

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761125Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

---

<b>Application Type</b>	BLA
<b>Application Number</b>	761125
<b>PDUFA Goal Date</b>	October 7, 2019
<b>OSE RCM #</b>	2019-444
<b>Reviewer Name(s)</b>	Ingrid N. Chapman, Pharm.D., BCPS
<b>Team Leader</b>	Donella Fitzgerald, Pharm.D.
<b>Deputy Division Director</b>	Jamie Wilkins, Pharm.D.
<b>Review Completion Date</b>	October 2, 2019
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Brolucizumab-dblI
<b>Trade Name</b>	Beovu
<b>Name of Applicant</b>	Novartis Pharmaceuticals Corp
<b>Therapeutic Class</b>	Monoclonal antibody, vascular endothelial growth factor (VEGF) inhibitor
<b>Formulation(s)</b>	120 mg/mL (b) (4) solution for injection
<b>Dosing Regimen</b>	6 mg (0.05 mL) injected intravitreally (b) (4) x 3 doses then every 8 – 12 weeks (b) (4)

---

## Table of Contents

EXECUTIVE SUMMARY .....	3
1 Introduction.....	3
2 Background .....	3
2.1 Product Information .....	3
2.2 Regulatory History.....	4
3 Therapeutic Context and Treatment Options .....	4
3.1 Description of the Medical Condition .....	4
3.2 Description of Current Treatment Options .....	4
4 Benefit Assessment .....	5
5 Risk Assessment & Safe-Use Conditions .....	7
5.1 Deaths .....	8
5.2 Increases in Intraocular Pressure .....	8
5.3 Arterial Thromboembolic Events.....	8
6 Expected Postmarket Use.....	9
7 Risk Management Activities Proposed by the Applicant.....	9
8 Discussion of Need for a REMS.....	9
9 Conclusion & Recommendations.....	9
10 Appendices .....	9
10.1 References.....	9

## EXECUTIVE SUMMARY

---

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Beovu (brolucizumab-dblI) is necessary to ensure the benefits outweigh its risks. Novartis submitted a Biologics Licensing Application (BLA 761125) for brolucizumab with the proposed indication: for the treatment of neovascular (wet) age-related macular degeneration (nAMD).

The serious risks associated with brolucizumab include increases in intraocular pressure and arterial thromboembolic events. The applicant did not submit a proposed REMS or risk management plan with this application. If brolucizumab is approved, labeling can communicate the associated serious risks and their respective management. Currently, these risks are addressed in the Warnings and Precautions section of the proposed label. The likely prescribers include ophthalmologists who specialize in the treatment of nAMD. These prescribers are likely to be familiar with the management of adverse events associated with intravitreal vascular endothelial growth factor (VEGF) inhibitors as there are other treatments approved for this indication in this class. DRISK and the Division of Transplant and Ophthalmology agree that a REMS is not necessary to ensure the benefits of brolucizumab outweigh its risk for the proposed indication, nAMD.

## 1 Introduction

---

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Beovu (brolucizumab-dblI) is necessary to ensure the benefits outweigh its risks. Novartis submitted a Biologics Licensing Application (BLA 761125) brolucizumab with the proposed indication: for the treatment of neovascular (wet) age-related macular degeneration. This application is under review in the Division of Transplant and Ophthalmology Products. The applicant did not submit a proposed REMS or risk management plan with this application.

## 2 Background

---

### 2.1 PRODUCT INFORMATION<sup>1</sup>

Beovu (brolucizumab), a new molecular entity,<sup>a</sup> is a monoclonal antibody/VEGF inhibitor proposed for the treatment of neovascular (wet) age-related macular degeneration. Brolucizumab is proposed as a 120 mg/mL (b) (4) sterile solution for ophthalmic injection. The recommended dose is 6 mg/0.05 mL injected intravitreally (b) (4) x 3 doses then every 8 – 12 weeks (b) (4). Treatment is continued based on disease activity or until unacceptable toxicity occurs.<sup>b</sup> Brolucizumab is not currently approved in any jurisdiction. If approved, brolucizumab will be the 4<sup>th</sup> drug in the pharmacologic class of intravitreal VEGF inhibitors. None of the intravitreal VEGF inhibitors marketed in the U.S. are approved with a Boxed Warning or REMS.

---

<sup>a</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

<sup>b</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761125 relevant to this review:

- 02/07/2019: BLA 761225 submission for the treatment of nAMD received
- 06/11/2019: A Post Mid-cycle meeting was held between the Agency and Novartis via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for brolocizumab.

## 3 Therapeutic Context and Treatment Options

---

### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

Age-related macular degeneration (AMD) is a disease that affects the macula (central part of the retina) that may result in the loss of central vision.<sup>c</sup> It is the leading cause of adult blindness in industrialized countries.<sup>2</sup> AMD is more common among older people, affecting more than 14% of white Americans age 80 and older (other races/ethnicities ~ 2%).<sup>3</sup> From 2000-2010, the number of people with AMD grew 18%, from 1.75 million to 2.07 million.<sup>3</sup> Neovascular AMD (nAMD) or wet AMD is characterized by the growth of abnormal vessels into the subretinal space and occurs in approximately 10% – 15% of patients with AMD.<sup>d</sup> nAMD results in significant morbidity as rapid distortion and loss of central vision occurs over a period of weeks to months.<sup>2</sup>

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS<sup>4</sup>

Non-pharmacologic treatment of nAMD includes photodynamic therapy (PDT), thermal laser photocoagulation, surgery, and radiation therapy. With the advent of VEGF inhibitors, PDT and thermal laser photocoagulation are no longer considered 1<sup>st</sup> line therapies. PDT is reserved for those who fail to respond to initial VEGF inhibitors. Thermal laser coagulation has the risk of scotoma and vision loss and is rarely recommended. There are varying success rates with surgery and the long-term safety of radiation therapy is unknown.

Pharmacologic treatment of nAMD primarily consists of intravitreal VEGF inhibitors with differing mechanisms of actions. Ranibizumab, aflibercept, and pegaptanib are the three FDA approved intravitreal VEG-F inhibitors indicated for the treatment of nAMD. Although pegaptanib was the first FDA-approved drug for AMD, it is rarely used because the newer agents have more favorable adverse effect profiles. Bevacizumab, FDA-approved as an intravenous infusion for colorectal cancer, is frequently used off-label to treat nAMD and other ophthalmic conditions due to its lower cost and comparable efficacy and safety.<sup>4</sup> Additionally, supplementation with zinc and antioxidant vitamins (e.g. AREDS and AREDS2 nutritional supplement)<sup>e</sup> is recommended to prevent the likelihood of progression to late AMD.<sup>5</sup>

---

<sup>c</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

<sup>d</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

<sup>e</sup> AREDS: vitamin C – 500 mg, vitamin E – 400 international units, beta-carotene – 15 mg, zinc as zinc oxide – 80 mg, copper as cupric oxide – 2 mg; AREDS2: replaces beta carotene in the AREDS formulation with lutein 10 mg and zeaxanthin 2 mg

## 4 Benefit Assessment<sup>f</sup>

The clinical development program for brolocizumab included two pivotal Phase 3 studies, Study RTH258-C001 and Study RTH258-C002.<sup>6</sup> These studies will be referred to as C001 and C002 respectively. Both studies were randomized, double-blind, multicenter studies that compared the efficacy and safety of brolocizumab with aflibercept in patients with nAMD. The primary objective of these studies was to demonstrate that brolocizumab is noninferior to aflibercept. The patient population included males and females greater than 50 years of age with active choroidal neovascularization (CNV) due to AMD who were not previously treated with anti-VEGF therapy. The total study duration for both studies was 96 weeks (including 4 weeks of follow up).

Study Number	Study Design	Total # of randomized patients	Treatment Duration	Treatment Regimen
RTH258-C001 NCT# 2307682	Phase 3, double-masked, multicenter study evaluating efficacy/safety vs. aflibercept in patients with nAMD	1082	96 weeks (92 weeks of treatment plus 4 weeks of follow-up)	*Brolocizumab 3 mg Q4Weeks x 3 doses (loading dose); then Q12Weeks/Q8Weeks (N = 360) *Brolocizumab 6 mg Q4Weeks x 3 doses (loading dose); then Q12Weeks/Q8Weeks (N = 361) Aflibercept 2 mg Q4Weeks x 3 doses; then Q8Weeks x 3 doses; and Q8Weeks x 2 doses (N = 361)
RTH258-C002 NCT# 02434328	Phase 3, double-masked, multicenter study evaluating efficacy/safety vs. aflibercept in patients with nAMD	743	96 weeks (92 weeks of treatment plus 4 weeks of follow-up)	*Brolocizumab 6 mg Q4Weeks x 3 doses (loading dose); then Q12Weeks/Q8Weeks (N = 372) Aflibercept 2 mg Q4Weeks x 3 doses; then Q8Weeks x 3 doses; and Q8Weeks x 2 doses (N = 371)

Note: Q12Weeks = every 12 weeks; Q8Weeks = every 8 weeks  
\*For brolocizumab Q12Weeks, if there was disease activity identified by a masked investigator, the frequency was changed from Q12Weeks to every Q8Weeks

For both studies, the primary endpoint was the change in best-corrected visual acuity (BCVA) from baseline to Week 48. The first key secondary endpoint was average change from baseline over the period of Week 36 through Week 48. The second key secondary endpoint was the proportion of patients randomized to brolocizumab maintaining Q12Week treatment status at Week 48. The third key secondary endpoint was the Q12Week treatment status at Week 48 within the patients randomized to

<sup>f</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

brolocizumab 3 mg and 6 mg and with no disease activity (i.e. no Q8Week-need) during the initial Q12Week interval (Weeks 16 and 20). See Table 2 for the study results below.

For the primary endpoint in Study C001, the Clinical Reviewer stated, “The lower limits of the 95% confidence intervals for the treatment differences between both brolocizumab arms and the aflibercept arm met the noninferiority margin of 4 letters and was statistically significant ( $p = 0.0003$ ) for brolocizumab 3 mg and  $p < 0.0001$  for brolocizumab 6 mg.”<sup>8</sup> For the primary endpoint in Study C002, the Clinical Reviewer stated, “The lower limit of the 95% confidence interval for the treatment difference between brolocizumab 6 mg and aflibercept 2 mg supports the noninferiority margin of 4 letters with a 95% confidence interval for the LS (least squares) mean difference ( $p = 0.0001$ ).”

Endpoints	Study RTH258-C001			Study RTH258-C002	
	Brolocizumab 3 mg (N = 358)	Brolocizumab 6 mg (N = 360)	Aflibercept 2 mg (N = 360)	Brolocizumab 6 mg (N = 370)	Aflibercept 2 mg (N = 369)
<i>Primary Endpoint</i> LS mean estimate of the change in BCVA from Baseline at Week 48 – Pairwise ANOVA (FAS – LOCF)	6.1	6.6	6.8	6.9	7.6
<i>First key secondary endpoint</i> LS mean estimate of the change in BCVA from Baseline from Week 36 through Week 48; Pairwise ANOVA (FAS – LOCF)	6.2	6.7	6.7	6.5	7.7
<i>Second key secondary endpoint</i> Proportion of patients maintaining Q12W treatment status at Week 48 in those randomized to brolocizumab	49.4%	55.6%	N/A	51.0%	N/A
	Brolocizumab 3 mg (N = 208)	Brolocizumab 6 mg (N = 222)		Brolocizumab 6 mg (N = 220)	
<i>Third key secondary endpoint</i> Probability of patients maintaining Q12W treatment status at Week 48 in those randomized to brolocizumab with no disease activity (did not need Q8Week frequency during the initial Q12Week interval – Week 16 and 20)	80.9%	85.4%		81.7%	
LS = least squares; BCVA = best-corrected visual acuity; FAS = full analysis set; LOCF = last observation carried forward					

For the primary endpoint in Study C001, the Clinical Reviewer states, “The lower limits of the 95% confidence intervals for the treatment differences between both brolocizumab arms and the aflibercept arm met the noninferiority margin of 4 letters and was statistically significant ( $p = 0.0003$ ) for

brolicizumab 3 mg and  $p < 0.0001$  for brolicizumab 6 mg.”<sup>8</sup> For the primary endpoint in Study C002, the Clinical Reviewer stated, “The lower limit of the 95% confidence interval for the treatment difference between brolicizumab 6 mg and aflibercept 2 mg supports the noninferiority margin of 4 letters with a 95% confidence interval for the LS (least squares) mean difference ( $p = 0.0001$ ).”

## 5 Risk Assessment & Safe-Use Conditions<sup>g</sup>

The safety database of brolicizumab was analyzed in two groups, RTHP1 and RTHP2. RTHP1, referred to as the loading safety pool, assessed safety from baseline up to Month 3/Week 12 during the monthly loading dose time period. This pool included studies RTH258-E003, C-12-006, and the two pivotal studies C001, and C002. See Table 3 below for study details. RTHP2, referred to as the long-term safety database, assessed safety from baseline to week 96 for the target dose of brolicizumab 6 mg Q4Weeks x 3 doses followed by Q12Week or Q8Week intravitreal injections. RTHP2 included the two pivotal studies C001 and C002 and pooled the brolicizumab 6 mg data ( $n = 730$ ) and aflibercept data ( $n = 729$ ) for analysis. The long-term safety database will be the focus of this discussion. See Table 3 in the appendix for additional study details.

Study Number	Study Design	Total # of randomized patients	Treatment Duration	Treatment Regimen
C-12-006 NCT# 01796964	Phase 2, randomized, double-masked, multi-center study evaluating efficacy and tolerability of brolicizumab versus aflibercept in patients with nAMD	N = 90	56 weeks (392 days)	Brolicizumab 6 mg Q4Weeks x 3 doses; then Q8Weeks x 3 doses; and Q12Weeks x 1 dose (N = 45) Aflibercept 2 mg Q4Weeks x 3 doses; then Q8Weeks x 3 doses; and Q8Weeks x 2 doses (N = 45)
RTH258-E003 NCT# 02507388	Randomized, double-masked, multi-center study evaluating pharmacokinetics, safety, and immunogenicity of brolicizumab in patients with active CNV secondary to AMD	N = 50	8 weeks (56 days)	Brolicizumab 3 mg at Days 0, 28, and 56 (N=25) Brolicizumab 6 mg at Days 0, 28, and 56 (N=25)

In the long-term safety database, 390 (53.4%) patients in the pooled brolicizumab group experienced at least one ocular treatment-emergent adverse event (TEAE) compared to 372 (51%) patients in the pooled aflibercept group. The most frequently reported ocular TEAEs were visual acuity reduced [brolicizumab – 53 (7.3%); aflibercept – 54 (7.4%)] and conjunctival hemorrhage [brolicizumab – 46 (6.3%); aflibercept – 51 (7%).] The most frequently reported serious adverse event (SAE) in the study eye was endophthalmitis [brolicizumab – 4 (0.5%); aflibercept – 1 (0.1%)] followed by uveitis [brolicizumab – 5 (0.7%); aflibercept – 0 (0%)] and retinal detachment [brolicizumab – 2 (0.3%); aflibercept – 2 (0.3%)].<sup>9</sup>

<sup>g</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*



The serious adverse events (referred to as risks) of special interest associated with brolocizumab include increases in intraocular pressure (IOP) and arterial thromboembolic events (ATEs).<sup>h</sup> The Warnings and Precautions section of the brolocizumab proposed label includes these risks and will be discussed below along with the deaths that occurred. Additionally, endophthalmitis and retinal detachments are included in the Warnings and Precautions section of the proposed label for brolocizumab. However, these risks are considered potential complications of the administration technique, intravitreal injection, and thus will not be discussed.

### **5.1 DEATHS**

Overall, 12 (1.6%) deaths occurred in the pooled brolocizumab treatment group compared to 19 (2.6%) deaths in the aflibercept treatment group. The Clinical Reviewer concluded, “The deaths which occurred during the studies are consistent with the age and past medical history of the subjects enrolled.”<sup>8</sup>

### **5.2 INCREASES IN INTRAOCULAR PRESSURE**

IOP increases are considered an adverse drug reaction (ADR) of intravitreal VEGF inhibitors including brolocizumab. In the long-term safety database, 28/730 (3.8%) patients receiving brolocizumab 6 mg experienced an ADR of IOP compared to 33/729 (4.5%) patients in the aflibercept treatment group. The Clinical Reviewer concluded, “The serious ocular adverse events reported were generally consistent with the underlying condition and the intravitreal injection procedure.”<sup>8</sup> The proposed label advises, “Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.”<sup>1</sup>

### **5.3 ARTERIAL THROMBOEMBOLIC EVENTS**

Overall, the number of patients experiencing at least one ATE included 33/730 (4.5%) in the pooled brolocizumab treatment group compared to 34/729 (4.5%) patients in the aflibercept treatment group. These include ocular and non-ocular ATEs. The most frequently reported ATEs were retinal artery occlusion (brolocizumab: n = 3; aflibercept: n = 1), transient ischemic attack (brolocizumab: n = 5; aflibercept: n = 5), cerebrovascular accident (brolocizumab: n = 4; aflibercept: n = 8), and myocardial infarction (brolocizumab: n = 4; aflibercept: n = 3). The Clinical Reviewer concluded, “Overall, the incidence of arterial thromboembolic events was similar across the treatment groups.”<sup>8</sup> The proposed label advises, “There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.”<sup>1</sup>

---

<sup>h</sup> Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

## 6 Expected Postmarket Use

---

Brolucizumab will likely be prescribed and administered primarily in outpatient surgery centers. The likely prescribers include ophthalmologists who specialize in the treatment of nAMD. These prescribers are likely to be familiar with the management of adverse events associated with intravitreal VEGF inhibitors like ranibizumab, aflibercept, and pegaptanib. The proposed labeling currently communicates the associated serious risks and management of increases in intraocular pressure and arterial thromboembolic events.

## 7 Risk Management Activities Proposed by the Applicant

---

The Applicant did not propose any risk management activities for brolucizumab beyond routine pharmacovigilance and labeling.

## 8 Discussion of Need for a REMS

---

The Clinical Reviewer recommends approval of brolucizumab based on the efficacy and safety information currently available. The clinical studies contained in this submission support the use of brolucizumab for the treatment of nAMD.<sup>8</sup>

AMD is the leading cause of adult blindness in industrialized countries with nAMD resulting in significant morbidity as rapid distortion and loss of central vision occurs over a short period of time. Brolucizumab offers an additional option to treat nAMD once diagnosed. The serious risks associated with brolucizumab are increases in intraocular pressure and arterial thromboembolic events. The healthcare providers prescribing brolucizumab should be familiar with managing these risks as they are well known to be associated with intravitreal VEGF inhibitors. Labeling will be used to communicate these risks. DRISK recommends that, should brolucizumab be approved, a REMS is not necessary to ensure its benefits outweigh its risk for the treatment of nAMD in adults.

## 9 Conclusion & Recommendations

---

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for brolucizumab to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

## 10 Appendices

---

### 10.1 REFERENCES

1. Novartis. Beovu (brolucizumab). BLA 761125. Prescribing Information, draft February 7, 2019.
2. Arroyo JG. Age-related macular degeneration: Clinical presentation, etiology, and diagnosis. *UpToDate*. May 29, 2018. Accessed July 8, 2019.
3. Age-Related Macular Degeneration (AMD). <https://nei.nih.gov/eyedata/amd#1>. Accessed June 17, 2019.
4. Arroyo JG. Age-related macular degeneration: Treatment and prevention. *UpToDate* April 9, 2019. Accessed July 8, 2019.

5. Age-Related Eye Disease Study 2 (AREDS2). <https://nei.nih.gov/areds2>. Accessed July 31, 2019.
6. Novartis. Beovu (brolocizumab). BLA 761125. Module 2.7.3 - Summary of Clinical Efficacy. In:February 7, 2019.
7. Novartis. Beovu (brolocizumab). BLA 761125. Module 2.5 - Clinical Overview. In:February 7, 2019.
8. Lloyd R. Food and Drug Administration. Division of Transplant and Ophthalmology Products. Beovu (brolocizumab). BLA 761125. Draft Review. Clinical Reviewer. July 17, 2019.
9. Novartis. Beovu (brolocizumab). BLA 761125. Module 2.7.4 - Summary of Clinical Safety. In:February 7, 2019.

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

/s/  
-----

INGRID N CHAPMAN  
10/02/2019 02:12:28 PM

DONELLA A FITZGERALD  
10/02/2019 02:15:18 PM

JAMIE C WILKINS PARKER  
10/03/2019 09:40:22 AM