

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761125Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 19, 2019

Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)

Application Type and Number: BLA 761125

Product Name and Strength: Beovu
(brolucizumab-dbil)
injection
6 mg/0.05 mL

Applicant/Sponsor Name: Novartis Pharmaceuticals Corporation

OSE RCM #: 2019-329-2

DMEPA Safety Evaluator: Sarah K. Vee, PharmD

DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 18, 2019 for Beovu. The Division of Transplant and Ophthalmology Products (DTOP) requested that we review the revised container label and carton labeling for Beovu (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Vee S. Label and Labeling Review for Beovu (BLA 761125). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 30. RCM No.: 2019-329.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 18, 2019

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Container labels



Carton labeling

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SARAH K VEE
09/19/2019 09:47:12 AM

IRENE Z CHAN on behalf of OTTO L TOWNSEND
09/27/2019 01:46:02 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: September 18, 2019

To: Dheera Semidey
Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **BLA: 761125**
BEOVU™ (brolucizumab-dbl) injection, for intravitreal use

OPDP has reviewed the proposed product labeling (PI) and carton and container labeling submitted for consult on April 2, 2019, for BEOVU™ (brolucizumab-dbl) injection, for intravitreal use. OPDP's review of the PI is based on the version emailed from DTOP to OPDP on September 6, 2019, attached below. OPDP's comments are provided directly below on the attached marked-up copy of the proposed PI. OPDP's review of the carton and container labeling is based on the version located in Sharepoint on September 17, 2019, also attached below. OPDP does not have any comments on the proposed carton and container labeling.

Thank you for your consult. If you have any questions on our review of the proposed labeling, please contact Carrie Newcomer at 301-796-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
09/18/2019 03:39:45 PM

Clinical Inspection Summary

Date	September 12, 2019
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	William Boyd, M.D., Clinical Team Leader Rhea Lloyd, M.D., Reviewer Judith Milstein/Dheera Semidey, Regulatory Project Managers Division of Transplant and Ophthalmology Products (DTOP)
BLA#	761125
Applicant	Novartis Pharmaceuticals Corporation
Drug	Brolucizumab (RTH258)
NME	Yes
Review Priority	Yes
Proposed Indication	Treatment of neovascular age-related macular degeneration (nAMD)
Consultation Request Date	March 5, 2019
Summary Goal Date	September 13, 2019
Action Goal Date	October 4, 2019
PDUFA Date	October 7, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Rich and Sararols were inspected in support of this NDA. Some regulatory violations were noted at Dr. Rich's site, and the review division should consider excluding the seven subjects impacted by discrepant ophthalmic assessments (not affecting the primary efficacy endpoint) in the per-protocol analysis. Otherwise, based on the results of these inspections, the studies (Protocols RTH258-C001 and RTH258-C002) appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

The Applicant submitted this BLA to support the use of brolucizumab for the treatment of neovascular age-related macular degeneration.

Clinical inspections were requested for the following protocols in support of this application:

Protocol RTH258-C001

Title: A two-year, randomized, double-masked, multicenter, three-arm study comparing the efficacy and safety of RTH258 versus aflibercept in subjects with neovascular age-related macular degeneration

The primary objective of the study was to demonstrate that brolocizumab was not inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from Baseline to Week 48.

This was a phase 3, prospective, randomized, double-masked, multicenter study designed to compare the efficacy and safety of brolocizumab 3 mg and 6 mg with aflibercept 2 mg in subjects with nAMD. Eligible subjects were randomized 1:1:1 to brolocizumab 3 mg, brolocizumab 6 mg, and aflibercept 2 mg. Subjects in all 3 treatment arms received 3 monthly loading doses (Day 0, Week 4 and Week 8), followed by every 12 week/every 8-week (q12w/q8w) maintenance regimen for the brolocizumab arms (3 mg and 6 mg) and q8w maintenance regimen for the aflibercept 2 mg arm. Subsequent treatment frequencies of q12w or q8w for the brolocizumab arms were based on disease activity assessments performed by the masked investigator at pre-specified visits.

The *primary efficacy endpoint* of the study was the change in BCVA from Baseline to Week 48.

Protocol RTH258-C002

Title: A two-year, randomized, double-masked, multicenter, two-arm study comparing the efficacy and safety of RTH258 6 mg versus aflibercept in subjects with neovascular age-related macular degeneration

The primary objective was to demonstrate that brolocizumab 6 mg is not inferior to aflibercept 2 mg with respect to the change in best-corrected visual acuity (BCVA) from Baseline to Week 48.

This was a Phase 3, prospective, randomized, double-masked, multicenter study designed to compare the efficacy and safety of brolocizumab 6 mg with aflibercept 2 mg in subjects with neovascular age-related macular degeneration (nAMD). Eligible subjects were randomized to brolocizumab 6 mg and aflibercept 2 mg in a 1:1 ratio. Subjects in both treatment arms received 3 monthly loading doses (Day 0, Week 4 and Week 8), followed by q12w/q8w maintenance regimen for the brolocizumab 6 mg arm and q8w maintenance regimen for the aflibercept 2 mg arm. Subsequent treatment frequencies of q12 w or q8w for the brolocizumab arm was based on disease activity assessments performed by the masked investigator at pre-specified visits.

The main inclusion and exclusion criteria were as described for Protocol RTH258-C001 above.

The *primary efficacy endpoint* was analogous to that for Protocol RTH258-001 other than the inclusion of the RTH258 3 mg treatment arm.

Rationale for Site Selection

The clinical sites of Drs. Rich and Sararols were chosen for inspection because of their relatively large enrollments and lack of recent inspections

III. RESULTS (by site)*:

**Note: Dual site numbers reflect different site numbers used by Novartis and Alcon*

1. Site #6221/5058

Ryan Rich, M.D.
Retina Consultants of Southern Colorado
2770 North Union Blvd. 20
Colorado Springs, CO 80909

At this site for Protocol RTH258-C001, 28 subjects were screened, and 20 subjects were enrolled into the study. Review of the informed consent forms for the 20 enrolled subjects revealed that not all subjects signed the most current version of the consent form at their next visit. For example, Subjects (b) (6) and (b) (6) did not sign the most updated consent form at the soonest available study visit but at later follow up visits. There did not appear to be significant changes in the consent forms that would have influenced the subjects' decisions to remain in the study.

Other records reviewed included, but were not limited to, IRB, monitoring, and sponsor correspondence; study approvals; financial disclosure forms; training logs; delegation logs; enrollment logs; source documents; case report forms; subject randomization and discontinuation; primary and secondary efficacy endpoints; adverse events; protocol deviations; and test article accountability.

As for the primary efficacy endpoint, BCVA reporting in the source records was reviewed for all enrolled subjects, and no discrepancies were noted. Review of adverse event reporting revealed that Subject (b) (6) who received brolocizumab 6mg reported visual disturbances (bright colored spots of light) that later resolved; however, source documentation, including the Adverse Event Log, failed to report this adverse event or any clinical follow up in response to the complaint.

Reviewer's comment: The Review Division may wish to consider this adverse event in its safety assessment of this study.

A Form FDA 483 was issued at the conclusion of the inspection with the following observations:

1. Subject (b) (6) (who received aflibercept 2 mg) was enrolled in the study despite a disqualifying BCVA of 19 in the study eye. The minimal BCVA for study inclusion was 23 letters. The protocol deviation was reported to the IRB and the sponsor. The site implemented corrective actions by retraining the Visual Acuity examiners and requiring verification of the BCVA scores by the Study Coordinators. The sponsor allowed the subject to remain in the study provided that it was safe to do so in the opinion of the clinical investigator.
2. Per protocol, unmasked site personnel and the unmasked injecting physician were not to perform assessments of any ocular or non-ocular safety parameters or assess causality AEs for subjects during the course of the study except for an event reported immediately following intravitreal injection. An unmasked injecting physician assessed adverse events at unscheduled visits for Subjects (b) (6) (brolocizumb 3mg), (b) (6) (brolocizumab 3mg), (b) (6) (brolocizuab 6mg),

and (b) (6) (brolucizumab 6mg). The site said that there were no masked investigators available at the time the assessments were made; however, there was no documentation that masked investigators were not available.

Reviewer’s comment: As unmasked investigators assessed adverse events for these subjects at unscheduled visits, a potential for bias existed. However, there would be no impact on the efficacy endpoint for this study and likely little impact on the overall safety assessment.

- Slit lamp examination results were changed for Subjects (b) (6) (aflibercept 2mg), (b) (6) (brolucizumb 3mg), (b) (6) (brolucizuab 6mg), (b) (6) (brolucizumb 3mg), and (b) (6) (brolucizumb 6mg) without justification. The results of dilated binocular indirect ophthalmoscopic exams for Subjects (b) (6) (brolucizumb 3mg) and (b) (6) (brolucizumb 6mg) were also changed without justification. Please see the table below for a summary of the changes:

Subject #	Week	Exam Type	Cataract Subcapsular (Original)	Cataract Subcapsular (Revised)
(b) (6)	36	Slit-lamp	2+	0
	40		2+	0
	44		2+	0
(b) (6)	Screening	Slit-lamp	2+	0
	Baseline		2+	0
Subject #	Week	Exam Type	Aqueous cell, flare, etc. (Original)	Aqueous cell, flare, etc. (Revised)
(b) (6)	24	Slit-lamp	NA	0
(b) (6)	Screening	Slit-lamp	NA	0
Subject #	Week	Exam Type	Posterior Vitreal Detachment (Original)	Posterior Vitreal Detachment (Revised)
(b) (6)	24	Dilated Binocular Indirect	No	Yes
(b) (6)	76	Dilated Binocular Indirect	No	Yes
Subject #	Week	Exam Type	Retinal Periphery/Choroid (Original)	Retinal Periphery/Choroid (Revised)
(b) (6)	12	Dilated Binocular Indirect	Blank	Normal

Subject #	Week	Exam Type	Cataract cortical (Original)	Cataract cortical (Revised)
(b) (6)	Baseline	Slit-lamp	0	Trace
	Week 4		0	Trace
	Week 8		0	Trace
	Week 12		0	Trace
	Week 16		0	Trace
	Week 20		0	Trace
	Week 24		0	Trace
	Week 28		0	Trace
	Week 32		0	Trace
	Week 36		0	Trace
	Week 40		0	Trace
	Week 44		0	Trace

Reviewer’s Comment: Per Dr. Rich’s written response to this observation, the wrong type of cataract was originally documented for Subjects (b) (6) and (b) (6). The source documents had erroneously reported 2+ subcapsular cataracts that were subsequently corrected to report 2+ nuclear cataracts. Dr. Rich stated that this was a transcription error and did not affect patient safety.

For Subject (b) (6) at Week 24 and Subject (b) (6) at Screening, the results of the slit-lamp exams for aqueous cell, aqueous flare, and vitreous cell were classified as “NA” and then changed to “0”. Dr. Rich reported these as transcription errors affecting neither patient safety nor study outcome.

For the study eye of Subject (b) (6) at Baseline and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44, the result of the slit-lamp exam of the “Cataract Cortical” was changed from “0” to “Trace”. Dr. Rich addressed this error stating that the study coordinator retrospectively changed the rating in error and that the changes did not affect patient safety or study outcome.

For the study eye of Subject (b) (6) at Week 24, Dr. Rich stated that the response to the presence of posterior vitreous detachment (PVD) was changed from “No” to “Yes”. Dr. Rich stated that the presence of PVD can be very difficult to determine, however, once present, the condition is not reversible. As subsequent review revealed prior evidence of PVD, the record was revised to indicate that PVD was present. As Dr. Rich acknowledged in his response, the rationale for this change was not documented in the source record.

For the study eye of Subject (b) (6) at Week 12, Dr. Rich confirmed that data indicating that the retinal periphery and choroid were normal were added late (source document dated June 28, 2016, with the addition dated October 12, 2016). Dr. Rich noted that previous and subsequent exams were normal but that the missing data should have been noted as an error and not filled in retrospectively.

Also, for the study eye of Subject (b) (6) at Week 76, the source document dated September 7, 2017, was revised on June 30, 2018, changing “Posterior Vitreal Detachment” from “No” to “Yes”. This observation was not addressed by Dr. Rich.

In summary, Dr. Rich responded in writing to the majority of the observations on the Form 483, attributing many of the observations to transcriptional errors. He acknowledged that the revisions to the source data lacked adequate explanation. Therefore, the review division may wish to consider whether the discrepant ophthalmic assessments detailed above should be included in their overall assessment of safety.

2. Site 6187/1143

Laura Sararols, M.D.
Pedro i Pons 1, Vallès Oftalmologia Recerca-Capio
Hospital General de Catalunya-Hospital
Sant Cugat Del Valles (BCN), NA 08195
Spain

At this site for Protocol RTH258-C002, 28 subjects were screened, 20 subjects were randomized, of which 19 received the investigational medical product (IMP) and completed the study through Week 48. The remaining subject experienced an SAE prior to receiving the IMP and was discontinued from the trial.

The informed consent documents were reviewed for all 28 screened subjects and no deficiencies were observed. Other records reviewed for the 20 enrolled subjects included, but were not limited to, IRB, sponsor, and monitor correspondence; study approvals; financial disclosure forms; facilities accreditation; training documentation; delegation logs; source records; case report forms, inclusion/exclusion criteria; visit worksheets; medical histories; laboratory results; concomitant medications; and test article accountability.

As the primary efficacy endpoint, BCVA reporting in the source records was reviewed for all enrolled subjects and there were no discrepancies between original scored BCVA values and the data listings. There appeared to be no under-reporting of adverse events.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
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Kassa Ayalew, M.D., M.P.H
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cc:

Central Doc. Rm.\BLA 761125
DTOP\Division Director\Ozlem Belen
DTOP\Team Leader\William Boyd
DTOP\Reviewer\Rhea Lloyd
DTOP\Project Managers\Judit Milstein\Dheera Semidey
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Yolanda Patague

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/s/

ROY A BLAY
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PHILLIP D KRONSTEIN
09/12/2019 03:55:34 PM

KASSA AYALEW
09/13/2019 07:37:07 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: August 21, 2019

Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)

Application Type and Number: BLA 761125

Product Name and Strength: Beovu
(brolocizumab-dblI)
injection
6 mg/0.05 mL

Applicant/Sponsor Name: Novartis Pharmaceuticals Corporation

OSE RCM #: 2019-329-1

DMEPA Safety Evaluator: Sarah K. Vee, PharmD

DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on August 16, 2019 for Beovu. The Division of Transplant and Ophthalmology Products (DTOP) requested that we review the revised container label and carton labeling for Beovu (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Vee S. Label and Labeling Review for Beovu (BLA 761125). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 30. RCM No.: 2019-329.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 16, 2019

Container labels



Carton labeling

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/s/

SARAH K VEE
08/21/2019 11:42:32 AM

OTTO L TOWNSEND
08/22/2019 10:54:19 AM

Date: 8 July 2019

From: Kristina Howard, D.V.M, Ph.D. & James Weaver Ph.D., Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP)

Through: David Strauss M.D., Ph.D., Director; DARS/OCP

To: Abhay Joshi, DCP4/OCP

Subject: Brolucizumab and Immunogenicity status, BLA 761125

Executive Summary

Brolucizumab is a humanized single chain protein that binds VEGF to treat neovascular age-related macular degeneration. 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.

Background

Brolucizumab is a humanized single-chain Fv protein that binds to human Vascular Endothelial Growth Factor (VEGF). The protein has a molecular weight of ~26 KD and is produced in *E. coli*. This drug is proposed for the treatment of Neovascular Age-Related Macular Degeneration (nAMD). There are two other anti-VEGF proteins, ranibizumab and aflibercept, previously approved to treat this disease.

Endogenous levels of VEGF are low, in circulation levels are around 0.1 – 0.2 ng/ml (Kut et al, 2007) while in the aqueous humor of the eye, levels are ~0.07 ng/ml (Selim et al, 2010). The drug is dosed by direct injection into the eye and can be detected in circulation with a Cmax of 49 ng/ml for the 6 mg dose. Clearance is conventional export through the kidney with a median T1/2 of 5 days. The drug is detectable in serum above the LLOQ of 0.5 ng/ml for at least 20 days.

The eye is an immunologically privileged site, meaning that there is blood-retinal barrier (BRB) that restricts transit of many cells into the eye (Stein-Streilein, 2013). Age-related macular degeneration has been shown to have an immune inflammatory etiology that results from genetic, environmental and epigenetic factors (Nussenblatt RB, 2014). One of the cells targeted in the disease are retinal pigmented epithelial cells, which are the cells that prevent systemic incursion into the eye (Nussenblatt RB, 2014). Macrophages reside in the eye, but generally control inflammation by converting inflammatory T-cells from systemic circulation to regulatory cells. Several forms of complement have been shown to be important in the pathogenesis of AMD.



Evaluation

- Discuss the design and interpretation of the analyses between IS vs. Δ BCVA that will be part of the clinical pharmacology review.

Antidrug antibody assay: The assay for anti-drug antibodies (ADA) is of a conventional design with a biotin-conjugated drug as the capture reagent adhered to an avidin-coated plate. Detection is by a separate sulfo-tagged drug using ECL signal as the readout. Sensitivity was reported as 39 ng/ml using rabbit anti-drug antibody as a positive control. The tolerance of the ADA assay to exogenous drug was reported to be 250 ng/ml, well above the reported Cmax.

Neutralizing antibody assay: The neutralizing ADA assay (nADA) is also of a conventional design with the nADA antibodies blocking the ability of the sulfo-tagged drug to bind to human VEGF which is bound to the plate. The nADA had a sensitivity of 488 ng/ml based on the rabbit positive control antibody. Assay interference by free drug was investigated and the critical level was shown to vary with the concentration of nADA as would be expected.

Pre-existing ADA and nADA: Across all four phase 2 & 3 studies an aggregate of 43.7% of 2,023 subjects had detectable ADA. In three of four studies, nADA were also measured and 15.6% of 1,117 patients had detectable nADA. Taken together, approximately 35% of ADA were in fact nADA. This rather high rate of pre-existing ADA may not be due to prior exposure to other anti-VEGF drugs. Instead, it could be a more common finding also seen with other small antibody segment drugs (Holland et al, 2013).

Treatment effects on ADA status: Following the initiation of treatment, several outcomes are possible. Patients negative for ADA at the start of the study may remain negative or convert to positive status. The conversion to positive status may be transient or be persistent. Similarly, patients positive at pretreatment may remain positive at the same titer (no additional effect) or they may show an increased antibody titer (boosted titer). The boost in titer may also be transient or be persistent. Therefore, there are three potential outcomes for patients that were ADA positive or negative at study commencement.

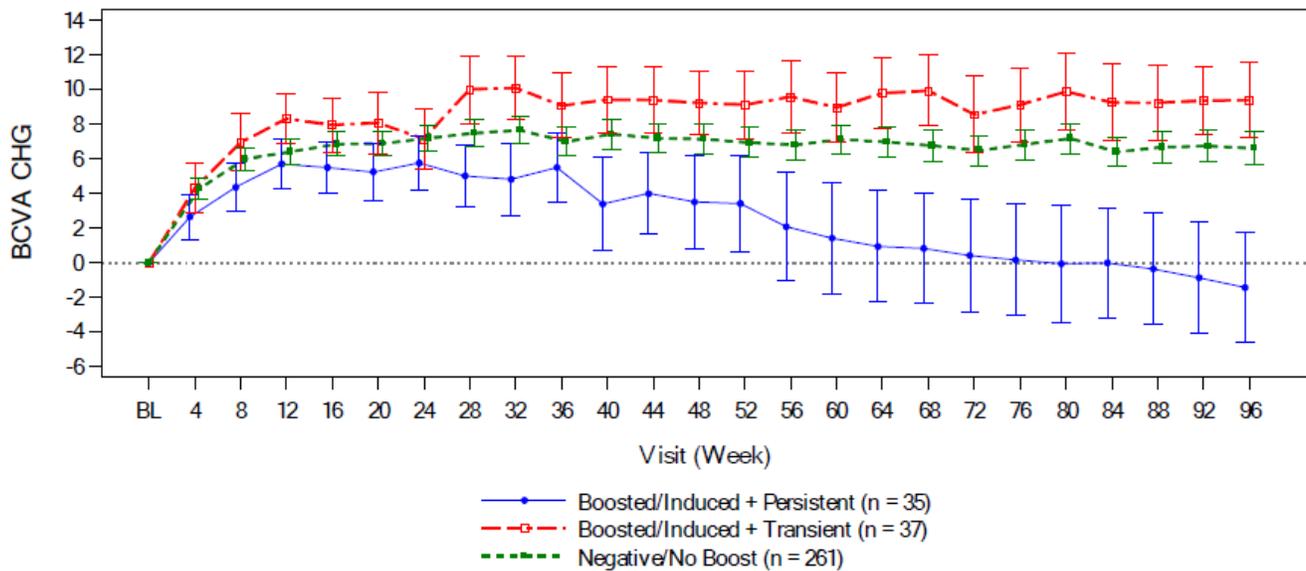
ADA status vs ocular improvement: Using sponsor package data, plots showing the effect of dividing and subdividing the data in relationship to changes in ocular status were presented. Data are taken from the two phase III clinical trials, RTH258-C001 and RTH258-C002. Overall, the data show an improvement in performance that reaches a plateau at 12-16 weeks and that persists out to 96 weeks. This profile is highly similar to the active control Aflibercept. Sponsor documents have a total of 22 plots, representing various slices through the data based on treatment effects on ADA status. For 21 of 22 plots there are no particular differences in change in ocular status in relation to subdivisions of ADA status. In the figure below showing the high dose of drug (6 mg) in trial RTH258-C001 there is an unusual decrease in ocular status back to baseline by week 72. The affected group is labeled as 'Boosted/Induced + Persistent (n-35)'. However, this pattern is not seen in the 3 mg dose group nor is it seen in the matching dose group from clinical trial RTH258-C002 (shown below).

An important difference in the enrollment of these two trials is that study RTH258-C001 was conducted primarily in the western hemisphere (USA, Canada, Mexico, etc) and study RTH258-C002 was conducted exclusively in Europe. Even though the patient population was predominantly female and largely Caucasian in both studies, the difference in location suggests that an environmental factor may be

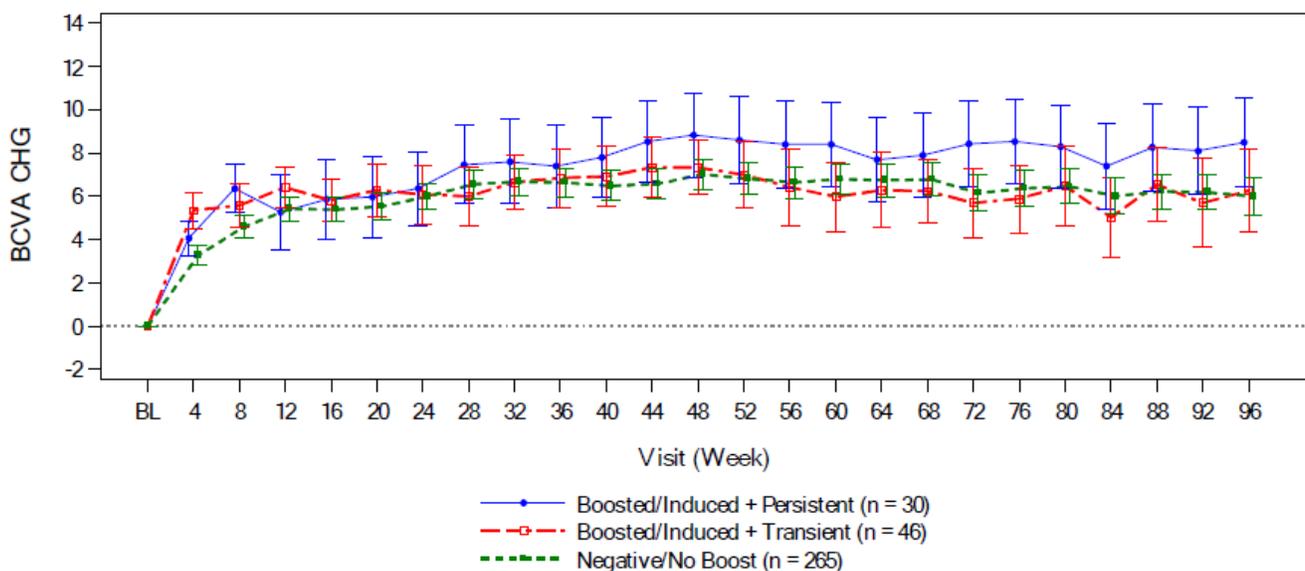


associated with the development of ADA that appeared to affect outcome as measured by BCVA change. However, this group of patients represents only 10% of the total in RTH258-C001. We have no detailed data for their prior treatment history, pre-existing antibody levels, individual disease severity or other factors that may have played a role in this response. As AMD is an immunologically based disease, it is possible that increased permeability of the BRB could have contributed to these patients having a poorer clinical outcome associated with persistent ADA in systemic circulation.

RTH258-C001 Brolucizumab 6 mg



RTH258-C002 Brolucizumab 6 mg



- Discuss the practicality of immunogenicity assessment as a patient screening tool, in case the clinical review team deems that the observed relationship is significant and such a tool is desired.

The data provided do not support the utility of screening patients prior to the start of treatment. Another factor is that > 98% of patients treated with Aflibercept were reported to have ADA as detected by the brolucizumab assay. Therefore, only newly diagnosed patients would be eligible for screening based on ADA status. Based on the available data, adverse outcomes would be most easily monitored using BCVA. To use ADA status, all patients would need an initial ADA assay. Then if a persistent decrease in BCVA was observed, additional testing of ADA titer could be done to determine if the ADA response had been induced or boosted. This test would need to be repeated to determine whether the boost was transient or persistent. It is not clear how this information provides additional benefit above that provided by a persistent decrease in BCVA alone. In addition, it is not clear whether this would be useful just in the US and not Europe. Detailed analysis of the 35 Boosted/Induced + Persistent patients in study RTH258-C001 might provide additional useful information for risk evaluation.

Another factor in this recommendation is the ability of the ADA and nADA assays to detect clinically meaningful responses. The assays used in this BLA submission are standard technology and as cited (Holland et al, 2013), it is possible that an improved assay would be required to determine true ADA levels that correlate well, given the format of the product. Also, whichever generation of assays was used the assays would need to be sufficiently developed for approval by CDRH before they could be used in patient monitoring.

Summary and Conclusions

Brolucizumab is a humanized single chain protein that binds VEGF to treat neovascular age-related macular degeneration. 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. The assays used to measure this effect were standard ELISA-based format assays that may not be able to clearly discern autoantibodies (pre-existing and cross-reactive to the drug but not due to treatment) from true anti-drug antibodies due to the structure of the drug. It is also possible that due to geographic differences in the location of the two trials, that cross-reactive pre-existing antibody bound the drug with greater frequency in one location versus the other. 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 ADA for this product. However, we recommend that BVCA is used to monitor this potential impact and consideration be given to ADA if overall response decreases over time as was observed in the clinical trial. In order to assess ADA, a CDRH approved/cleared assay would need to be developed that could discern cross-reactive pre-existing antibodies as compared to actual ADA. In addition, a pre-therapeutic serum sample would be required for proper interpretation of results if a loss of efficacy is identified.

References and Supporting Documents

Holland MC, Wurthner JU, Morley PJ, Birchler MA, Lambert J, Albayaty M, Serone AP, Wilson R, Chen Y, Forrest RM, Cordy JC, Lipson DA, Bayliffe AI. (2013) Autoantibodies to variable heavy (VH) chain Ig



sequences in humans impact the safety and clinical pharmacology of a VH domain antibody antagonist of TNF- α receptor 1. *J Clin Immunol* **33**, 1192-203.

Kut C, Gabhann FM, Popel AS (2007) Where in VEGF in the body? A meta-analysis of VEGF distribution in cancer. *Br J Cancer* **97**, 978-985.

Nussenblatt RB, Liu B, Wei L, Sen HN. (2013) The immunological basis of degenerative disease of the eye. *Int Rev Immunol*. 2013 Feb;32(1):97-112.

Nussenblatt RB, Lee RW, Chew E, Wei L, Liu B, Sen HN, Dick AD, Ferris FL. Immune responses in age-related macular degeneration and a possible long-term therapeutic strategy for prevention. *Am J Ophthalmol*. 2014 Jul;158(1):5-11.e2.

Selim KM, Sahan D, Muhittin T, Osman C, Mustafa O (2010) Increased levels of vascular endothelial growth factor in the aqueous humor of patients with diabetic retinopathy. *Ind J Ophthalmol* **58**, 375-379.

Stein-Streilein J. Mechanisms of immune privilege in the posterior eye. *Int Rev Immunol*. 2013 Feb;32(1):42-56.

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/s/

TRACEY B LEE
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 30, 2019
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	BLA 761125
Product Name and Strength:	Beovu (brolucizumab-dblI) injection 6 mg/0.05 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis
FDA Received Date:	February 7, 2019
OSE RCM #:	2019-329
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS

1 REASON FOR REVIEW

As part of the approval process for Beovu (brolocizumab-dbl) injection, Division of Transplant and Ophthalmology Products (DTOP) requested that we review the proposed Beovu Prescribing Information (PI), carton labeling, container labels, and observational study report for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Observational Study Report	B
Labels and Labeling	C

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION & RECOMMENDATIONS

3.1 OBSERVATIONAL STUDY REPORT

While conducting the clinical trials, the Applicant collected observational data on how the clinicians used the RTH vial kit. Although the data was not obtained from a simulated use human factors validation study or with the intend to market product, we can glean insight on users' experiences with the product that may help mitigate potential use errors that may occur in a real use setting. We focus on the data that relate to critical tasks^a in the use process for Beovu injection. For example, the user must withdraw the injection using a filter needle, then discard the filter needle before attaching the injection needle. One user did not discard the filter needle before priming the syringe and setting the dose to 0.05 mL. According to the Observational Study Report, the user (b) (4) during the injection process and stated that *"the practice of all the staff in the facility to prime with the filter needle on and then apply whatever sized injection needle is required for the procedure."* Although a comprehensive use related risk analysis was not submitted, we can rely on our

^a A user task which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care.

knowledge and postmarket experience with similar products that are on the market, that this type of use error could result in an underdose, because the final dose volume (0.05 mL) should be set with the injection needle in place.

We compared labeling for other intravitreal injections that require the use of a filter needle to draw up the injection to the [REDACTED] (b) (4) for Beovu. We found labeling for currently marketed products include a similar cautionary statement to remove the filter needle; however, the statement is prominent. Our evaluation of this use error indicated that this step can be revised in the Beovu [REDACTED] (b) (4)

[REDACTED] This labeling modification ensures alignment and consistency with other similar marketed products.

3.2 LABELS AND LABELING

We also performed a risk assessment of the proposed PI, container labels, and carton labeling for Beovu for areas of vulnerability that may lead to medication errors. Our review of the proposed labeling identified several areas that can be improved to increase the readability and prominence of important information. We provide recommendations for the Division in section 4.1 and the Applicant in section 4.2.

4 CONCLUSIONS AND RECOMMENDATIONS

We recommend that these revisions to be implemented prior to approval of the BLA.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

To increase readability, reduce clutter, remove duplicate information, and to remove information that belongs in other sections of the PI, we recommend the following revisions.

1. Dosage and Administration Section

a. 2.1 General Dosing Information

i. Remove [REDACTED] (b) (4)

2. Currently proposed Sections [REDACTED] (b) (4)

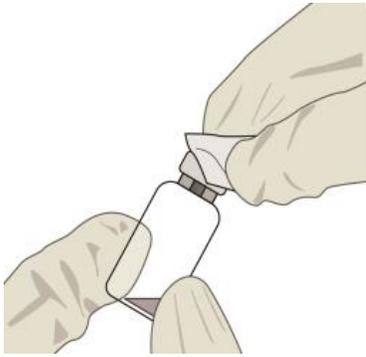
:

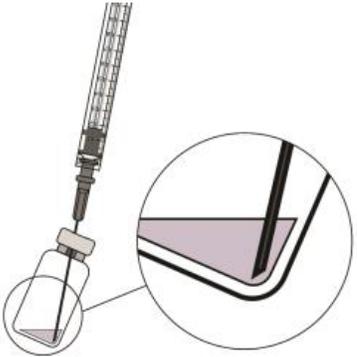
[REDACTED] (b) (4)

The intravitreal injection procedure must be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent), and the availability of sterile paracentesis equipment (*if required*). Adequate anesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid, and ocular surface should be administered prior to the injection. (b) (4)

[Redacted]

[Redacted] (b) (4)

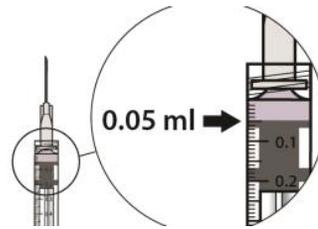
<p>Step 1: Gather the supplies needed.</p> <p>Beovu kit contains:</p> <ul style="list-style-type: none"> • One Beovu vial • One 5 µm blunt filter needle (18G x 1½", 1.2 mm x 40 mm), sterile <p>(b) (4) not included:</p> <ul style="list-style-type: none"> • One 30G x ½" injection needle, sterile • 1 mL syringe with a 0.05 mL dose mark, sterile • (b) (4) Alcohol swab 	
<p>Step 2: Allow vial to come to room temperature and inspect the solution. If particulates, cloudiness, or discoloration are visible, discard the vial and obtain a new vial.</p>	
<p>Step 3</p> <p>Remove the vial cap and clean the vial septum (e.g., with (b) (4) alcohol swab).</p>	<p>Figure 1:</p>  <p>The illustration shows a hand holding a small white vial. Another hand is using a white alcohol swab to clean the top of the vial, specifically the septum where the cap would be. The vial is tilted slightly to the right.</p>

<p>Step 4</p> <p>Assemble the filter needle onto a 1 mL syringe using aseptic technique.</p>	
<p>Step 5</p> <p>Push the filter needle into the center of the vial septum until the needle touches the bottom of the vial.</p>	
<p>Step 6</p> <p>To withdraw the liquid, hold the vial slightly inclined and slowly withdraw all the liquid from the vial and filter needle.</p> <p>Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle</p>	<p>Figure 2:</p> 
<p>Step 7</p> <p>Disconnect the filter needle from the syringe in an aseptic manner and dispose of it. The filter needle is not to be used for intravitreal injection.</p>	
<p>Step 8</p> <p>Aseptically and firmly assemble a 30G x 1/2" injection needle onto the syringe.</p>	
<p>Step 9</p> <p>Check for air bubbles by holding the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.</p>	<p>Figure 3:</p> 

Step 10

Carefully expel the air from the syringe and adjust the dose to the 0.05 mL mark. The syringe is ready for the injection.

Figure 4:



(b) (4)

(b) (4)

4.2 RECOMMENDATIONS FOR NOVARTIS

A. General Comments (Container labels & Carton Labeling)

1. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.
2. Lot number is required on all container labels and carton labeling per 21 CFR 201.10(i), include the lot number on the label and ensure it is clearly differentiated from the expiration date.

3. Expiration date is required on all container labels and carton labeling per 21 CFR 201.17, include the expiration date on the label and ensure it is clearly differentiated from other numbers on the label.
 - a. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Beovu received on February 7, 2019 from Novartis.

Table 2. Relevant Product Information for Beovu	
Initial Approval Date	N/A
Active Ingredient	brolocizumab-dbli
Indication	For the treatment of Neovascular (Wet) Age- Related Macular Degeneration (AMD)
Route of Administration	Intravitreal injection
Dosage Form	injection
Strength	6 mg/0.05 mL
Dose and Frequency	6 mg (0.05 mL) (b) (4) for the first three doses. (b) (4)
How Supplied	Single-dose, 2 mL glass vial with a (b) (4) cap and 5 µm blunt filter needle
Storage	Store in a refrigerator at 2°C to 8°C (36°F-46°F). Prior to use, the unopened vial may be kept at room temperature (b) (4) for up to 24 hours. Do not freeze. Keep the vial in the outer carton in order to protect from light.

APPENDIX B. OBSERVATIONAL STUDY REPORT

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amd\5354-other-stud-rep\observational-study-report](#)

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Beovu labels and labeling submitted by Novartis.

- Container label received on February 7, 2019
- Carton labeling received on February 7, 2019
- Prescribing Information (Image not shown) received on February 7, 2019

C.2 Label and Labeling Images



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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