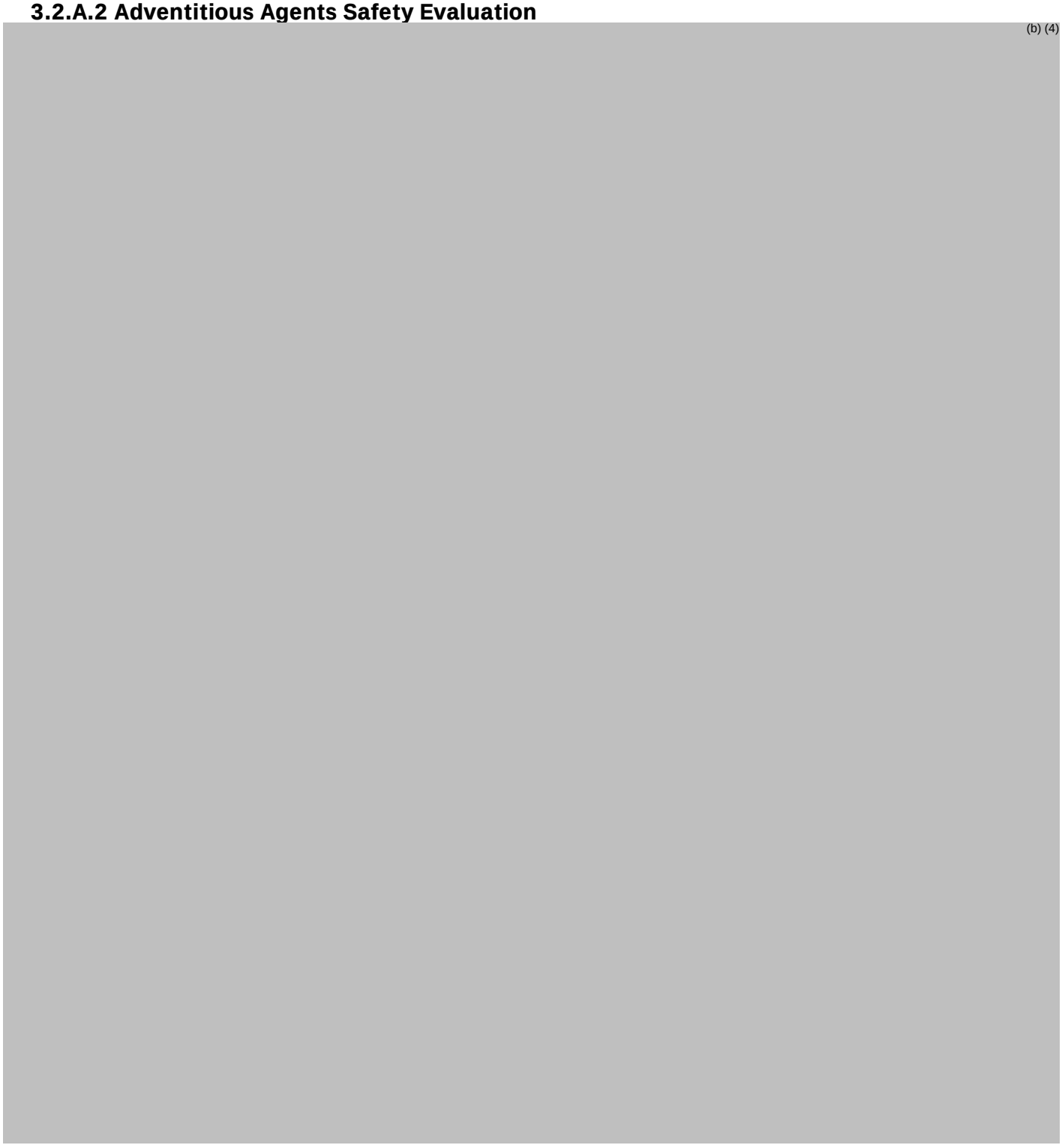
## 3.2.A Appendices Table of Contents

### 3.2.A.1 Facilities and Equipment

***Assessor comment:*** *This section will be assessed by the OPQ/DIA assessor.*

### 3.2.A.2 Adventitious Agents Safety Evaluation

(b) (4)





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(b) (4)

[redacted]

### 3.2.R.1 Executed Batch Records

***Assessor comment:*** *The provided batch records for DS batch 1012 and DP lot S0004 were assessed and the relevant information and assessor comments were incorporated in the reviews for section 3.2.S.2.6 and 3.2.P.2.3.*

### 3.2.R.2 Method Validation Package

***Assessor comment:*** *The analytical method validation, qualification and transfer reports submitted with this application are assessed in the section 3.2.S.4.3 Validation of Analytical Procedures for DS and 3.2.P.5.3 Validation of Analytical Procedures for DP.*

### 3.2.R.3 Comparability Protocols

No comparability protocols were provided with the submission.

### 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

*1. Overview*

The current immunogenicity assay is a homogeneous bridging ligand binding electrochemiluminescence (ECL) format for the measurement of anti-drug antibodies (ADA) in human serum. The neutralizing antibody (nAb) assay utilizes a competitive ligand binding ECL format to detect the presence of nAb to brolucizumab in serum. The following table provided by the sponsor includes a summary of characteristics of all biopharmaceutical assays used:

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**Table 1-2 Summary of analytical methods used in clinical studies**

| Analyte | Matrix | Method ID | LLOQ[1] or Sensitivity [2] or drug tolerance [3] | Method validation report | Clinical studies which used this method |
|---|---|---|---|---|---|
| Free brolucizumab | Serum | A - PK | 0.500 ng/mL[1] | TDOC-0017387 | C-10-083 |
| Anti-brolucizumab antibodies | Serum | B - ADA | 250 ng/mL[2] | TDOC-0017570 | C-10-083 |
| Free brolucizumab | Serum | C - PK | 0.500 ng/mL[1] | TDOC-0054943 | RTH258-E003, RTH258-C-001, RTH258-C-002, A2301E1 |
| Anti-brolucizumab antibodies | Serum | D - ADA | 39.1 ng/mL [2]<br>>100.0 µg/mL of drug at 5000 ng/mL antibody [3]<br>50.0 µg/mL of drug at 1000 ng/mL antibody [3]<br>25.0 µg/mL of drug at 250.0 ng/mL antibody [3]<br>10.0 µg/mL of drug at 125 ng/mL antibody [3] | TDOC-0054944 | RTH258-E003, RTH258-C-001, RTH258-C-002, A2301E1 |
| Neutralizing anti-brolucizumab antibodies | Serum | E - nAb | 487.8 ng/mL [2]<br>100 µg/mL drug at 5000.0 ng/mL antibody [3]<br>50.0 µg/mL drug at 1250.0 ng/mL antibody [3]<br>0 µg/mL drug at ≤ 312.5 ng/mL antibody [3] | TDOC-0054944 | RTH258-E003, RTH258-C-001, RTH258-C-002, A2301E1 |

PK: Pharmacokinetics; ADA: Anti-Drug Antibodies; nAb: Neutralizing antibody

Note: No data provided for RTH258-C-12-006 and RTH258-C-13-001; No PK or ADA assessments were conducted in those studies

The previous ADA assay (B-ADA) was used only with samples from the phase 1 clinical trial C-10-083 before the sponsor updated to the current version (D-ADA), which was used with the phase 2-3 trials and is being used with the extension trials.

***Assessor comment:*** *The indication (nAMD) and resulting dose strength and volume (6 mg/50 µL), dose frequency (3xq4w+q12w/q8w to 92 weeks, either 10 or 13 doses), route of administration (intravitreal injection) and the nature of the product itself all minimize the risk for harmful ADA. The sponsor states the following "The free brolucizumab concentrations in serum were generally low (geometric mean Cmax 9.76 and 49.0 ng/mL for brolucizumab 3 mg and 6 mg, respectively) but quantifiable in most subjects following a single intravitreal injection." Based on an email from clinical pharmacology reviewer Abhay Joshi received 5/21/2019, the maximum concentrations of serum brolucizumab ranged from 2.7-117 ng/mL in the pivotal studies RTH258-C001 and RTH258-C002, confirming the sponsor's contention that serum concentrations are generally low. Based on the above factors, the risk from ADA is considered to be low by the assessor.*
*An additional complicating factor is the high rate of pre-existing ADA detected in the treatment-naïve patients (49.2%) due to the scFv nature of the molecule. The sponsor states that this is "analogous to other antibody fragments such as nanobodies and single domain antibodies". In all clinical trials, just under half of the patients had pre-existing antibodies. The sponsor stated that a parametric statistical analysis was used to calculate a cutpoint factor due to the high level of pre-existing ADA.*
*According to the information provided in section 2.5 Clinical Overview, RTH258-E003 is a phase 2 study, both RTH258-C001 and RTH258-C002 are pivotal phase 3 studies, and A2301E1 is a phase 3 extension study. The current (D-ADA) immunogenicity assay was used for these clinical studies including the pivotal clinical studies used for determination of immunogenicity incidence reported in the*

*prescribing information. Therefore, the following assessment focuses on the current (D-ADA) immunogenicity assay validation.*
*Review of the PK assays listed above is deferred to the assigned clinical pharmacology assessor.*

*2. Screening Assay (D-ADA)*
The screening assay was a homogeneous bridging ligand binding assay in an ECL format. The following table prepared by the reviewer summarizes the characteristics of the assay:

| **ADA Screening Assay** | | |
|---|---|---|
| **Parameter** | **Assay Design and Results** | ***Assessor comment*** |
| Positive Control (PC) | Rabbit anti-RTH258 (brolucizumab) polyclonal antibodies<br>High PC (HPC): 5000.0 ng/mL<br>Medium PC (MPC): 1000.0 ng/mL<br>Low PC1 (LPC1): 250.0 ng/mL<br>Low PC2 (LPC2): 125.0 ng/mL. | *Provided by Alcon Research, Ltd, the original DP manufacturer. Lot # SQ14AK02201 used in studies. The sponsor included a CoA from* (b) (4) *for affinity purified rabbit serum for the antibody. The PC is acceptable.* |
| Minimum required dilution (MRD) | 1:10 | *Samples are also treated with 326 mM acetic acid at a 1:5 ratio for 30 minutes to dissociate any complexes present. The 1:10 MRD is consistent with FDA's recommendation which is lower than 1:100 for immunogenicity assays.* |
| Assay Cut Point Factor | **Drug Naïve:** 100 human serum individuals (50 per gender) diluted 1:10 in assay buffer tested in duplicate, 3 independent runs, 2 analysts for a total of approximate 18 runs<br><br>1.32<br><br>**Disease population:** At least 59 disease population samples tested the same way for of ~13 runs<br><br>1.40 | *As noted above, a parametric screening floating cutpoint was determined based on the analysis of the normal distribution and variances of the samples. Linear mixed effects ANOVA models were used remove identified outliers from the entire dataset as well as in subsets from the healthy subjects and patients. All values for individual samples identified as biologic outliers were removed and the statistical analysis was repeated until no outliers were present. Using this potentially positive population (85 healthy subjects and 101 disease subjects) the sponsor defined the assay cut point with a 5% false positive rate. The number of samples, approach to determine the cutpoint factor and the false positive rate of 5% are in alignment with FDA's expectations. In addition, the disease specific cutpoint factor was determined using the appropriate approach. Therefore, this disease-specific cutpoint factor can be directly used to determine ADA incidence for the patients enrolled in the clinical studies.* |
| Assay Sensitivity | Performed by spiking 10,000.0 ng/mL PC into 100% low background pool then diluting 1:10 to 1000.0 ng/mL and a subsequent eleven 2-fold dilutions to 0.49 ng/mL and testing samples in duplicate<br><br>39.1 ng/mL | *The lowest antibody concentration to have a mean signal above the NC cut point of 1.32 was 3.91 ng/mL. Factoring in the MRD yields a sensitivity of 39.1 ng/mL. The approach to determine the assay sensitivity counted the MRD and the assay sensitivity is less than 100 ng/mL, which meets FDA's expectations.* |
| Drug Tolerance | PC were spiked with 100, 50, 25, 10, 1 and 0 μg/mL of RTH258 and assessed in duplicate after one hour of incubation and MRD dilution<br><br>250 ng/mL (LPC1) in the presence of 25.0 μg/mL RTH258, 125 ng/mL (LPC2) in the presence of 10 μg/mL RTH258 | *The drug tolerance was identified as the highest concentration of RTH 258 (25.0 μg/mL) that resulted in an assay value above the cut point. While the use of the 250 ng/mL LPC1 to declare drug tolerance is relatively higher than the FDA recommends, the value for LPC2 (125 ng/mL) provided (10 μg/mL) is ~100-fold greater than the highest serum concentration of brolucizumab observed. Most importantly, the maximal levels of on-* |

| | | |
|---|---|---|
| | | *board drug in the patients of the pivotal clinical studies ranged from 2.7-117 ng/mL. This supports that the ADA below 125 ng/mL in the patient serum can be detected by the current immunogenicity assay when brolucizumab is present at the maximal level determined by PK analysis.* |
| Specificity | **Drug Naïve:** 100 human serum individuals tested spiked with 10.0 mg/mL RTH258 with unspiked serum controls included on the plate tested in 3 independent runs using 2 analysts for a total of ~ 18 runs<br><br>**Disease Population:** 59 disease samples tested the same way for a total of ~13 runs | *Results and approach are acceptable.* |
| Selectivity | PC spiked in 10 neat human serum individuals (5 male/5 female) at the high PC, low PC 1, low PC 2 concentrations and unspiked. All samples diluted 1:10 in assay buffer then plated in duplicate.<br><br>All PC samples passed in 10/10 individuals | *The assay demonstrated acceptable specificity for the PC range tested, which is suitably wide.* |
| Precision | PC spiked in neat low background pool at 5000, 1000, 250 and 125 ng/mL. Used in each assay, stored frozen at -70±10˚C. | *Inter- (3.8 to 5.5%) and Intra- (5.4-7.3%) Assay variability of the PC listed returned low % cv results across 30 assays. The results are acceptable.* |
| Robustness and Sample Stability | **Bench top stability**: Assessed by leaving the spiked precision PCs at room temperature for at least 24 hours prior to analysis<br><br>No change in any sample after 24 hours<br><br>**Freeze/Thaw stability:** Assessed by subjecting the spiked precision samples up to 10 F/T cycles at -70±10˚C and -20±5˚C with each freeze period lasting 12-24 hours<br><br>Minimal change in HPC and MPC but well within acceptance criteria and acceptable. No change to LPC1 and LPC2<br><br>**Long term stability**: Assessed stability of HPC, MPC and LPC1 over the course of baseline, 1, 3, 6, 9 and 12 months for PCs stored at -20±5˚C and 1, 3, 6, 12, 18 and 24 months for PCs stored at -70±10˚C | *The results for the long-term stability were submitted as an addendum to the BLA and all samples passed long term stability testing up to 18 months for -70±10˚C and 12 months at -20±5˚C. The assay samples showed acceptable stability.* |

*3. Confirmatory Assay (D-ADA)*

The confirmatory assay utilized the same format, so the majority of the assay validation is covered above. The parameters specific to the confirmatory assay are summarized below:

| **ADA Confirmatory Assay** | | |
|---|---|---|
| **Parameter** | **Assay Design and Results** | ***Assessor comment*** |

| | | |
|---|---|---|
| Assay Cut Point Factor | The mean percent inhibition was determined for each individual following immunodepletion by incubation with 10 μg/mL RTH258 and a cut point calculated based on a 1.0% false positive rate. For each normal and diseased individual the %inhibition is calculated as 100% * (1-(mean of spiked sample/mean of unspiked sample).<br><br>**Cutpoint used for all samples:** 49.20% | *The same parametric statistical analysis was performed to generate assay cutpoint. Using this population, the sponsor defined the assay cut point with a 1% false positive rate, which meets FDA's expectations.*<br>*The cutpoints were calculated for both diseased and normal populations and found to be within 25% of each other (49.2% and 53.5%) so the sponsor used the same cutpoint for both populations and chose the lower cutpoint to increase stringency.* |
| Assay Sensitivity | Assay sensitivity not specifically assessed for confirmatory assay | *While the sponsor did not perform a specific experiment to establish assay sensitivity for the confirmatory assay, the drug tolerance data from spiking with 100.0, 50.0, 25.0, **10.0**, 1.0 and 0.0 μg/mL RTH258 with both LPC1 and LPC2 can be used to support the ability of the assay to detect %inhibition by 10 μg/mL RTH258 at the LPC2 level (125 ng/mL). FDA guidance recommends sensitivity at the level of 100 ng/mL but allows for higher values depending on risk and prior knowledge. Given the high sensitivity of the screening assay, the proximity of the sensitivity and the overall risk assessment for ADA with this product, this sensitivity is acceptable.* |
| Precision | Assay precision not specifically assessed for confirmatory assay | *While the sponsor did not perform a specific experiment to establish assay precision for the confirmatory assay, the % CV values obtained for the drug tolerance assay run in a similar format for HPC, MPC, LPC2 and LPC1 were all ≤10%* |

*4. ADA Titering Assay (D-ADA)*
The titer assay utilizes the same format as the screening assay. Titered samples that passed the confirmatory assay were prepared at the MRD (1:10) and dilutions of 1:3, 1:9, 1:27, 1:81, 1:243, 1:729, 1:2187 and 1:6561. The largest dilution for which the mean response ≥ the titer cutpoint (1.69 for normal population, 1.79 for disease population) was evaluated as the final titer of the sample and the titer was reported as dilution multiplied by the MRD.

***Assessor comment:*** *The titer cut point from the samples were established as 1.69 (normal) or 1.79 (disease) populations respectively. The approach to determine the titer cutpoints is acceptable.*

*5. Neutralizing Antibody Assay (E-nAb)*
The nAb assay utilized a competitive ligand binding ECL format. Samples were diluted 1:5 in assay buffer and then co-incubated with Sulfo-Tag labeled brolucizumab. After incubation samples were plated into a blocked MSD Streptavidin Gold Plate coated with biotinylated rhVEGF$_{165}$. The presence of nAb were indirectly detected by a decrease (inhibition) in response of the Sulfo-Tag brolucizumab:rhVEGF$_{165}$ complex. The following table prepared by the assessor summarizes the characteristics specific to the nAb assay:

***Assessor comment:*** *Although the cell-based assay is preferred and recommended by the FDA to detect nAb, it is acceptable to use the non-cell-based competitive ligand-binding assays because brolucizumab binds VEGF-A to prevent the interaction between VEGFA and its extracellular receptors.*

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| nAb Assay | | |
|---|---|---|
| **Parameter** | **Assay Design and Results** | ***Assessor comment*** |
| Positive Control (PC) | Rabbit anti-RTH258 polyclonal antibodies<br>High PC (HPC): 5000.0 ng/mL<br>Medium PC (MPC): 1250.0 ng/mL<br>Low PC1 (LPC1): 625.0 ng/mL<br>LPC2: 312.5 ng/mL<br>LPC3: 156.3 ng/mL<br>LPC4: (78.1 ng/mL) | *Provided by Alcon Research, Ltd, the original DP manufacturer. Lot # SQ14AK02201 used in studies. The sponsor included a CoA from* (b) (4) *for affinity purified rabbit serum for the antibody. The PC is acceptable.* |
| Minimum required dilution (MRD) | 1:5 | *The 1:5 MRD is consistent with FDA's recommendation for MRD, which is lower than 1:100 for immunogenicity assays.* |
| Assay Cut Point Factor | **Healthy Population:** At least 50 samples tested in 4 runs<br><br>0.891<br><br>**Disease population:** At least 50 disease population samples tested in 4 runs<br><br>0.676 | *As noted above, a parametric statistical analysis was performed to generate assay cutpoint. Using this population, the sponsor defined the assay cut point with a 1% false positive rate, which meets the FDA's expectations.* |
| Assay Sensitivity | Performed by spiking 5000.0 ng/mL PC into 100% normal human serum then eight subsequent 2-fold serial dilutions to 19.5 ng/mL. Samples were frozen for at least 12 hours then analyzed. Sensitivity was assessed across 6 plates on 3 days with 2 analysts.<br><br>487.8 ng/mL | *While targeted sensitivity for ADA assays is 100 ng/mL according to FDA Guidance, it is acknowledged that nAb assay sensitivity can be higher due to the lack of true nAb positive controls. This sensitivity is supported by the data.* |
| Drug Tolerance | PC were spiked with 100, 50, 25, 10, 1 and 0 μg/mL of RTH258 and assessed in duplicate after one hour of incubation and MRD dilution<br><br>HPC (5000.0 ng/mL) could tolerate 100.0 ng/mL<br><br>MPC (1250.0 ng/mL) tolerated 50.0 ng/mL | *The assay has low drug tolerance. However, considering the low serum levels noted above and the MRD of 1:5, the maximal theoretical brolucizumab concentration is 23.4 ng/mL, which is below the reported drug tolerance for the MPC. Given the low risk assessment for the product ADA based on the route of administration and mechanism of action, the assay drug tolerance is acceptable.* |
| Selectivity | PC spiked in 10 neat human serum individuals (5 male/5 female) at the HPC and LPC1 concentrations and unspiked and assayed in duplicate.<br><br>All PC samples passed in 10/10 individuals with %CV ≤20. | *The assay demonstrated acceptable specificity for the PC range tested, which is suitably wide.* |
| Precision | HPC, MPC, LPC1-4 all run in 2 sets along with four sets of negative control (NC). Intra-assay variability was assessed with six sets on a single plate. | The intra- and inter- run precision at the LPC1, MPC and HPC are all ≤ 20%. |

Brian Roelofs

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Yan Wang (OPQ/OBP)

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