APPLICATION NUMBER:

761125Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)
<table>
<thead>
<tr>
<th><strong>BLA Number</strong></th>
<th>761125</th>
</tr>
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<tbody>
<tr>
<td><strong>Link to EDR</strong></td>
<td><a href="#">Link</a></td>
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<tr>
<td><strong>Submission Date</strong></td>
<td>02/07/2019</td>
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<tr>
<td><strong>Submission Type</strong></td>
<td>Priority</td>
</tr>
<tr>
<td><strong>Proposed Brand Name</strong></td>
<td>Beovu</td>
</tr>
<tr>
<td><strong>Generic Name</strong></td>
<td>Brolucizumab (RTH258)</td>
</tr>
<tr>
<td><strong>Dosage Form and Strength</strong></td>
<td>120 mg/mL solution for intravitreal injection</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Local</td>
</tr>
<tr>
<td><strong>Proposed Indication</strong></td>
<td>Treatment of neovascular age-related macular degeneration (AMD)</td>
</tr>
<tr>
<td><strong>Applicant</strong></td>
<td>Novartis Pharmaceuticals Corporation</td>
</tr>
<tr>
<td><strong>Associated IND</strong></td>
<td>IND 112023</td>
</tr>
</tbody>
</table>
| **OCP Review Team** | Abhay Joshi, Ph.D.  
Philip Colangelo, Pharm.D., Ph.D. |
| **OCP Final Signatory** | John A. Lazor, Pharm.D.  
Office of Clinical Pharmacology Division IV Director |
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1. EXECUTIVE SUMMARY

This submission is a 351(a) BLA for Beovu\textsuperscript{TM}, which is a 120 mg/mL brolucizumab (a.k.a. RTH258, ESBA1008, AL-86810) solution for local intravitreal (IVT) injection into the eye for the treatment of neovascular (or wet) Age-related Macular Degeneration (nAMD). The key clinical studies in this submission are two Phase 3 studies, one Phase 1 study, and one Phase 2 study. The efficacy evaluations in Phase 3 studies included the effect of brolucizumab treatment on improvement of best-corrected visual acuity (BCVA). The key clinical pharmacology review questions focus on the proposed brolucizumab dosing regimen for the proposed indication and the evaluation of relationship between a patient’s immunogenicity status and the observed change in BCVA from baseline.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the relevant Clinical Pharmacology information provided by the Applicant in BLA 761125 for brolucizumab 120 mg/mL for IVT injection (Beovu) and recommends approval of this BLA.

<table>
<thead>
<tr>
<th>Review Issue</th>
<th>Recommendations and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal or supportive evidence of effectiveness</td>
<td>Pivotal evidence of effectiveness is derived from two Phase 3 studies: Studies RTH258-C001 and RTH258-C002. These studies evaluated the safety and efficacy of the proposed brolucizumab dosing regimen in patients with nAMD in comparison to the approved dosing regimen of aflibercept (Eylea). The aflibercept dose regimen used in these studies was 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 doses, followed by 2 mg once every 8 weeks.</td>
</tr>
<tr>
<td>General dosing instructions</td>
<td>The proposed brolucizumab dosing regimen is 6 mg (0.05 mL) administered by IVT injection monthly for the first 3 doses followed by 6 mg monthly. The proposed 6 mg brolucizumab dose regimen was part of the brolucizumab dosing regimens that were evaluated in pivotal Phase 3 Studies RTH258-C001 and RTH258-C002.</td>
</tr>
<tr>
<td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td>
<td>The Applicant has not proposed dose adjustments based on any intrinsic or extrinsic factors. The Applicant’s proposal of no dosage adjustments in any patient subgroup (e.g., renal or hepatic impairment) is acceptable.</td>
</tr>
<tr>
<td>Labeling</td>
<td>Labeling recommendations are not finalized at the time of this review and discussions on labeling language are ongoing.</td>
</tr>
<tr>
<td>Bridge between the to-be-marketed and clinical trial formulations</td>
<td>A bridging pharmacokinetic study between the to-be-marketed and clinical trial formulation is not warranted since the clinical trial formulation is similar to the to-be-marketed formulation.</td>
</tr>
</tbody>
</table>
1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The proposed drug product is 120 mg/mL brolucizumab solution for local IVT injection into the eye for the treatment of nAMD, which is characterized by pathologic choroidal neovascularization. Brolucizumab is a humanized single-chain Fv (scFv) antibody fragment that inhibits vascular endothelial growth factor A (VEGF-A). VEGF-A plays a role in neovascularization and vascular permeability and its inhibition reduces neovascularization and decreases vascular permeability.

The proposed dosing regimen is three monthly 6 mg (0.05 mL) brolucizumab doses administered by IVT injection.

Evaluation of the systemic PK exposure to brolucizumab was primarily derived from Study RTH258-E003 in 25 nAMD patients. In this study, free brolucizumab (unbound to VEGF-A) serum concentration versus time profiles were assessed following a single IVT injection and following 3 monthly IVT injections of 6 mg brolucizumab doses in the affected eye in patients with nAMD. Systemic PK findings are summarized below; refer also to Section 4.2 for additional PK information:

Absorption: Following a single IVT dose of 6 mg brolucizumab, the mean Cmax in serum was 78 ng/mL (range: 9-548 ng/mL) and median Tmax was 1 day (range: 6 hours – 3 days). No systemic accumulation of brolucizumab was observed following three monthly doses as the 24 hour post injection serum brolucizumab concentrations on Day 1 and Day 57 were comparable.

Elimination: The mean estimate of the serum half-life of brolucizumab is 5 days.

Metabolism: The metabolism of brolucizumab has not been fully characterized. However, as with most monoclonal antibody products, brolucizumab is hypothesized to undergo metabolism via proteolysis.

Excretion: The excretion of brolucizumab has not been fully characterized. However, brolucizumab appears to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF-A and/or passive renal elimination.

Immunogenicity:

Pre-treatment/Baseline Immunogenicity: For patients who were part of the safety population in Studies RTH258-C001 and RTH258-C002 and received brolucizumab 6 mg (n=729), at baseline (pre-treatment), 321 (44%) patients had serum samples that were positive (+) for anti-drug antibodies (ADA(+)) for brolucizumab and 120 (17%) patients had serum samples that were (+) for neutralizing antibodies (nAb(+)) for brolucizumab.
Overall Immunogenicity Findings: For patients that were part of the safety population in Studies RTH258-C001 and RTH258-C002 and received brolucizumab 6 mg (n=729), 522 (71.6%) patients had at least one ADA(+) brolucizumab serum sample and 232 (31.8%) patients had at least one nAb(+) brolucizumab serum sample.

Relationship Between Immunogenicity and BCVA: The efficacy evaluation in Studies RTH258-C001 and RTH258-C002 included the change in BCVA from baseline ($\Delta$BCVA), in terms of gain in letters, with treatment. Based on the combined data from both studies with the 6 mg brolucizumab dose regimen, the reviewer’s analyses suggested that there was a trend towards a lower mean $\Delta$BCVA in ADA(+) brolucizumab patients when compared to patients who were ADA negative (-) for brolucizumab and those patients who received aflibercept (Figure 1). However, at the end of the study period, mean $\Delta$BCVA estimates in ADA(+) brolucizumab patients were somewhat comparable to the mean $\Delta$BCVA in patients enrolled in the aflibercept arm (Figure 1). It also appeared that ADA(-) brolucizumab patients had a somewhat greater $\Delta$BCVA (gain in letters) as compared to the aflibercept arm as the study progressed to completion (Figure 1).

These findings were discussed between the Clinical Pharmacology and Clinical review teams. However, the clinical relevance of these findings had not been determined. See Section 4.3 for additional details and the reviewer’s analyses regarding the relationship between a patient’s immunogenicity status and $\Delta$BCVA.
2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing
The proposed dosing regimen for brolucizumab is 6 mg (0.05 mL) by IVT injection for the first three doses.

2.2.2 Therapeutic individualization
The Applicant has not proposed any therapeutic individualization. The available clinical pharmacology information does not warrant a need for therapeutic individualization.

2.3 Outstanding Issues
None.
2.4 Summary of Labeling Recommendations
Labeling recommendations are not finalized at the time of this review and discussions on labeling language are ongoing.
3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background
The proposed brolucizumab dosing regimen was evaluated in the two Phase 3 studies: Study RTH258-C001 and Study RTH258-C002, which are pivotal studies for this submission. Study CRTH258A2301E1 was a 24-week extension study that enrolled a subgroup of nAMD patients who completed Study RTH258-C001. Additional supportive studies include a Phase 2 study (Study C-12-006) and a PK study (Study RTH258-E003).

Information on the systemic PK exposure to brolucizumab is primarily derived from Study RTH258-E003, which evaluated brolucizumab PK following a single IVT injection and following 3 monthly IVT injections of 3 mg and 6 mg brolucizumab in 25 nAMD patients. Systemic PK findings from this study are summarized in the table in Section 3.2 only for the 6 mg IVT dose since this is the clinically recommended dose.

3.2 General Pharmacology and Pharmacokinetic Characteristics
Brolucizumab clinical pharmacology information is presented in table below.

<table>
<thead>
<tr>
<th>Pharmacology</th>
<th>6 mg/0.05 mL sterile solution for IVT injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Wet AMD is characterized by pathologic choroidal neovascularization. Vascular endothelial growth factor A (VEGF-A) plays a role in neovascularization and vascular permeability. Brolucizumab is a humanized single-chain Fv (scFv) antibody fragment that binds to and inhibits VEGF-A and thereby reduces neovascularization and decreases vascular permeability.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic Exposure Parameter Estimates (Mean ± SD) Following Single 6 mg IVT Dose of Brolucizumab in Study RTH258-E003¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
</tr>
<tr>
<td>AUC0-Inf (ng*Days/mL)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution</th>
<th>280 ± 231</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination</td>
<td></td>
</tr>
<tr>
<td>Total Clearance (L/h)²</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Half-Life (days)²</td>
<td>5 ± 2</td>
</tr>
</tbody>
</table>

¹ Measured as free brolucizumab concentration in serum
² Estimates from patients receiving 6 mg brolucizumab dose
Metabolism & Excretion

No biotransformation studies have been conducted. Brolucizumab has molecular weight of ~26 kDa and its metabolic pathway is theorized to be degradation to small peptides and individual amino acids. Brolucizumab is anticipated to be eliminated through target mediated disposition and renal elimination in a manner similar to cytokines, growth factors, and other small proteins with a molecular weight of <69kDa.

### Immunogenicity

<table>
<thead>
<tr>
<th>Immunogenicity Status</th>
<th>Number of patients (%) who received brolucizumab 6 mg and were part of the safety population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study RTH258-C001 (N=360)</td>
</tr>
<tr>
<td>Baseline ADA Positive (+)</td>
<td>128 (36%)</td>
</tr>
<tr>
<td>At least one Sample ADA(+)</td>
<td>241 (67%)</td>
</tr>
<tr>
<td>Baseline nAb(+)</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>At least one Sample nAB(+)</td>
<td>81 (23%)</td>
</tr>
</tbody>
</table>

### In Vitro & In Vivo Drug Interaction Findings

Since this is a monoclonal antibody, no drug-drug interaction studies were conducted nor warranted, either in vitro or in vivo.

### 3.3 Clinical Pharmacology Review Questions

#### 3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The safety and efficacy of the proposed brolucizumab dosing regimen in nAMD patients was evaluated in two Phase 3 studies: Studies RTH258-C001 and RTH258-C002. These studies provide pivotal evidence of effectiveness for the proposed indication of nAMD.

#### 3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general nAMD patient population for which the indication is being sought.

#### 3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

An alternate dosing regimen is not needed. For the proposed drug product, the intended site of drug delivery and action is the eye; therefore, the extent of systemic exposure does not relate with the proposed drug product’s efficacy. From a perspective of safety, no clinically significant differences in the systemic PK of brolucizumab were observed based on age (>50 years), sex, or mild to moderate renal

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3 See Section 4.4 for Definitions/Glossaries
impairment (measured based on glomerular filtration rate (GFR)= 30 to 70 mL/min, estimated using the Modification of Diet in Renal Disease (MDRD) equation).

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?
- The drug product is given via IVT injection; therefore, the issue of a food-drug interaction is not relevant.
- No drug-drug interaction studies were conducted in vitro or in vivo. However, drug-drug interactions are not expected based on CYP450, other metabolizing enzymes, or transporters, since brolucizumab’s metabolism does not utilize these pathways.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Brolucizumab Serum Quantification: Information on the systemic PK of brolucizumab is primarily derived from Study RTH258-E003. Study RTH258-E003 evaluated free brolucizumab concentrations in human serum using immunoaffinity-LC-MS/MS method. The rhVEGF165 bound to Streptavidin coated magnetic beads was used to capture brolucizumab and the captured brolucizumab was subject to proteolysis with trypsin followed by protein denaturation, reduction, and alkylation processing steps. A signature peptide from the digestion with trypsin was used as a surrogate for the quantitation of free brolucizumab by LC-MS/MS. Review of this method utilized to quantify brolucizumab (Also referred as RTH258 or ESBA1008 in this section) is summarized in the table below.

<table>
<thead>
<tr>
<th>Study</th>
<th>RTH258-E003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyte/Assessment</td>
<td>Brolucizumab</td>
</tr>
<tr>
<td>Method</td>
<td>LC-MS/MS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Validation Report</th>
<th>Validation report provided: TDOC-0054943</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes:</td>
<td>Validation report acceptable:</td>
</tr>
<tr>
<td>Range: 0.5 ng/mL (LLOQ) to 80 ng/mL</td>
<td></td>
</tr>
<tr>
<td>1. The validation report notes that the solvent (50:50 acetonitrile / water,v/v) used to pre-fortify impacted the results and low (&lt; 5% capture efficiency) and variable analyte was detected in pre-capture samples compared to post-capture samples. When the same solvent was used to post-fortify the capture efficiency samples with no impact. Consequently, digestion efficiency was higher (approximately 450%). The validation report cites non-specific binding of the analyte as a likely cause. Consequently, to assess capture efficiency, existing quality controls were used as PRE-samples and post-capture by adding the solvent. The approach appears to show biased but consistent immunoaffinity capture (%CV= 7.89%); therefore, the proposed approach appears reasonable.</td>
<td></td>
</tr>
<tr>
<td>2. Negative bias was observed when ADA (+/-) human serum was spiked with brolucizumab at 0.5 ng/mL. The report concludes that these findings indicate varying concentrations of endogenous VEGF and or pre-existing anti-drug antibodies could have a “negative interference”. Given that the</td>
<td>☒ Yes ☐ No</td>
</tr>
</tbody>
</table>

Reference ID: 4471993
use of PK data is limited to characterize systemic safety and the assay results report free brolucizumab concentrations, these findings do not appear to be of a significant concern.

3. The method validation reported noted carryover (0-42% of mean LLOQ response) and consequently provisions were made to the method to minimize its impact. The Applicant’s approach appears adequate.

Performance Report

- Performance report provided: TDOC-0053390
- Samples analyzed within the established stability period
- Note: An addendum document (TDOC-0054943-01) provides stability information
- Quality control (QC) samples range acceptable
  - QC: 1 ng/mL, 32 ng/mL, 60 ng/mL, 160 ng/mL
- Chromatograms provided
- Accuracy and precision of the calibration curve acceptable
- Accuracy and precision of the quality control samples acceptable
- Incurred sample reanalysis (ISR) acceptable
- Overall performance reasonable

Inspection

- Will the bioanalytical site be inspected?

Anti-brolucizumab Antibodies in Human Serum: A homogenous bridging ligand binding electrochemiluminescence (ECL) assay was utilized for assessing anti-brolucizumab antibody (ADA) levels in human serum from the samples collected from Studies RTH258-E003 (Phase 1), RTH258-C-001 (Phase 3), RTH258-C-002 (Phase 3). The diluted and acid treated samples were co-incubated with Biotinylated brolucizumab and Sulfo Tag brolucizumab. The resulting complexes were captured on a Streptavidin plate and detected after addition of MSD Read Buffer T (2X) with an MSD Sector™ Imager 2400. Due to the high incidence of pre-existing ADA to brolucizumab in treatment-naive samples (49.2%), using the samples from healthy subjects and nAMD patients and parametric statistical analysis, a cutpoint factor was determined to identify a potentially ADA positive sample for the screening assay (Tier 1). The cutpoints for confirmation (Tier 2) and titer (Tier 3) assays were also determined using parametric statistical analysis. For the purpose of this review, findings from Tier 2 assay were utilized. Refer to the CMC/OBP immunogenicity review for further details on the assays.

Neutralizing Anti-brolucizumab Antibodies in Human Serum: The Applicant suggests that given the complex anatomy and dynamic physiological barrier of the eye, and no clear relationship between ocular and serum ADA and nAb, the scientific rationale for the development of a neutralizing antibody assay is questionable. Despite this uncertainty, a competitive ligand binding ECL assay was developed for measuring nAb to further characterize confirmed ADA(+) samples. The diluted samples were co-incubated with Sulfo-Tag labeled brolucizumab. After incubation, an aliquot of the sample was plated into a blocked MSD Streptavidin Gold Plate coated with biotinylated rhVEGF165. The plate was read following addition of MSD Read Buffer T (2X) on the MSD QuickPlex SQ120. The presence of nAb were indirectly detected by a decrease (inhibition) in response of the Sulfo-Tag brolucizumab:rhVEGF165 complex. Refer to the CMC/OBP immunogenicity review for further details on the assays.
4.2 Clinical PK Assessments

The information on systemic PK of brolucizumab was available from Study RTH258-E003 that enrolled 25 nAMD patients. Very limited PK information is also available from pivotal Phase 3 Studies RTH258-C001 and RTH258-C002.

*Study RTH258-E003*

This was a multi-center, randomized, double-masked, three dose study that evaluated the safety and PK following IVT injection of 6 mg brolucizumab in 25 nAMD patients. The study evaluated 3 monthly IVT injections of brolucizumab 6 mg/50 μL. PK assessments were performed by collecting eight serial serum samples over the course of 28 days after the first IVT injection: pre-injection, 6 hours, 1 day (24 hours), 3 days (72 hours), 7 days (168 hours), 14 days (336 hours), 21 days (504 days), and 28 days (672 hours). One sample was also collected at 24 hours after the third IVT injection.

Based on the serum brolucizumab concentration-time profiles following first IVT administration, PK parameters were derived using noncompartmental methods and resultant estimates are reported in Table 1. As shown in Table 1, estimates of AUC and Cmax were low (i.e., in ng/mL concentrations) and highly variable (CVs 133% and 135%, respectively). The comparison of serum brolucizumab concentrations at 24 hours after the third dose and the first dose indicated the lack of systemic accumulation of brolucizumab.

*Table 1: Mean±SD Exposure and Pharmacokinetic Parameter Estimates*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Brolucizumab IVT 6 mg (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng·day/mL)</td>
<td>369±489</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>78±105</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (day)</td>
<td>1 [0-3]&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (days)</td>
<td>5±2</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Median [Range]

*Studies RTH258-C001 and RTH258-C002*

Both of these Phase 3 studies evaluated the proposed 6 mg brolucizumab IVT dosing regimen and both studies evaluated free serum brolucizumab concentrations (unbound to VEGF-A) as part of the immunogenicity assessment. The reported minimum, median, and geometric mean serum concentrations were below or near the limit of quantitation (0.5 ng/mL). The Cmax ranged between 2.70 ng/mL to 117 ng/mL.

4.3 Immunogenicity Evaluation: Reviewer’s Analyses

For the purpose of this review, definitions/criteria that were used to characterize a patient’s immunogenicity status is as follows:

- **Anti-Drug Antibodies (ADA):**
• **Positive (ADA(+)**: Patients with at least one positive serum sample for Tier 2 (confirmation) assay
• **Negative/No Info (ADA(-))**: Patients with (a) serum samples that were negative for Tier 2 assay or (b) with missing information

**Neutralizing antibodies (nAb):**
• **Positive (nAb(+))**: Patients with at least one positive serum sample for Nab
• **Negative/No Info (nAb(-))**: Patients with (a) serum samples that were negative for nAb or (b) with missing information

Using the aforementioned criteria, a distribution of immunogenicity status was derived for patients who (1) Were enrolled in Studies RTH258-C001 and RTH258-C002 and received the 6 mg IVT brolucizumab dose regimen, and (2) Were part of the safety population. The distribution is reported in Table 2.

**Table 2: Immunogenicity Status: Number of nAMD Patients in Safety Population Who Received Brolucizumab 6 mg IVT Dose Regimen**

<table>
<thead>
<tr>
<th></th>
<th>Study RTH258-C001</th>
<th>Study RTH258-C002</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total N=360 (%)</td>
<td>Total N=369 (%)</td>
<td>N=729 (%)</td>
</tr>
<tr>
<td>Baseline ADA Positive (+)</td>
<td>128 (36%)</td>
<td>193 (52%)</td>
<td>321 (44%)</td>
</tr>
<tr>
<td>At least one Sample ADA(+)</td>
<td>241 (67%)</td>
<td>281 (76%)</td>
<td>522 (72%)</td>
</tr>
<tr>
<td>Baseline nAb(+)</td>
<td>15 (4%)</td>
<td>105 (29%)</td>
<td>120 (17%)</td>
</tr>
<tr>
<td>At least one Sample nAb(+)</td>
<td>81 (23%)</td>
<td>151 (41%)</td>
<td>232 (32%)</td>
</tr>
</tbody>
</table>

The efficacy parameter in Studies RTH258-C001 and RTH258-C002 includes change in BCVA from baseline ($\Delta$BCVA), in terms of gain in letters. To assess impact of a patient’s immunogenicity status on efficacy, trends in $\Delta$BCVA were compared between ADA(+) and ADA(-) patients who received the 6 mg brolucizumab IVT regimen. These trends in ADA(+) and ADA(-) patients were also compared against the overall trends in patients who received the reference treatment, i.e., aflibercept 2 mg IVT at the approved dosing regimen for Eylea (Figure 2). Overall, the findings in Figure 2 indicated that mean $\Delta$BCVA tended to be lower in ADA(+) brolucizumab patients when compared to ADA(-) brolucizumab patients and aflibercept treated patients. The observed differences between ADA(+) and ADA(-) brolucizumab patients were more prominent in Study RTH258-C001 compared to Study RTH258-C002 (Figure 2). At the end of the study period, i.e., at Week 96, mean $\Delta$BCVA in ADA(+) brolucizumab patients were more comparable to the mean $\Delta$BCVA in patients who received aflibercept; however the ADA(-) brolucizumab patients tended to show greater $\Delta$BCVA as compared to the aflibercept treated patients (Figure 2).

In addition to evaluating mean trends, the proportions of patients who attained different $\Delta$BCVA thresholds: $\geq$15 letters, $\geq$10 letters, $\geq$5 letters, were also determined for each visit and compared (Figure 3). Based on the discussion with the Clinical review team, attainment of $\Delta$BCVA of $\geq$15 letters appears to be clinically meaningful. Overall, for both Study RTH258-C001 and RTH258-C002, the findings from this analysis appeared to show less of a difference in the $\Delta$BCVA thresholds for ADA(+) or ADA(-) brolucizumab patients, particularly for Study RTH258-C002. In Study RTH258-C001, the percentage of
patients reaching threshold values appeared to be relatively higher in ADA(-) brolucizumab patients compared to ADA(+) brolucizumab patients, although there appeared to be similar trend of attainment of ∆BCVA thresholds of ≥10 and ≥15 letters for the ADA(+) brolucizumab and aflibercept patients. At the end of the study period, i.e., at Week 96, the percent of ADA(+) brolucizumab patients reaching threshold values were comparable to the aflibercept 2mg control arm (Figure 3). In Study RTH258-C002, the percentage of patients reaching the ∆BCVA threshold of ≥15 letters was relatively higher in ADA(-) brolucizumab patients compared to ADA(+) brolucizumab patients. For the ≥10 letters and ≥5 letters ∆BCVA thresholds, the percentage of patients reaching these threshold values were comparable across all three treatment arms (Figure 3).

Similar analysis was conducted by the reviewer using a patient’s immunogenicity status with respect to presence or absence of nAb; however, no notable differences were identified in ∆BCVA trends or threshold attainment between patients who were nAb(+) and nAb(-) for brolucizumab.

A consult was sent to the Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP) regarding the observed impact of a patient’s immunogenicity status and ∆BCVA. Based on the review of the Applicant’s analysis, on this issue, the DARS/OCP consult response’s summary indicated the following:

- Development of this product demonstrated divergent immunogenicity results for studies RTH258-C001 and RTH258-C002, with the former having apparent impact on a key clinical endpoint in approximately 10% of patients and the other showing no impact. Geographic differences in conduct of these trials as well as pre-existing autoantibodies could be responsible for these differences. However, additional data related to the individuals who experienced this effect would be needed to better understand this outcome.
- Given the relatively small number of overall patients affected, it is not reasonable to screen all patients for anti-drug antibodies (ADA) for this product. However, we recommend that Best Corrected Visual Acuity (BVCA) could be used to monitor this potential impact and consideration be given to ADA if overall response decreases over time as was observed in one of the clinical trials.
Figure 2: Anti-brolucizumab Antibody Status and ΔBCVA Trends in the nAMD Patients Who Received Either the Brolucizumab 6 mg IVT or the Aflibercept-2mg IVT Dose Regimen

ΔBCVA = Changes in best-corrected visual acuity from baseline, SE = Standard error, N= Number of patients for whom BCVA observations were available and ΔBCVA could be derived, RTH258 = brolucizumab, Negative/No Info = patients with (a) serum samples that were negative for Tier 2 assay or (b) with missing information, POSITIVE = patients with at least one positive serum sample for Tier 2 (confirmation) assay.
Reviewer Conclusions:

These analyses appear to show a trend in reduced change in BCVA from baseline for ADA(+) brolicizumab nAMD patients who were enrolled in the two Phase 3 Studies RTH258-C001 and RTH258-C002. The reviewer’s findings, as reported in this section of the review, were discussed with the Clinical Review team and the clinical relevance of these findings has not been determined at the time of this review.

The Clinical Pharmacology Review team and the Clinical Review team will work collaboratively to determine the need for adding and/or revising the language in the labeling regarding the effect of immunogenicity of brolucizumab on BCVA.
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/s/

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