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RESEARCH**

APPLICATION NUMBER:

761125Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW of BLA 761125

Application Type	BLA
Application Number	761125
Priority or Standard	Priority
Submit Date	February 7, 2019
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Division/Office	DTOP/OND
Reviewer Name	Rhea A. Lloyd, MD
Review Completion Date	
Established/Proper Name	brolocizumab-dbll
(Proposed) Trade Name	BEOVU
Applicant	Novartis Pharmaceuticals Corporation
Dosage Form(s)	intravitreal injection
Applicant Proposed Dosing Regimen(s)	Brolocizumab is recommended to be administered (b) (4) for the first (b) (4) three doses, (b) (4)
Applicant Proposed Indication	Treatment of neovascular age-related macular degeneration
Recommended Regulatory Action	Approval
Recommended Indication	Treatment of neovascular age-related macular degeneration

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Glossary

AC	advisory committee
ADA	antidrug antibodies
AE	adverse event
AMD	age-related macular degeneration
ANOVA	analysis of variance
ATE	arterial thromboembolic events
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CF	color fundus
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNV	choroidal neovascularization
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
coBL	Core Study Baseline visit
coWeek	Core Study Week (xx) visit
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSFT	central subfield thickness
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
exBL	Extension Study Baseline visit
exWeek	Extension Study Week (xx) visit
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IFU	Instructions for Use
IND	Investigational New Drug Application

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PED	persistent epithelial defect
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
VEGF	vascular endothelial growth factor

1. Executive Summary

1.1. Product Introduction

Brolocizumab (RTH258) is a humanized single-chain Fv antibody fragment (scFv) inhibitor of VEGF-A with a molecular weight of approximately 26 kDa which inhibits binding of VEGF to the VEGFR1 and VEGFR2 receptors.

1.2. Conclusions on the Substantial Evidence of Effectiveness

BLA 761125 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of BEOVU for the treatment of neovascular (wet) age-related macular degeneration.

1.3. **Benefit-Risk Assessment**

Benefit-Risk Integrated Assessment

The adequate and well controlled studies contained in this submission establish the efficacy of BEOVU (brolucizumab-dbl) injection, 6 mg/ 0.05 mL for the treatment of neovascular (wet) age-related macular degeneration (AMD) when the product is administered intravitreally every 4 weeks (approximately every 28 days) for the first three doses, and then administered at intervals of every 8 weeks or 12 weeks.

Studies RTH258-C001 and RTH258-C002 demonstrated that brolucizumab (6 mg/ 0.05 mL) is not inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from baseline to Week 48. The most common ocular adverse events after treatment with brolucizumab were reduced visual acuity, cataracts, conjunctival hemorrhage, uveitis, and vitreous floaters.

There is a favorable benefit-risk ratio of brolucizumab 6mg/ 0.05 mL in the treatment of neovascular (wet) age-related macular degeneration (AMD).

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> Age-related macular degeneration (AMD) is a chronic eye disease characterized by progressive degeneration in the central retina (macula) and is a leading cause of severe vision loss worldwide. The neovascular form of AMD makes up about 10% of all AMD cases, but accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments. The natural history of untreated wet AMD is that most eyes will develop poor central vision ($\leq 20/200$) within 12 months. 	The goal of treatment of wet AMD is the preservation of the central retina (macula) and the preservation of central visual acuity.
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> Lucentis and Eylea have been shown to be safe and effective and are approved for the treatment of wet AMD. The use of Avastin is supported by adequate and well controlled studies, but a BLA for its use intravitreal use has never been submitted. 	BEOVU was noninferior to Eylea in the treatment of wet AMD. BEOVU will provide practitioners with an additional treatment option.
<u>Benefit</u>	<ul style="list-style-type: none"> Studies RTH258-C001 and RTH258-C002 demonstrated that brolucizumab was not inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from baseline to Week 48 in patients with wet AMD. 	Adequate and well controlled studies support the efficacy. Use of the product led to a 6-7 letter improvement in visual acuity.
<u>Risk and Risk Management</u>	<ul style="list-style-type: none"> BEOVU in studies RTH258-C001 and RTH258-C002 demonstrated a safety profile which was similar to Eylea through 48 weeks of treatment. The long-term safety beyond 96 weeks has not been established. 	Routine monitoring and reporting of all adverse events are expected to be adequate to monitor for potential new adverse reactions.

2. Therapeutic Context

2.1. Analysis of Condition

Age-related macular degeneration (AMD) is a chronic eye disease characterized by progressive degeneration in the central retina (macula) and is a leading cause of severe vision loss worldwide. Ten to 13% of individuals over age 65 in North America, Europe and Australia are affected. Genetic, environmental, and health factors are strongly associated with development of AMD. AMD is classified into two different forms: the non-neovascular or atrophic form and the neovascular or exudative (wet) form.

Neovascular age-related macular degeneration (nAMD) is characterized by the new growth of abnormal blood vessels (neovascularization) emanating from the subjacent choroid in the subretinal pigment epithelium (RPE) space and the subretinal space. These growths are termed choroidal neovascular membranes (CNV or CNVM). These newly formed vessels have an increased likelihood to leak blood and serum causing separation of Bruch's membrane, RPE and retina from each other and resulting in the accumulation of sub-RPE, sub-retinal or intra-retinal fluid. Fluid accumulation leads to a generalized thickening of the retina and/or the formation of cystic spaces. These pathological manifestations of the retina cause the photoreceptors to become misaligned and eventually degenerative changes occur with cell loss and eventual fibrosis and scar tissue formation. This damage to the retina results in progressive, severe vision loss, metamorphopsia, scotoma, photopsia, and impaired dark adaptation. Without treatment, most affected eyes will have poor central vision (20/200) within 12 months. Although the neovascular form of the disease is only present in about 10% of all AMD cases, it has accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments.

2.2. Analysis of Current Treatment Options

Lucentis (ranibizumab injection) was approved for the treatment of neovascular AMD in 2006. Eylea (aflibercept) was approved for the treatment of neovascular AMD in 2011. Avastin (bevacizumab) is prescribed off-label for the indication.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Brolucizumab is a new molecular entity which has not yet been marketed.

3.2. Summary of Presubmission/Submission Regulatory Activity

- End-of-Phase 2 (Type B) meeting was held May 8, 2013
- Type C meeting was held September 1, 2015
- Type C meeting was held September 20, 2017
- Pre-BLA (Type C) meeting was held May 17, 2018
- Pre-BLA (Type B) meeting was held August 27, 2018

3.3. Foreign Regulatory Actions and Marketing History

Brolucizumab has not been approved for marketing in any other countries.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

See CDTL memorandum. No clinical integrity issues identified.

4.2. Product Quality

From the February 7, 2019 submission:

The brolucizumab drug substance is alternatively known under the development code of RTH258 and product code and/or trivial names such as ESBA1008, AL-86810 and

(b) (4). All those terms are used interchangeably throughout the submission. (b) (4)

Brolucizumab drug product is formulated for intravitreal administration as solution for injection in a dosage strength of 6 mg/0.05 mL. Each vial of brolucizumab contains the active ingredient brolucizumab, 10 mM sodium citrate buffer, 0.02% polysorbate 80, 5.8% sucrose and water for injection and has a pH of approximately 7.2.

Brolucizumab solution for injection is packaged in glass vials with (b) (4) rubber stoppers sealed with aluminum caps with plastic flip-off disks. Each vial contains approximately (b) (4) mL solution to allow intravitreal administration of 0.05 mL. The product is withdrawn using a filter needle (co-packaged) and administered using a 30G injection needle (not co-packaged). Each pack contains one vial of medication and a filter needle. The brolucizumab solution for injection vials are supplied as a sterile and preservative-free solution for injection designated for single use administration.

Development of brolucizumab 6 mg/0.05 mL Solution for injection was initiated by ESBA Tech, Switzerland (initial formulation for phase 1) and transferred to Alcon Laboratories, Inc., USA (formulation A for phase 2 and 3 clinical trials). The commercial formulation was developed by Novartis Pharma AG, Basel Switzerland (commercial formulation B for the phase 3 clinical trial extension study using the commercial manufacturing process). The final commercial scale manufacturing process was developed and validated at Novartis Pharma Stein AG, Switzerland. An overview of the changes during drug product development from clinical phase 3 supply to intended commercial product is summarized in Table 4.2-1.

In the initial Phase 1 formulation, the brolucizumab

(b) (4)

Comparability has been demonstrated between the material used in Phase 3, pilot scale and the intended commercial product in nonclinical and clinical studies.

Table 4.2-1 Overview of Changes during Drug Product Development from Clinical Phase 3 Supply to Intended Commercial Product

	Phase III Clinical Supply	Registration Stability (Pilot Scale)	Intended commercial process (Process Validation)
DP Production site	Alcon Laboratories Inc.	Novartis Pharma Stein AG	Novartis Pharma Stein AG

(b) (4)

(b) (4)		
Final Formulation	(b) (4)	Brolucizumab: 120 mg/mL Sucrose: 5.8% Citrate (b) (4) 10 mM Polysorbate 80: 0.02% pH: 7.2
Primary Packaging	(b) (4)	Colorless 2 mL (b) (4) glass vial, (b) (4) rubber stopper (b) (4)
Long term storage	(b) (4)	2 – 8 °C
NA: not applicable		

Source: Module 3.2.P.2, Section 1.4, Table 1-3

Table 4.2-2 Overview on Brolucizumab Drug Product Formulations and Use

Strength	4 mg/mL	10 mg/mL	60 mg/mL	120 mg/mL	120 mg/mL
Dosage	NA	NA	NA	6 mg/0.05 mL	6 mg/0.05 mL
Use	Phase 1	Phase 1	Phase 1	Phase 2 and 3 Formulation A ^{1), 2)}	Phase 3 extension Formulation B (commercial)
pH	(b) (4)				7.2
Component (mg/mL)					
Brolucizumab drug substance					120
Sucrose					58
Sodium citrate (b) (4)					2.58
Polysorbate 80					NA
Water for injection					0.2
(b) (4)					q.s. to 1.0 mL
(b) (4)					NA
(b) (4)					q.s.

¹⁾

²⁾ In clinical studies a 60 mg/mL brolucizumab presentation was used (see [3.2.P.2 addendum CTFO] for details)

Source: Module 3.2.P.2, Section 3.1, Table 3-1

Refer to the Product Quality review for further details.

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

The final nonclinical pharmacology/toxicology review is pending. See CDTL review for complete findings.

4.5. **Clinical Pharmacology**

See CDTL memorandum.

4.6. **Devices and Companion Diagnostic Issues**

Not applicable. There is not a companion device or diagnostic.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Name / Phase	Study Design	Number of Patients Enrolled	Study Drug Treatment Groups Duration	Primary Efficacy Analysis / Outcome Measures (as amended)
Phase 1 and 2 Studies				
C-10-083 (SEE) Module 5.3.5.1	Study Design: Phase 1 study to evaluate safety & tolerability, efficacy vs. ranibizumab in subjects with nAMD	194 N=10 N=35 N=48 N=40 N=61	Single injections of: Brolucizumab 0.5mg/50mcL Brolucizumab 3mg/50mcL Brolucizumab 4.5mg/50mcL Brolucizumab 6mg/50mcL Ranibizumab 0.5mg/50mcL 6 months (180 days)	<ul style="list-style-type: none"> • Change from baseline in CSFT • Time to standard of care • Change from baseline in BCVA
C-12-006 (OSPREDY) Module 5.3.5.1	Study Design: Phase 2, double-masked, multicenter study evaluating efficacy/tolerability vs aflibercept in subjects with nAMD	90 N=45 N=45	Brolucizumab 6mg/ 50mcL 3xq4w + 3xq8w + 1xq12w Aflibercept 2 mg/ 50 mcL 3xq4w + 3xq8w + 2xq8w 56 weeks (392 days)	<ul style="list-style-type: none"> • Change from baseline in BCVA • CSFT • q12w proportion for brolucizumab • Confirmation of 6 mg dose

Study Name / Phase	Study Design	Number of Patients Enrolled	Study Drug Treatment Groups Duration	Primary Efficacy Analysis / Outcome Measures (as amended)
C-13-001 (OWL) Module 5.3.5.4	Study Design: Prospective, randomized, single-masked, multi-center, 4-cohort, dose-ranging study evaluating efficacy and safety of brolucizumab in subjects with an untreated and active CNV lesion in at least one eye due to AMD	52 N=10 N=10 N=6 N=10 N=10 N=6	<u>Stage 1:</u> Brolucizumab 1.2 mg/10 mcL single injection on Day 0 + 6 mg/50 mcL injection on Day 28 Brolucizumab 1.0 mg/8.3 mcL single infusion on Day 0 + 6 mg/50 mcL injection on Day 28 Ranibizumab 0.5 mg/50 mcL injection on Days 0 and 28 <u>Stage 2:</u> Brolucizumab 0.6 mg/10 mcL single injection on Day 0 + 6 mg/50 mcL injection on Day 28 Brolucizumab 0.5 mg/8.3 mcL single infusion on Day 0 + 6 mg/50 mcL injection on Day 28 Ranibizumab 0.5 mg/50 mcL injection on Days 0 and 28	<ul style="list-style-type: none"> • Response based on CSFT and BCVA outcomes at Days 14 and 28
RTH258-E003 (SHRIKE)	Study Design: Randomized, double-masked, multi-center study evaluating PK, safety, and immunogenicity of brolucizumab in subjects with CNV secondary to AMD	50 N=25 N=25	Brolucizumab 3 mg/50mcL at Days 0, 28, and 56 Brolucizumab 6 mg/50 mcL at Days 0, 28, and 56	<ul style="list-style-type: none"> •

Study Name / Phase	Study Design	No. of Patients Randomized	Treatment Groups / Treatment Regimen Treatment Duration	Primary Efficacy Analysis / Outcome Measures (as amended)
Controlled Studies – Safety and Efficacy				
RTH258-C001 (HAWK) Module 5.3.5.1	Study Design: Phase 3, multicenter, randomized (1:1:1), double-masked, active-controlled, parallel group study Evaluations: Safety and efficacy of RTH258 vs. aflibercept in patients with nAMD	1082 N=360 N=361 N=361	Brolucizumab 3mg/50mcL 3xq4w + q12w/q8w Brolucizumab 6mg/50mcL 3xq4w + q12w/q8w Aflibercept 2 mg/ 50 mcL 3xq4w + q12w/q8w 92 wks + 4 wk follow-up	<ul style="list-style-type: none"> • Change in BCVA • Disease activity • q12w proportion for brolucizumab • CSFT • Area of CNV • Presence of IRF, SRF and sub-RPE fluid
RTH258-C002 (HARRIER) Module 5.3.5.1	Study Design: Phase 3, multicenter, randomized (1:1), double-masked, active-controlled, parallel group study Evaluations: Safety and efficacy of RTH258 vs. aflibercept in patients with nAMD	743 N=372 N=371	Brolucizumab 6mg/50mcL 3xq4w + q12w/q8w Aflibercept 2 mg/ 50 mcL 3xq4w + q12w/q8w 92 wks + 4 wk follow-up	<ul style="list-style-type: none"> • Change in BCVA • Disease activity • q12w proportion for brolucizumab • CSFT • Area of CNV • Presence of IRF, SRF and sub-RPE fluid

The main differences between the two studies were as follows:

- Study RTH258-C001 (HAWK) included a brolucizumab 3 mg treatment arm in addition to the brolucizumab 6 mg and aflibercept 2 mg treatment arms, to assess the potential safety and efficacy relationship of different brolucizumab doses.
- Study RTH258-C001 (HAWK) was conducted in centers in North America, Latin America, Japan, Australia, New Zealand and Israel, whereas Study RTH258-C002 (HARRIER) was conducted in centers in the EU, Middle East, Asia and Russia.
- To address a Health Authority request raised during the European CTA review (voluntary harmonization procedure, VHP), Study RTH258-C002 included additional disease activity assessments at Week 28, 40, 52, 64, 76, and 88.

Study Name / Phase	Study Design	No. of Patients Randomized	Treatment Groups / Treatment Regimen Treatment Duration	Primary Efficacy Analysis / Outcome Measures (as amended)
Uncontrolled Studies – Safety and Efficacy				
CRTH258A2301E1 Module 5.3.5.1	Study Design: Extension study of Phase 3, double-masked, multicenter study collecting data on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization Evaluations: Safety and efficacy of RTH258 vs. aflibercept in patients with nAMD	150 N=107 N=43	Brolucizumab 6mg/50mcL 2xq8w+1xq12w/q8w Aflibercept 2 mg/ 50 mcL 3xq8w 20 weeks of treatment + 4 weeks follow-up (total 24 weeks)	<ul style="list-style-type: none"> • Change in BCVA • CSFT • Disease activity • q12w treatment status

To address a request a from the FDA to test the brolucizumab formulation intended for commercialization, subjects in the US who completed Study RTH258-C001 were offered the opportunity to participate in an extension study, CRTH258A2301E1. This extension study included subjects who could be enrolled within 12 weeks of completing Study RTH258-C001.

5.2. Review Strategy

Clinical data for Studies RTH258-C001, RTH258-C002 and CRTH258A2301E1 listed in Section 5.1 were reviewed to support safety and efficacy. Clinical data from the additional studies in Section 5.1 were reviewed as appropriate to support safety.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study RTH258-C001 (HAWK) – 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

6.1.1. Study Design

Primary Objective: To demonstrate that brolucizumab is not inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from baseline to Week 48

Key Secondary Objectives:

- To demonstrate that brolucizumab is not inferior to aflibercept with respect to the change in BCVA from baseline averaged over the period Week 36 to Week 48
- To estimate the proportion of subjects receiving q12w (1 injection every 12 weeks) up to Week 48 in the brolucizumab treatment arms (“maintaining on q12w”)
- To estimate the predictive value of the first (“initial”) q12w cycle for maintenance of q12w treatment up to Week 48 in the brolucizumab treatment arms (“remaining on q12w”)

Other Secondary Objectives:

- To evaluate the efficacy of brolucizumab relative to aflibercept over the time period up to Week 96 by assessing changes in:
 - BCVA
 - Anatomical parameters of disease activity including central subfield thickness (CSFT) and CNV area

Note: Based upon the corresponding results observed in the RTH258-C002 study, this evaluation was supplemented by superiority testing. Corresponding hypotheses were prespecified in the statistical analysis plan (SAP) for this study prior to database lock.

 - Presence of “q8w treatment need” (1 injection every 8 weeks), including assessment of q12w status for subjects in the brolucizumab 3 mg and 6 mg treatment arms
- To assess visual function-related subject reported outcomes following treatment with brolucizumab relative aflibercept
- To assess the safety and tolerability of brolucizumab relative to aflibercept

List of Investigators

There were study center(s) in the following countries: Argentina (1), Australia (12), Canada (14), Colombia (5), Israel (10), Japan (34), Mexico (4), New Zealand (3), Panama (1), Puerto Rico (2), USA (126).

Table 6.1.1-1 Investigator(s) Who Randomized More than 10 Subjects

Alcon Site Number	Novartis Site Number	Principal Investigator Site Address	Number of Subjects Randomized
3947	5028	David Brown 6560 Fannin, Houston TX 77030	20
6221	5058	Ryan Rich * 2770 North Union Blvd., Colorado Springs, CO 80909	20
7376	5170	Andres Emanuelli 452 Rivera Aulet, Arecibo, PR 00612	19
7354	5141	Grant Janzen 5441 Health Center Drive, Abilene, TX 79606	18
7071	5095	Gregory Cohen 950 Ryland Street, Reno, NV 89502	17
7200	2209	Laurent Lalonde 4800 Ambroise-Lafortune, Boisbriand, QU J7H1S6	17
4046	5006	Pravin Dugel 1101 E. Missouri Avenue, Phoenix, AZ 85014	15
6824	2103	Andrew Chang Level 7&13, Park House, 187 Macquarie Street, Sydney, NSW, 2000 Australia	15
6997	5078	Eric Guglielmo 427 South Bernard Spokane, WA 99204	14
7342	5138	James Earl 13923 W. Wainwright Dr., Boise, ID 83713	14
5773	5042	Carmeline Gordon 850 W. North Street Jackson, MI 49202	13
5897	5046	Adam Berger 2815 Lakeland Hills Blvd, Suite 200 Winter Haven, FL 33805	13
7007	5084	Gary Shienbaum 351 NW 42 nd Avenue Miami, FL 33126	13
7426	5149	Patrick Williams 1101 6 th Avenue Fort Worth, TX 76104	13

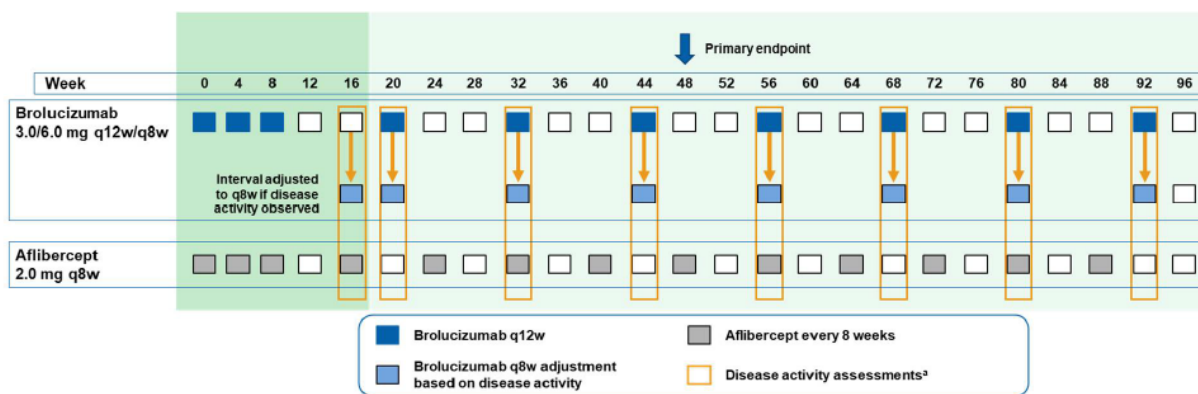
Alcon Site Number	Novartis Site Number	Principal Investigator Site Address	Number of Subjects Randomized
7730	7002	Adiel Barak 6 Weizmann Street Tel Aviv, NA 64239	13
6328	5063	Robert Sisk 1945 CEI Drive Cincinnati, OH 45242	12
7655	6034	Atsushi Hayashi 2630, Sugitani Toyama-shi, Toyama NA Japan	12
7068	5092	William Freeman 9415 Campus Point Drive La Jolla, CA 92093-0706	11
7106	2207	Raman Tuli 2211 Carling Avenue Ottawa, ON K2B7E9	11
7360	5145	Everton Arrindell 345 23 rd Avenue North Nashville, TN 37203	11

* Routine site inspection of this site was performed by the Office of Scientific Investigations.

Overall Design:

This was a Phase 3, prospective, randomized, double-masked, multicenter study designed to compare the efficacy and safety of brolucizumab 3 mg and 6 mg with aflibercept 2 mg in subjects with neovascular age-related macular degeneration (nAMD) who had not received prior anti-VEGF treatments. Approximately 330 subjects per treatment arm were planned for randomization. The primary efficacy and safety analyses were assessed at Week 48. The total study duration was 96 weeks to allow for long term assessment of efficacy and safety.

Figure 6.1.1-1 Study Design



After confirmation of eligibility at Baseline, subjects were randomized to brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg in a 1:1:1 ratio. Subjects in all 3 treatment arms received 3 monthly loading doses (Day 0, Week 4 and Week 8), followed by maintenance regimens:

- Brolucizumab 3 mg q12w/q8w

- Brolucizumab 6 mg q12w/q8w
- Aflibercept 2 mg q8w

After the loading phase of 3 doses administered every 4 weeks, subjects in the brolucizumab arms were scheduled for an initial q12w dosing interval. Based on an assumption that in individual nAMD patients anti-VEGF need is stable over time, the objective of this initial q12w dosing interval was to identify subjects not suitable for q12w treatment (“initial q12w interval concept”). For this purpose, Disease Activity Assessments (DAAs) were conducted by a masked Investigator at Weeks 16 and 20. Subjects identified with a q8w need were switched to a q8w treatment interval for the remainder of the study. Subjects selected for q12w during this initial q12w interval continued on a q12w treatment frequency unless DA was identified at any of the subsequent DAA visits.

The ‘q12w/q8w’ represents a brolucizumab treatment regimen where the interval could be adjusted according to the subject's individual treatment need as identified by disease activity assessments (DAAs) performed by the masked investigator at pre-specified visits. Disease activity was assessed by masked Investigators at Week 16 and at scheduled q12w treatment visits (Weeks 20, 32, 44, 56, 80 and 92. The disease activity (DA) identification was at the discretion of the masked investigator with guidance in the protocol based on anatomical and functional parameters (Table 6.1.1-2).

Table 6.1.1-2 – Guidance Criteria for Disease Activity Assessment

At Week	Criterion
Week 16	Decrease in BCVA of ≥ 5 letters compared with Baseline Decrease in BCVA of ≥ 3 letters and CSFT increase $\geq 75\text{mcm}$ compared with Week 12 Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with Week 12 New or worse IRC/IRF compared with Week 12
Weeks 20, 28 ^a , 32, 40 ^a and 44	Decrease in BCVA of ≥ 5 letters due to nAMD disease activity ^b compared with Week 12
Weeks 52 ^a , 56, 64 ^a , 68, 76 ^a , 80, 88 ^a , and 92	Decrease in BCVA of ≥ 5 letters due to nAMD disease activity ^b compared with Week 48

Source: Sections 9.5.2.1.4 in CSRs for Studies RTH258-C001 and RTH258-C002.

^a Study RTH258-COO1 only

^b Assessed by anatomical parameters, e.g., CSFT or IRF

Reviewer’s Comment:

The FDA Clinical Review staff does not agree that the clinical assessment provided in the protocol is necessarily capable of predicting which patients have a greater need for additional treatments. The applicant has not evaluated to ability of the DAA to predict additional needed treatments. Other Anti-VEFG products have conducted clinical trials using very similar DAAs. In these clinical trials, DAA have failed to predict additional need as assessed by final visual acuity.

Within the q12w/q8w regimen, the initial treatment schedule after the loading phase was q12w. If disease activity (DA) was identified by the masked investigator in brolucizumab-treated subjects at any of the DAAs, dosing was adjusted to q8w (“q12w/q8w regimen”). Once subjects

were adjusted to a q8w interval, they stayed on that interval until the end of the study (Week 96/Exit).

Up until Week 16, treatment exposure was identical allowing a matched comparison of brolucizumab and aflibercept up to 8 weeks of loading. Due to the differences in treatment regimens (q8w vs. q12w/q8w), to maintain masking, subjects not scheduled for an active treatment received a sham injection starting at Week 16. Subjects who were switched from q12w to q8w continued a q8w regimen for the remainder of the study.

Aflibercept was administered as labeled for the Neovascular (Wet) Age-Related Macular Degeneration (AMD) indication: 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).

Diagnosis and Main Criteria for Inclusion

The study population was planned to consist of approximately 990 subjects with neovascular age-related macular degeneration in the study eye (330 per treatment arm). Overall, 1082 subjects were randomized and comprised All Randomized Set [RAN]. Of these randomized subjects, 1078 received study treatment and comprised the Full Analysis Set [FAS] and Safety Analysis Set [SAF]).

The main inclusion criteria were:

- Subjects must have been 50 years or older at Screening
- Active CNV lesions secondary to AMD that affected the central subfield (including retinal angiomatous proliferation lesions with a CNV component) in the study eye at Screening.
- Total area of CNV (including both classic and occult components) must have comprised > 50% of the total lesion area in the study eye at Screening.
- Intraretinal and/or subretinal fluid affecting the central subfield of the study eye at Screening.
- BCVA between 78 and 23 letters, inclusive, in the study eye at Screening and Baseline using ETDRS testing.

The main exclusion criteria were:

- Any active intraocular or periocular infection or active intraocular inflammation in either eye at Baseline.
- Central subfield of the study eye affected by fibrosis or geographic atrophy or total area of fibrosis \geq 50% of the total lesion in the study eye at Screening.
- Subretinal blood affecting the foveal center point and/or \geq 50% of the lesion of the study eye at Screening
- Any approved or investigational treatment for nAMD in the study eye at any time.
- Retinal pigment epithelial rip/tear in the study eye at Screening or Baseline or current vitreous hemorrhage or history of vitreous hemorrhage in the study eye within 4 weeks prior to Baseline.
- Stroke or myocardial infarction in the 90-day period prior to Baseline.

Inclusion and exclusion criteria related to anatomical ocular characteristics were to be confirmed by the Central Reading Center (CRC).

Test and Reference Therapies

Brolucizumab solution for IVT injection was supplied to the Investigators in single use, sterile glass vials. Aflibercept was obtained as commercially available, single use glass vials. The batch and formulation numbers of brolucizumab and aflibercept treatments are presented below.

Table 6.1.1-3

Study drug and strength	Formulation identification	Lot numbers
Brolucizumab solution for IVT injection, 3 mg/50 µL	120525A	15-501536-1, 14-501480-1, 15-501583-1, 16-501603-1, 17-501644-1
Brolucizumab solution for IVT injection, 6 mg/50 µL	120852A	15-501537-1, 14-501526-1, 15-501555-1, 17-501646-1, 15-501588-1, 16-501602-1
Aflibercept solution for IVT injection, 2 mg/50 µL	Not applicable	14-501527-1, 15-501528-1, 15-501551-1, 15-501562-1, 15-501565-1, 15-501570-1, 15-501577-1, 15-501579-1, 16-501598-1, 16-501600-1, 16-501606-1, 16-501635-1, 17-501639-1, 17-501647-1, 17-501652-1, 17-501653-1

The study kits consisted of a carton that contained 1 vial containing 3 mg or 6 mg of brolucizumab. The contents were not to be split. All study kits were to have been stored at 2°C to 8°C (35.6°F – 46.4°F). The study centers were instructed not to freeze the kits and to maintain a daily temperature log to document the study treatment storage conditions.

Treatment masking

This was a double-masked study. The subjects, Investigators, study center staff (except for the unmasked study center personnel and unmasked injecting physician), Sponsor personnel (except for those who have been delegated responsibility for working with the study treatment), and data analysts remained masked to the identity of the treatment from the time of randomization until Week 48 and final database locks. Study treatment injections were performed by an unmasked injecting physician.

To maintain the masking and data integrity, at least 2 Investigators (and corresponding study center staff) were involved in the study at each study center: 1 masked (evaluating) Investigator performed all assessments and captured data in the electronic data capture system, and 1 unmasked (treating) Investigator administered the randomized study treatment according to the protocol. The Investigators were to maintain the same role throughout the study. A detailed list of study tasks performed by the masked and unmasked Investigators and other study center personnel is provided in the Manual of Procedures.

Rescue treatment was not permitted in the study eye. Treatment with ranibizumab was allowed in the fellow eye. With implementation of Protocol Amendment 2 (Appendix 16.1.1), treatment

with an approved anti-VEGF treatment for exudative AMD in the respective country was permitted in the fellow eye at the discretion of the Investigator and in accordance with the administration procedures established at the study center.

Concomitant and Prohibited Medications

Prohibited treatments were not allowed after the Screening visit. In addition, certain washout periods as specified in the exclusion criteria were followed.

Table 6.1.1-4 – Prohibited Treatments

Route	Medication
Study Eye	Intraocular or periocular corticosteroids Laser treatment for AMD Anti-VEGF therapy other than the study treatment
Fellow Eye	Unapproved or investigational treatment
Systemic	Use of systemic corticosteroids for 30 or more consecutive days (except low stable doses of corticosteroids [defined as ≤ 10 mg prednisolone or equivalent dose], inhaled, nasal, or dermal steroids were permitted Anti-VEGF therapy
Any investigational drug, biologic, or device (with the exception of OTC vitamins, supplements, or diets)	

a Study RTH258-COO1 only

b Assessed by anatomical parameters, e.g., CSFT or IRF

Pharmacokinetics

Serum samples for the analysis of systemic brolucizumab levels and anti-drug antibodies (immunogenicity) were collected prior to first injection of the study drug (Baseline) and at Week 4, Week 12, Week 24, Week 36, Week 48, Week 68 and Week 88. Neutralizing antibodies (nAb) were assessed in the pre-dose samples from all subjects receiving brolucizumab and in the post-dose samples of brolucizumab subjects with induced or boosted integrated ADA status.

Safety Assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), ophthalmic examinations (slit-lamp biomicroscopy, IOP measurements, and fundus examinations), post-injection assessments (including IOP), clinical laboratory testing (hematology, blood chemistry, and urinalysis), vital sign measurements, and physical examinations. Other diagnostic tests included CF photography, ICG imaging (conducted at study centers in Japan only), and fundus autofluorescence (conducted at a subset of study centers).

Statistical Methods

Primary Efficacy Endpoint-Change in BCVA from Baseline to Week 48

Analysis Sets

- All enrolled analysis set – all subjects who signed an informed consent and were assigned a subject number
- All randomized analysis set – all subjects who were randomized in the IRT.
- Full analysis set (FAS) – all randomized subjects who received at least 1 IVT injection of study treatment. The FAS was the primary analysis set for all efficacy analyses and was the

analysis set that was most closely aligned with the intent to treat principle of including all randomized subjects. Subjects were analyzed according to the treatment arm they were assigned at randomization.

- Per protocol analysis set (PPS) – a subset of the FAS that excluded subjects with protocol deviations and violations of analysis requirements that were expected to have a major effect on the validity of the Week 48 assessment of efficacy.
- Safety analysis set (SAF) – all subjects who received at least 1 IVT injection. Subjects were analyzed according to the study treatment from which they received the majority of treatments up to and including Week 44.

Sample Size Calculation

A sample size of 297 subjects per treatment arm was considered sufficient to demonstrate noninferiority (margin = 4 letters) of brolocizumab 3 mg/6 mg versus aflibercept 2 mg with respect to the change in BCVA from Baseline to Week 48 at a 2-sided alpha level of 0.05 with a power of approximately 90%, assuming equal efficacy and a common SD of 15 letters. A power of at least 90% can be expected for the first key secondary efficacy endpoint, assuming that averaging over the 4 time points would not lead to an increase in the SD. To account for a dropout rate of 10%, a total of 330 subjects were planned for randomization into each treatment arm (i.e., a total of 990 randomized subjects).

Noninferiority Margin

The FDA Clinical Review team agreed to a noninferiority margin of 4 letters using aflibercept 2mg dosed every 8 weeks after an initial 3 doses of q4w aflibercept.

Statistical Analysis - see Statistical Review for full details

Non-inferiority would be demonstrated if the lower limit of the two-sided 95% confidence interval for the corresponding treatment difference (RTH258 – aflibercept) was greater than -4 letters. No hypothesis was tested for the second and third key secondary objectives.

There were no formal safety hypotheses in this study. The safety analyses were conducted using the safety analysis set on a treatment-emergent basis. For treatment-emergent safety analyses, subjects were analyzed according to the actual study treatment they received.

Interim analysis

No interim analysis prior to the primary analysis at Week 48 was planned or conducted for this study.

Compliance with Good Clinical Practices

This study was conducted per the principles of Good Clinical Practices (GCP).

Figure 6.1.1-2 Evaluation and Visit Schedule

Visit	Screening	V1/ Baseline	V2	V3	V4 ⁷	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Week	Day	Day 0	W4	W8	W8 + 1 day	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit window (days)	-14 to -2		± 3	± 3		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Informed consent ¹	X														
Demographics and Medical history	X														
Concomitant Medications	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Monitor for AEs	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X ²													
VFQ-25 ³		X							X						X
General Physical Exam ⁴	X														X
Vital signs	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Pregnancy test ⁵	X														X
Lab Tests: Chemistry/Hematology/ Urinalysis ⁶	X					X									X
Blood Draw for ADA ⁶		X	X			X			X			X			X
Blood Draw for Systemic Brolucizumab ⁶		X	X			X			X			X			X
BCVA	X ⁸	X ⁸	X	X		X ⁸	X	X	X ⁸	X	X	X ⁸	X	X	X ⁸
Complete Ophthalmic Exam ⁹	X ⁸	X	X	X		X	X	X	X	X	X	X	X	X	X ⁸
SD-OCT	X ⁸	X	X	X		X	X	X	X	X	X	X	X	X	X ⁸
FA ¹⁰	X ⁸					X									X ⁸
Color Fundus Photography	X ⁸					X									X ⁸
ICG ¹¹	X ⁸														
FAF ¹²		X ¹²				X ¹²									X ¹²
Disease Activity Assessment							X	X			X			X	
Contact IRT	X	X	X	X			X	X	X	X	X	X	X	X	X
Administer Study Injection or Sham ¹³ / Postinjection Assessment ¹⁴		X	X	X			X	X	X	X	X	X	X	X	X

Figure 6.1.1-2 Evaluation and Visit Schedule (continued)

Visit	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26/ Exit ¹⁵
Week	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
Visit window (days)	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Changes in Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Monitor for AEs	X	X	X	X	X	X	X	X	X	X	X	X
VFQ-25 ³						X						X
General Physical Exam ⁴												X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test ⁵												X
Lab Tests: Chemistry/Hematology/ Urinalysis ⁶												X
Blood Draw for ADA ⁶					X					X		(X) ¹⁶
Blood Draw for Systemic Brolucizumab ⁶					X					X		(X) ¹⁶
BCVA	X	X	X ⁸	X	X	X ⁸	X	X	X ⁸	X	X	X ⁸
Complete Ophthalmic Exam ⁹	X	X	X	X	X	X	X	X	X	X	X	X ⁸
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X ⁸
FA ¹⁰												X ⁸
Color Fundus Photography												X ⁸
FAF ¹²												X ¹²
Disease Activity Assessment		X			X			X			X	
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	
Administer Study Injection or Sham ¹³ / Postinjection Assessment ¹⁴	X	X	X	X	X	X	X	X	X	X	X	
Complete Exit Form ¹⁵												X

ADA = antidrug antibodies; AE = adverse event; BCVA = best-corrected visual acuity; FA = fluorescein angiography; FAF = fundus autofluorescence; ICG = indocyanine green; IRT = interactive response technology; SD-OCT = spectral domain-optical coherence tomography; VFQ-25 = Visual Function Questionnaire-25

1. The informed consent form must have been signed/dated prior to performing any study procedures, including screening procedures.
2. The inclusion/exclusion criteria must have been verified at Baseline, prior to assignment of study treatment.
3. Questionnaires were to be administered at those study centers where validated translations were available and where they were approved by the corresponding IEC/IRB. Questionnaires must have been administered prior to any examination.
4. All clinically significant findings were recorded as medical history or AEs, as appropriate.
5. Required for all female subjects of childbearing potential. Urine pregnancy tests were performed unless local regulations required a serum pregnancy test.

Figure 6.1.1-2 Evaluation and Visit Schedule (continued)

6. All blood draws and urine collections should have been performed prior to receiving the IVT or sham injection and prior to injection of fluorescein dye.
7. Week 8 + 1 day only applied to the subset of subjects who were randomly selected to complete it and did so before Amendment 2 of the protocol became effective.
8. Both eyes; all other assessments were study eye only.
9. Included slit-lamp exam, IOP measurement, and fundus exam. Dilation for the fundus exam was at the discretion of the Investigator.
10. Other FA assessments, done outside of the visit schedule, may have been performed at Investigator's discretion based on exam findings, observations, etc.
11. Indocyanine green imaging applied only to subjects screened at study centers in Japan.
12. Fundus autofluorescence was performed at a subset of study centers.
13. Subjects were randomized to one of the following treatments: brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg. Beginning at Week 16, when subjects did not receive an active injection, a sham injection was performed. The injection may have been performed at a later time, as long as it was within 7 days of the scheduled visit and within the visit window.
14. Regardless of whether the subject received an active or sham injection, the study eye was evaluated 0-5 minutes and 30 (± 15) minutes postinjection to ensure that the injection procedure and/or the study treatment did not endanger the health of the eye. This included an evaluation of central retinal artery perfusion via gross assessment of vision and measurement of IOP. Direct visualization to assess the central retinal artery, presence of retinal detachment and presence of new intraocular hemorrhage(s) might have been appropriate at the discretion of the Investigator and/or based on the results of gross assessment of vision and IOP measurement.
15. All exit procedures should have been followed, regardless of when the subject exited the study.
16. Blood draws for antidrug antibodies and systemic brolucizumab were performed if the subject exited at or before Week 88.

6.1.2. Study Results

Table 6.1.2-1 Subject Disposition - Week 48 Analysis - All Enrolled Analysis Set

	Brolucizumab 3 mg n (%)	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
All randomized	360 (100)	361 (100)	361 (100)
Randomized and treated	358 (99.4)	360 (99.7)	360 (99.7)
Completed Week 48	334 (92.8)	333 (92.2)	327 (90.6)
Discontinued the study prior to Week 48	26 (7.2)	28 (7.8)	34 (9.4)
Adverse event	6 (1.7)	7 (1.9)	8 (2.2)
Physician decision	2 (0.6)	1 (0.3)	4 (1.1)
Progressive disease	1 (0.3)	0	0
Protocol deviation	0	0	2 (0.6)
Withdrawal by subject	10 (2.8)	15 (4.2)	11 (3.0)
Death	4 (1.1)	3 (0.8)	6 (1.7)
Lost to follow-up	1 (0.3)	2 (0.6)	3 (0.8)
Other reason	2 (0.6)	0	0
Discontinued the study treatment prior to Week 48	31 (8.6)	37 (10.2)	46 (12.7)
Adverse event	8 (2.2)	11 (3.0)	8 (2.2)
Lack of efficacy	0	0	3 (0.8)
Physician decision	2 (0.6)	1 (0.3)	5 (1.4)
Progressive disease	3 (0.8)	0	7 (1.9)
Protocol deviation	1 (0.3)	1 (0.3)	2 (0.6)
Withdrawal by subject	10 (2.8)	19 (5.3)	11 (3.0)
Death	4 (1.1)	3 (0.8)	6 (1.7)
Lost to follow-up	1 (0.3)	2 (0.6)	3 (0.8)
Other reason	2 (0.6)	0	1 (0.3)

Source: RTH258-C001 CSR, Table 14.1-1.1

All enrolled = Total number of subjects who signed informed consent. Percentages (%) are calculated based on “n” from “All randomized” category. The reason for discontinuation as given by the Investigator in the CRF. Study discontinuations are included in treatment discontinuation category. Completed Week 48 = Subjects have Week 48 visit. Early treatment discontinuation visit is based on subjects’ last attended visit. One subject (b) (6) developed unrelated SAE prior to discontinuation from the study (Reason for study discontinuation: Withdrawal by subject). After study discontinuation, the SAE had a fatal outcome.

Reviewer’s Comment: Over 90% of subjects in all groups completed Week 48. Similar numbers of patients discontinued study treatment prior to Week 48 most frequently due to adverse events. The number of subjects who discontinued the study prior to Week 48 was 8.6%, 10.2% and 12.7% for the brolucizumab 3mg, brolucizumab 6mg and aflibercept treatment groups, respectively. Withdrawal by subject was the most common reason.

Table 6.1.2-2 Subject Disposition - Week 96 Analysis - All Enrolled Analysis Set

	Brolucizumab 3 mg n (%)	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
All randomized	360 (100)	361 (100)	361 (100)
Randomized and treated	358 (99.4)	360 (99.7)	360 (99.7)
Completed Week 96	310 (86.1)	304 (84.2)	297 (82.3)
Discontinued the study prior to Week 96	50 (13.9)	57 (15.8)	64 (17.7)
Adverse event	9 (2.5)	8 (2.2)	12 (3.3)
Lack of efficacy	1 (0.3)	0	1 (0.3)
Physician decision	2 (0.6)	2 (0.6)	8 (2.2)
Progressive disease	1 (0.3)	0	0
Protocol deviation	0	0	2 (0.6)
Withdrawal by subject	26 (7.2)	34 (9.4)	23 (6.4)
Death	9 (2.5)	7 (1.9)	12 (3.3)
Lost to follow-up	1 (0.3)	5 (1.4)	6 (1.7)
Other reason	1 (0.3)	1 (0.3)	0
Discontinued the study treatment prior to Week 96	63 (17.5)	68 (18.8)	80 (22.2)
Adverse event	14 (3.9)	13 (3.6)	14 (3.9)
Lack of efficacy	4 (1.1)	1 (0.3)	4 (1.1)
Physician decision	3 (0.8)	2 (0.6)	10 (2.8)
Progressive disease	4 (1.1)	3 (0.8)	8 (2.2)
Protocol deviation	1 (0.3)	1 (0.3)	2 (0.6)
Withdrawal by subject	25 (6.9)	36 (10.0)	23 (6.4)
Death	9 (2.5)	6 (1.7)	12 (3.3)
Lost to follow-up	1 (0.3)	5 (1.4)	6 (1.7)
Other reason	2 (0.6)	1 (0.3)	1 (0.3)

Source: RTH258-C001 CSR, Table 14.1-1.2_y2

All enrolled = Total number of subjects who signed informed consent. Percentages (%) are calculated based on “n” from “All randomized” category. The reason for discontinuation as given by the Investigator in the CRF. Study discontinuations are included in treatment discontinuation category. Completed Week 96 = Subjects have Week 96 visit. Early treatment discontinuation visit is based on subjects’ last attended visit. One subject (b) (6) developed unrelated SAE prior to discontinuation from the study (Reason for study discontinuation: Withdrawal by subject). After study discontinuation, the SAE had a fatal outcome.

Reviewer’s Comment: *Between 82-86% of subjects completed Week 96, 14-18% discontinued the study and 18-22% discontinued study treatment. The highest number of subjects in both categories were in the aflibercept group. Withdrawal by subject was the most frequent reason given.*

Table 6.1.2-3 Study and Treatment Discontinuations Prior to Week 48 Due to Serious Adverse Events and Death by Treatment Group - All Randomized Analysis Set

Reason for Discontinuation	Age / Sex	Subject Number	Last Study/ Treatment Day (Death Day)
Brolucizumab 3 mg			
AE – Bleeding duodenal ulcer	81 F	(b) (6)	171
AE – Choledocholithiasis	86 F		167
AE – Central retinal artery occlusion	82 M		307
AE – Dementia	82 M		254
AE – Endophthalmitis, retinal detachment	78 M		158
AE – Endophthalmitis	78 F		30
AE – Hyphema	80 M		210
AE – Intraocular inflammation	76 F		125
AE – Keratic precipitates	79 F		248
AE – Retinal artery occlusion	78 M		113
AE – Worsening AMD	69 M		232
AE – Worsening AMD	68 M		316
Death – Cause unknown	84 F		253 (272)
Death – Dementia, failure to thrive, malnourishment	80 F		139 (154)
Death – Drug overdose, suicide	84 M		224 (244)
Death – Recurrent TIAs/ Possible thromboembolic events	91 F		113 (121)
Brolucizumab 6 mg			
AE – Alzheimer’s disease	89 M	(b) (6)	82
AE – Bladder cancer	76 M		316
AE – Central retinal artery occlusion	81 F		47
AE – Cerebrovascular accident	82 F		176
AE – Iritis	78 F		57
AE – Iritis	75 M		28
AE – Macular hole	74 M		248
AE – Panuveitis	62 F		169
AE – Panuveitis	77 M		116
AE – Proliferative diabetic retinopathy	84 F		252
AE – Retinal perivascular sheathing	62 M		197
AE – Uveitis	79 F		246
AE – Uveitis	68 F		120
AE – Vitritis	82 F		119
Death – Cardiac arrest	65 M		220 (270)
Death – Cerebrovascular accident	94 M		141 (192)
Death – Cerebrovascular accident	85 F		200 (230)

Reason for Discontinuation	Age / Sex	Subject Number	Last Study/ Treatment Day (Death Day)
Death – Lung cancer, Stage 4	85 F	(b) (6)	255 (325)
Aflibercept 2 mg			
AE – Brain cancer *	78 F	(b) (6)	141
AE – Dementia	84 M		242
AE – Fall, spinal fracture	88 F		1
AE – Geographic atrophy	86 F		283
AE – Headache, severe	67 F		225
AE – Ischemic stroke	71 F		162
AE – Motor vehicle accident	74 M		309
AE – RPE tear	88 F		106
AE – RPE tear	73 M		83
AE – Stroke	89 F		117
AE – Worsening AMD	81 M		57
AE – Worsening AMD	61 M		145
AE – Worsening AMD	79 F		120
AE – Worsening AMD	71 F		118
AE – Worsening AMD	87 F		106
AE – Worsening AMD	81 M		167
AE – Worsening AMD	73 F		161
AE – Worsening AMD	77 M		145
AE – Worsening AMD	76 F		222
AE – Worsening AMD	73 M		120
AE – Worsening of multiple medical problems	75 F		302
Death – Acute MI, cardiopulmonary decompensation	89 F		85 (99)
Death – Aortic stenosis	93 F		110 (117)
Death – Bowel perforation, Cardiovascular arrest	75 M		225 (250)
Death – H1N1 influenza	78 M		277 (308)
Death – Myocardial infarction	79 M		1 (20)
Death – Pneumonia, COPD exacerbation, respiratory failure	82 F		147 (180)

* Subject discontinued to participate in oncology trial
Source: Study RTH258-C001 CSR, Listing 16.2.1-1.2, -1.4

Reviewer's Comment:

The most frequent adverse events causing study or treatment discontinuation were intraocular inflammatory conditions in the brolucizumab 6mg treatment group and worsening of macular degeneration in the aflibercept treatment group.

Table 6.1.2-4 Protocol Deviations by Deviation Category (RAN) – Week 48 Analysis

	Brolucizumab 3 mg n (%)	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
Total number of subjects with at least one protocol deviation	58 (16.1)	46 (12.7)	52 (14.4)
Inclusion/ exclusion criteria not met	16 (4.4)	12 (3.3)	13 (3.6)
Withdrawal criteria met but subject not withdrawn	0	0	0
Deviation related to active treatment	36 (10.0)	26 (7.2)	30 (8.3)
Prohibited concomitant medication administered	6 (1.7)	7 (1.9)	4 (1.1)
Other	6 (1.7)	4 (1.1)	7 (1.9)

Source: RTH258-C001 CSR, Table 14.1-2.1

A subject with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category. A subject may have protocol deviations in more than one protocol deviation category. Percentages (%) are calculated based on N. Deviations related to active treatment include subjects who were randomized but not treated, received wrong treatment, missed active treatment due to reason other than lack of efficacy or any safety event, received active treatment when schedule was for sham or were reassigned to q8w regimen although no disease activity was identified by the Investigator.

Reviewer's Comment: *Similar percentages of subjects had at least one protocol deviation. The most frequent being deviations related to active treatment which was comprised of subjects who were randomized but not treated, received wrong treatment, missed active treatment due to reason other than lack of efficacy or any safety event, received active treatment when schedule was for sham or were reassigned to q8w regimen although no disease activity was identified by the Investigator.*

Table 6.1.2-5 Protocol Deviations and Analysis Restrictions leading to Exclusion from Analysis Sets (RAN) – Week 48 Analysis

Analysis Population/ Protocol Deviation or Analysis Restriction	Brolucizumab 3 mg N=360 n (%)	Brolucizumab 6 mg N=361 n (%)	Aflibercept 2 mg N=361 n (%)
Excluded from Full Analysis Set (FAS)	2 (0.6)	1 (0.3)	1 (0.3)
Protocol Deviation	2 (0.6)	1 (0.3)	1 (0.3)
Randomized but not treated	2 (0.6)	1 (0.3)	1 (0.3)
Excluded from Safety Analysis Set (SAF)	2 (0.6)	1 (0.3)	1 (0.3)
Protocol Deviation	2 (0.6)	1 (0.3)	1 (0.3)
Randomized but not treated	2 (0.6)	1 (0.3)	1 (0.3)
Excluded from Per Protocol Analysis Set (PPS)	35 (9.7)	33 (9.1)	49 (13.6)
Protocol Deviation	17 (4.7)	12 (3.3)	25 (6.9)
Inclusion/ exclusion not met	5 (1.4)	2 (0.6)	5 (1.4)
Absence of confirmed active nAMD in the study eye	2 (0.6)	1 (0.3)	1 (0.3)
Baseline/ Screening BCVA criterion not met	3 (0.8)	1 (0.3)	4 (1.1)
Deviation related to active treatment	14 (3.9)	10 (2.8)	20 (5.5)

Analysis Population/ Protocol Deviation or Analysis Restriction	Brolucizumab 3 mg N=360 n (%)	Brolucizumab 6 mg N=361 n (%)	Aflibercept 2 mg N=361 n (%)
Randomized but not treated	2 (0.6)	1 (0.3)	1 (0.3)
Wrong study drug administered	0	2 (0.6)	1 (0.3)
Missed active treatment at a single visit during loading for reasons other than lack of efficacy or any safety event	0	1 (0.3)	2 (0.6)
Missed active treatment at a single visit after loading for reasons other than lack of efficacy or any safety event	12 (3.3)	4 (1.1)	17 (4.7)
Assigned to q8w regimen in error	0	2 (0.6)	0
Analysis Restrictions	19 (5.3)	23 (6.4)	31 (8.6)
Early treatment/ study discontinuation	14 (3.9)	20 (5.5)	28 (7.8)
No valid BCVA assessment between Week 36 to 48	2 (0.6)	2 (0.6)	1 (0.3)
Missed active treatment during/ after loading phase	5 (1.4)	4 (1.1)	7 (1.9)

Source: RTH258-C001 CSR, Table 14.1-2.3, Listing 16.2.2-1.2

Analysis restrictions due to lack of efficacy and/or safety will not result in exclusion from the PPS. A subject with multiple occurrences of a protocol deviation or analysis restriction within a given category is counted only once in that category. Percentages (%) are calculated based on N.

Reviewer's Comment: A total of 117 subjects 35 (9.7%) in the brolucizumab 3 mg arm, 33 (9.1%) in the brolucizumab 6 mg arm, and 49 (13.6%) in the aflibercept 2 mg arm were excluded from the PPS. Among those subjects, 54 were excluded due to protocol deviations (inclusion/exclusion criteria not being met or deviations related to active treatment) and 73 were excluded due to analysis restrictions (early study treatment/study discontinuation, not having valid BCVA data between Week 36 and 48, and missing active study treatment after the loading phase); some subjects had both protocol deviations and analysis restrictions.

Table 6.1.2-6 Analysis Sets – Week 48 Analysis

Analysis Population	Screen failure/ Not randomized	Brolucizumab 3 mg n (%)	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)	Overall n (%)
All Enrolled Analysis Set	693	360	361	361	1775
All Randomized Analysis Set (RAN)		360 (100)	361 (100)	361 (100)	1082 (100)
Full Analysis Set (FAS)		358 (99.4)	360 (99.7)	360 (99.7)	1078 (99.6)
Safety Analysis Set (SAF)		358 (99.4)	360 (99.7)	360 (99.7)	1078 (99.6)
Per Protocol Analysis Set (PPS)		325 (90.3)	328 (90.9)	312 (86.4)	965 (89.2)

Source: RTH258-C001 CSR, Table 14.1-2.2

All enrolled = Total number of subjects who signed informed consent. Percentages (%) are based on "n" from All Randomized Analysis Set. Screen failures are those who were screened but failed to meet all inclusion or met at least 1 exclusion criterion. All Enrolled Analysis Set includes subjects who signed an informed consent and were assigned to a subject number.

Table 6.1.2-7 Subject Demographics (FAS) – Week 48 Analysis

	Brolucizumab 3 mg N=358	Brolucizumab 6 mg N=360	Aflibercept 2 mg N=360
Age (years)			
N	358	360	360
Mean (SD)	76.7 (8.28)	76.7 (8.95)	76.2 (8.80)
Min, Median, Max	50, 78, 96	51, 78, 97	51, 77, 96
Mean (SD)	76.7 (8.28)	76.7 (8.95)	76.2 (8.80)
Age group, n(%)			
N	358	360	360
< 50 years	0	0	0
50-64 years	31 (8.7)	35 (9.7)	37 (10.3)
65-74 years	103 (28.8)	103 (28.6)	112 (31.1)
75-84 years	162 (45.3)	155 (43.1)	148 (41.1)
≥ 85 years	62 (17.3)	67 (18.6)	63 (17.5)
Sex, n(%)			
Male	148 (41.3)	155 (43.1)	166 (46.1)
Female	210 (58.7)	205 (56.9)	194 (53.9)
Race, n(%)			
N	358	360	360
White	302 (84.4)	285 (79.2)	287 (79.7)
Black or African American	1 (0.3)	1 (0.3)	1 (0.3)
American Indian	1 (0.3)	1 (0.3)	1 (0.3)
Asian	44 (12.3)	61 (16.9)	53 (14.7)
Native Hawaiian of Other Pacific Islander	0	0	0
Other	9 (2.5)	9 (2.5)	17 (4.7)
Multiple	1 (0.3)	3 (0.8)	1 (0.3)
Ethnicity, n(%)			
N	358	360	360
Hispanic/Latino	32 (8.9)	29 (8.1)	40 (11.1)
Not Hispanic or Latino	323 (90.2)	329 (91.4)	319 (88.6)
Not Reported	1 (0.3)	1 (0.3)	0
Unknown	2 (0.6)	1 (0.3)	1 (0.3)
Japanese ancestry	41 (11.5)	60 (16.7)	53 (14.7)

Source: RTH258-C001 CSR Table 14.1-3.2
Percentages are calculated based on N.

Reviewer's Comment: Overall, the study population had a mean age of 77 years, was majority female (57%), and white (82%) which is consistent with the disease population. Fourteen percent of the patient population was of Japanese ancestry.

Table 6.1.2-8 Baseline Ocular Characteristics (FAS) – Week 48 Analysis

Baseline Characteristic	Brolucizumab 3 mg n (%)	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
Time since diagnosis of nAMD, n(%)			
N	358	360	360
< 1 month	155 (43.3)	159 (44.2)	154 (42.8)
1 – 3 months	183 (51.1)	184 (51.1)	190 (52.8)
> 3 months	20 (5.6)	17 (4.7)	16 (4.4)
Unilateral versus bilateral nAMD, n(%)			
N	358	360	360
Unilateral	269 (75.1)	271 (75.3)	268 (74.4)
Bilateral	89 (24.9)	89 (24.7)	92 (25.6)
BCVA (letters read)			
N	358	360	360
Mean (SD)	61.0 (13.57)	60.8 (13.66)	60.0 (13.92)
Min, Median, Max	23, 65, 85	23, 64, 85	16, 63, 83
BCVA (letters read), n(%)			
N	358	360	360
≤ 55 letters	109 (30.4)	101 (28.1)	116 (32.2)
56-70 letters	138 (38.5)	157 (43.6)	153 (42.5)
≥ 71 letters	111 (31.0)	102 (28.3)	91 (25.3)
CSFT-total (mcm)			
N	358	360	360
Mean (SD)	466.6 (167.4)	463.1 (166.6)	457.9 (146.4)
Min, Median, Max	168, 427, 1392	217, 417, 1204	215, 425, 1082
CSFT-total (mcm), n(%)			
N	358	360	360
< 400 mcm	157 (43.9)	157 (43.6)	146 (40.6)
≥ 400 mcm	201 (56.1)	203 (56.4)	214 (59.4)
Type of CNV, n(%)			
N	358	360	359
Predominantly classic	122 (34.1)	113 (31.4)	116 (32.3)
Minimally classic	32 (8.9)	39 (10.8)	34 (9.5)
Occult	204 (57.0)	208 (57.8)	209 (58.2)
Area of Lesion associated with CNV (mm²), n(%)			
N	358	360	359
Mean (SD)	4.5 (4.70)	4.6 (4.08)	4.4 (3.72)

Baseline Characteristic	Brolucizumab 3 mg n (%)	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
Min, Median, Max	0, 3.2, 28	0, 3.4, 20	0, 3.7, 19
Presence of subretinal fluid, n(%)			
N	358	360	360
Present	244 (68.2)	250 (69.4)	245 (68.1)
Absent	114 (31.8)	110 (30.6)	115 (31.9)
Presence of intraretinal fluid/cyst, n(%)			
N	358	360	360
Present	196 (54.7)	194 (53.9)	194 (53.9)
Absent	162 (45.3)	166 (46.1)	166 (46.1)
Presence of SRF and/or IRF, n(%)			
N	358	360	360
Present	330 (92.2)	334 (92.8)	336 (93.3)
Absent	28 (7.8)	26 (7.2)	24 (6.7)
Presence of sub RPE fluid, n(%)			
N	358	360	360
Present	147 (41.1)	168 (46.7)	158 (43.9)
Absent	211 (58.9)	192 (53.3)	202 (56.1)
Presence of PCV (Japan subjects only), n(%)			
N	40	59	53
Present	20 (50.0)	39 (66.1)	30 (56.6)
Absent	20 (50.0)	20 (33.9)	23 (43.4)

Source: RTH258-C001 CSR, Tables 14.1-3.5, 14.1-4.3, 14.2-33.3, and Table 14.2-34.1.

Percentages (%) are calculated based on N.

Occult is considered present if at least one of the 3 subtypes (Fibrovascular PED, Serous PED and Late Leakage) is present. "Predominantly classic" category includes both "Predominantly classic" and "Pure classic" subcategories.

Reviewer's Comment: *The majority of subjects had unilateral AMD at baseline with approximately 95% diagnosed ≤ 3 months prior to study entry. The mean baseline BCVA was 60.6 letters with 28% of subjects having BCVA ≥ 71 letters. These findings were comparable across all treatment groups.*

Primary Efficacy Results

**Table 6.1.2-9 Change from Baseline in Best Corrected Visual Acuity (Letters Read)
Summary Statistics and ANOVA - Week 48 (FAS – LOCF)**

	Brolucizumab 3 mg N=358	Brolucizumab 6 mg N=360	Aflibercept 2 mg N=360
Mean (SD)	5.9 (13.5)	6.4 (14.4)	7.0 (13.2)
SE	0.71	0.76	0.69
Median	7.0	7.5	8.0
Min, Max	-57, 51	-69, 52	-57, 54
95% CI for mean ¹	(4.5, 7.3)	(4.9, 7.9)	(5.6, 8.3)
Pairwise ANOVA ²			
LS mean estimate (BRO3 vs AFL2)			
LS mean (SE)	6.1 (0.69)		6.8 (0.69)
95% CI for LS mean	(4.8, 7.5)		(5.4, 8.1)
LS mean estimate (BRO6 vs AFL2)			
LS mean (SE)		6.6 (0.71)	6.8 (0.71)
95% CI for LS mean		(5.2, 8.0)	(5.4, 8.2)
LS mean difference (Brolucizumab – Aflibercept)			
Difference (SE)	-0.6 (0.98)	-0.2 (1.00)	
95% CI for treatment difference	(-2.5, 1.3)	(-2.1, 1.8)	
p-value for treatment difference (2-sided)	0.5237	0.8695	
p-value for non-inferiority (4-letter margin) (1-sided)	0.0003	<0.0001	

Source: RTH258-C001 CSR, Table 14.2-1.1

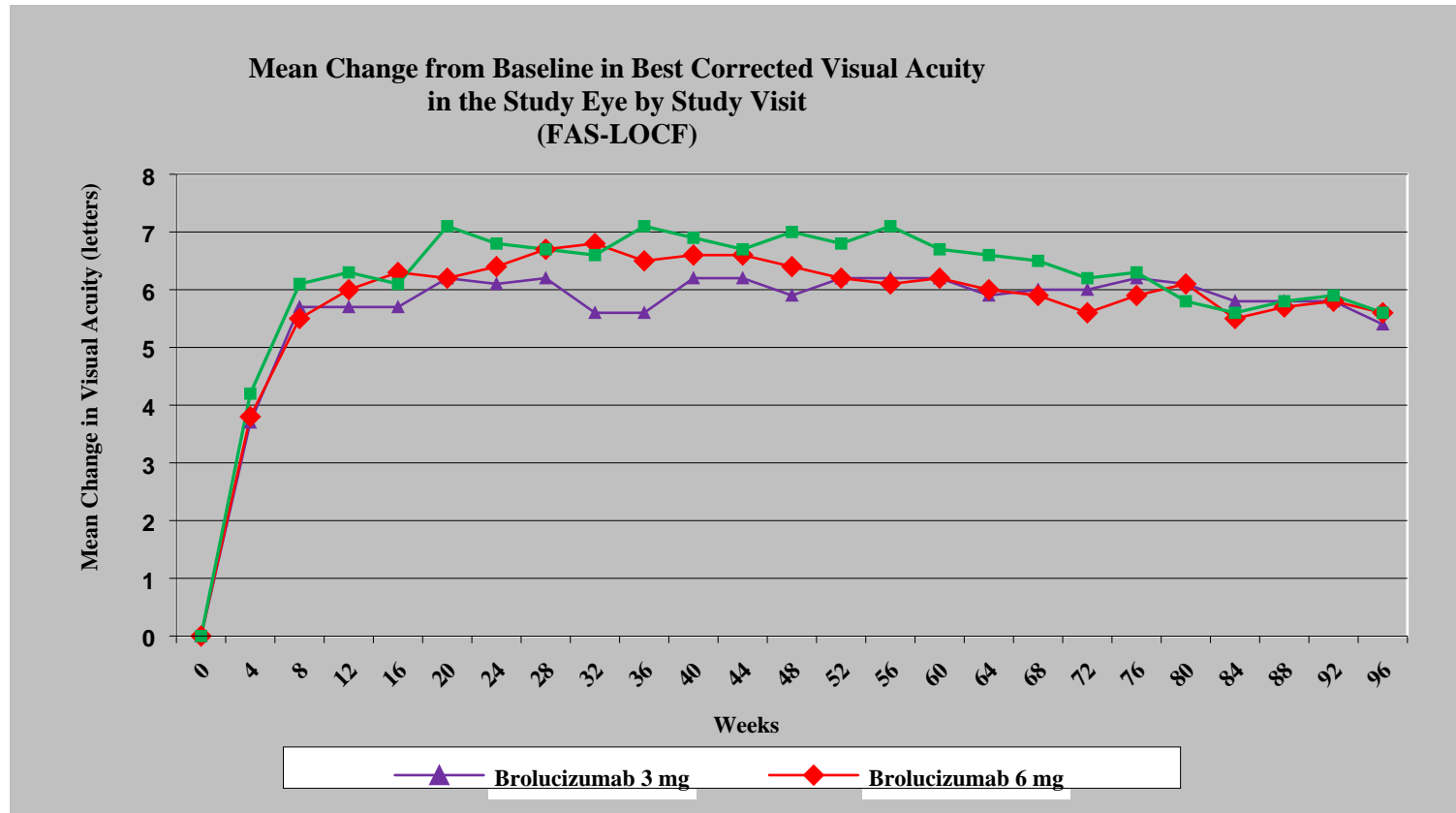
¹ 95% CI for the mean are based on t-distribution.

² Analyzed using ANOVA model with Baseline BCVA categories (≤ 55 , 56-70, ≥ 71 letters), age categories (< 75 , ≥ 75 years) and treatment as fixed effect factors. BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

Reviewer's Comment: *The LS mean difference between the brolucizumab and aflibercept arms was -0.6 letters for brolucizumab 3 mg group with a lower limit of the 95% confidence interval = -2.5 letters, and -0.2 letter for the brolucizumab 6 mg group with a lower limit of the 95% confidence interval = -2.1 letters.*

The lower limits of the 95% confidence intervals for the treatment differences between both brolucizumab arms and the aflibercept arm met the noninferiority margin of 4 letters.

Figure 6.1.2-3



Sensitivity Analysis

Table 6.1.2-10 Change from Baseline in Best Corrected Visual Acuity (Letters Read) Summary Statistics and ANOVA - Week 48 (PPS – LOCF)

	Brolucizumab 3 mg N=325	Brolucizumab 6 mg N=328	Aflibercept 2 mg N=312
Descriptive Statistics			
Mean (SD)	6.3 (13.37)	6.6 (14.68)	7.4 (12.71)
SE	0.74	0.81	0.72
Median	7.0	8.0	8.0
Min, Max	-56, 51	-69, 52	-57, 51
95% CI for mean ¹	(4.9, 7.8)	(5.0, 8.2)	(6.0, 8.8)
Pairwise ANOVA ²			
LS mean estimate (BRO3 vs AFL2)			
LS mean (SE)	6.5 (0.71)		7.2 (0.73)
95% CI for LS mean	(5.1, 7.9)		(5.7, 8.6)
LS mean estimate (BRO6 vs AFL2)			
LS mean (SE)		6.9 (0.74)	7.1 (0.76)
95% CI for LS mean		(5.4, 8.3)	(5.7, 8.6)
LS mean difference (Brolucizumab – Aflibercept)			
Difference (SE)	-0.6 (1.02)	-0.3 (1.06)	
95% CI for treatment difference	(-2.6, 1.4)	(-2.4, 1.8)	
p-value for treatment difference (2-sided)	0.5355	0.7844	
p-value for non-inferiority (4-letter margin) (1-sided)	0.0005	0.0003	

Source: RTH258-C001 CSR, Table 14.2-1.2

¹ 95% CI for the mean are based on t-distribution.

² Analyzed using ANOVA model with Baseline BCVA categories (≤ 55 , 56-70, ≥ 71 letters), age categories (< 75 , ≥ 75 years) and treatment as fixed effect factors. BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

Reviewer's Comment: *The successful noninferiority findings at the 4-letter margin were confirmed in the sensitivity analysis using the PPS – LOCF population.*

Key Secondary Efficacy Results

Table 6.1.2-11 Change from Baseline in Best Corrected Visual Acuity (Letters Read) – Average from Week 36 through Week 48 Summary Statistics and ANOVA - Week 48 (FAS – LOCF)

	Brolucizumab 3 mg N=358	Brolucizumab 6 mg N=370	Aflibercept 2 mg N=369
Descriptive Statistics			
Mean (SD)	6.0 (13.37)	6.5 (13.85)	6.9 (12.61)
SE	0.71	0.73	0.66
LS mean difference (Brolucizumab – Aflibercept)			
Difference (SE)	-0.5 (0.95)	0.0 (0.96)	
95% CI for treatment difference	(-2.4, 1.3)	(-1.9, 1.9)	

Source: RTH258-C002 CSR, Table 14.2-2.1

1 95% CI for the mean are based on t-distribution.

2 Analyzed using ANOVA model with Baseline BCVA categories (≤ 55 , 56-70, ≥ 71 letters), age categories (< 75 , ≥ 75 years) and treatment as fixed effect factors. BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

Reviewer's Comment: *This endpoint confirmed the primary endpoint.*

The estimate of the probability for a subject to be maintained on the q12w regimen up to the DAA at Week 44 was 49% in the brolucizumab 3 mg arm and 56% in the brolucizumab 6 mg arm, based on the applicant's criteria.

Table 6.1.2-12 Time-to-first q8w Treatment Need: Summary for Brolucizumab Subjects by Disease Activity Assessment Visit (FAS – 'Efficacy/Safety' Approach)

Time	No. of subjects with first q8w need at visit	No. of subjects under risk at this visit	No. censored at the visit	Prob. of maintaining on q12w (survival)	95% CI for probability of maintaining on q12w
Brolucizumab 3 mg (N=358)					
0	0	358	5	1.00	1.00, 1.00
16	99	353	9	0.72	0.67, 0.76
20	37	245	12	0.61	0.56, 0.66
32	26	196	8	0.53	0.48, 0.58
44	11	162	151	0.49	0.44, 0.55

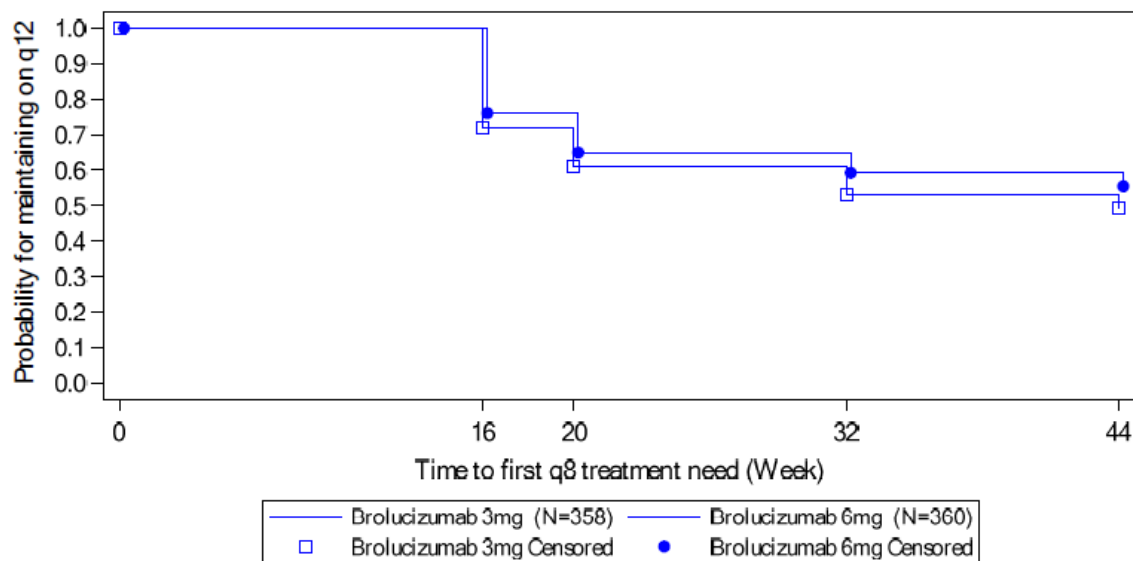
Time	No. of subjects with first q8w need at visit	No. of subjects under risk at this visit	No. censored at the visit	Prob. of maintaining on q12w (survival)	95% CI for probability of maintaining on q12w
Brolucizumab 6 mg (N=360)					
0	0	360	14	1.00	1.00, 1.00
16	83	346	4	0.76	0.71, 0.80
20	37	259	5	0.65	0.60, 0.70
32	19	217	11	0.59	0.54, 0.64
44	12	187	175	0.56	0.50, 0.61

Source: RTH258-C001 CSR, Table 14.2-6.1

Censored: Subjects are considered to be not anymore under risk for a q8w need identification at later visits.

Efficacy/ Safety Approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w need = Yes at the next disease activity assessment visit.

Figure 6.1.2-4 Time to First q8w Treatment Need: Kaplan-Meier Plot for Brolucizumab Subjects (FAS – ‘Efficacy/ Safety’ Approach)



Censored: subjects are considered to be not anymore under risk for a q8w need identification at later visits.

Efficacy/Safety approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w need = Yes at the next DAA visit.

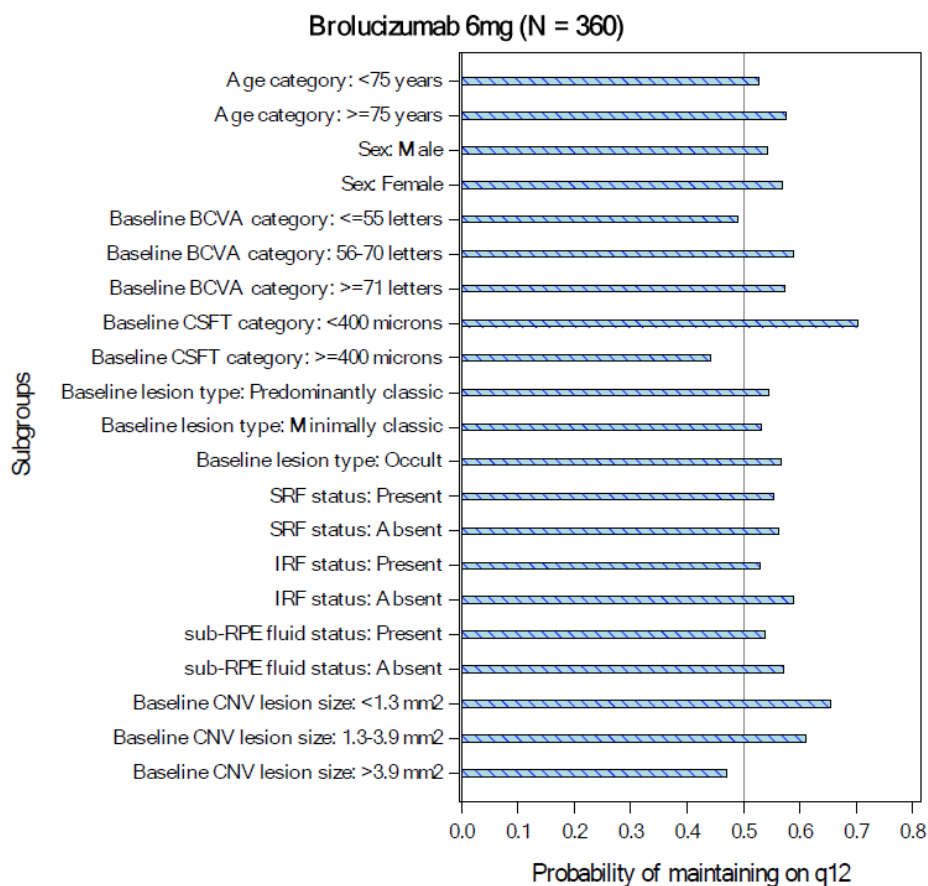
Source: [Table 14.2-6.1](#)

Reviewer’s Comment: *The majority of the subjects who were switched to q8w dosing were identified at Week 16 and Week 20. Approximately 50% of subjects were maintained on the q12 week regimen.*

Q12w Treatment Status: Subgroup Analysis

Subgroup analyses for the proportion of subjects continuing on q12w up to Week 44 revealed subjects with smaller size lesions and less edema at baseline were more likely to be continued on every 12-week dosing.

Figure 6.1.2-12 Time-to-First Q8w Treatment Need for Probability of Maintaining on Q12w at Week 44 for Brolucizumab 6 mg Subjects by Subgroups of Interest – FAS – ‘Efficacy/Safety’ Approach



Censored: subjects are considered to be not anymore under risk for a q8w need identification at later visits. Efficacy/Safety approach: censored data attributable to lack of efficacy and/or safety are imputed with q8w need= Yes at the next DAA visit.
Source: Table 14.2-6.5

6.2. Study RTH258-C002 (HARRIER) – 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

6.2.1. Study Design – Same as Study RTH258-C001 except that only a single dose level of brolucizumab (6 mg) was included and **the study was conducted entirely outside the United States.**

List of Investigators

There were study center(s) in the following countries: Austria (2), Belgium (2), Croatia (3), Czech Republic (4), Denmark (2), Estonia (2), Finland (1), France (16), Germany (15), Greece (3), Hungary (10), Ireland (1), Italy (8), South Korea (6), Latvia (2), Lithuania (2), Netherlands (3), Norway (1), Poland (8), Portugal (4), Russia (2), Singapore (2), Slovakia (8), Spain (15), Switzerland (3), Taiwan (4), Turkey (4), UK (12), and Vietnam (2).

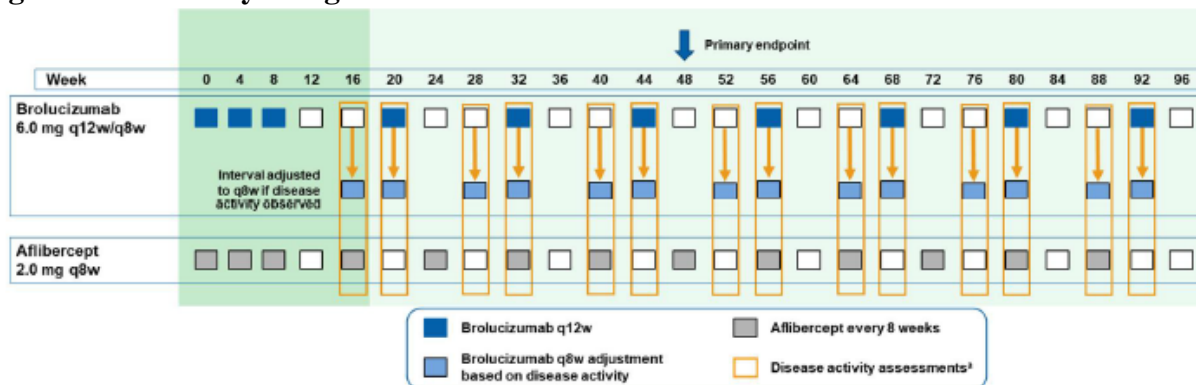
Table 6.2.1-1 Investigator(s) Who Randomized More than 10 Subjects

Alcon Site Number	Novartis Site Number	Principal Investigator Site Address	Number of Subjects Randomized
7412	1140	Jose Juan Escobar-Barranco Dos de Maig 301 Hopital Dos de Maig. Dpto. Oftalmologia Barcelona, NA 08025 Spain	22
6187	1143	Laura Sararols * Pedro I Pons 1, Valles Oftalmologia Recerca-Capio Hospital General de Catalunya-Hospital Sant Cugat Del Valles (BCN), NA 08195 Spain	20
7637	1520	Miroslav Veith Srobarova 50, Fakultni nemocnice Kralovske Vinohrad y- Oftalmologicka klinika Praha 10, NA 100 34 Czech Republic	20
5966	1066	Andreas Papp Tomo u. 25-29 Ssemelweis University_Ophthalmology Department Szemeszeti Klinika Budapest, NA H-1083 Hungary	16
5382	1102	Krystyna Raczynska Ul. Cienista 30 Profesorskie Centrum Okulistyki, Optimum Sp. Z o.o Gdansk, NA 80-809 Poland	15
2881	1060	Andras Berta Nagyerdei krt. 98 Debreceni Egyetem Klinikai Kozpont University Szemklinika Debrecen, NA 4032 Hungary	14
5660	1065	Alexis Tsorbatzoglou Szent Istvan u. 68 SzSzB Megyei Korhazak eEq., Oktatokorhaz – Hospital, Szemeszeti Osztaly Nyiregyhaza, NA H-4400 Hungary	13

Alcon Site Number	Novartis Site Number	Principal Investigator Site Address	Number of Subjects Randomized
6769	1068	Katalin Kiss Zrinyi M. u. 1., Zala Megyei Korhaz Szemeszeti Osztaly Zalaegerszeg, NA H-8900 Hungary	12
7569	1044	Benjamin Wolff 6 Rue de l'eglise Centre Medical et Chirurgical de la Retine Maison Rouge Strasbourg, NA 67000 France	11
7585	1045	Sam Razavi 6 Rue Therese et Ren Planiol CMCT – Ophtalmologie Saint Cyr sur Loire, NA 37540 France	11
7586	1110	Wojciech Omulecki Przedzalniana 66 Str Ksiezy Mlyn Sp.z o.o Okulistyka Lodz, NA 90-388 Poland	11

*Routine site inspection was performed by the Office of Scientific Investigations.

Figure 6.2.1-1 Study Design



Diagnosis and Main Criteria for Inclusion

The study population was planned to consist of approximately 660 subjects with neovascular age-related macular degeneration in the study eye (330 per treatment arm) across 200 study centers. Overall, 743 subjects were randomized (and comprised All Randomized Set [RAN]): 372 into the brolucizumab 6 mg arm, and 371 into the aflibercept 2 mg arm. Of these randomized subjects, 739 received study treatment (and comprised Full Analysis Set [FAS] and Safety Analysis Set [SAF]): 370 in the brolucizumab 6 mg arm and 369 in the aflibercept 2 mg arm.

Inclusion and Exclusion Criteria were the same as those in Study RTH258-C001.

Test and Reference Therapies

Brolucizumab solution for IVT injection was supplied to the Investigators in single use, sterile glass vials. Aflibercept 2 mg active comparator (EYLEA, purchased from the manufacturer), was provided as a commercially available single use glass vial repackaged as study drug supply.

The batch and formulation numbers of brolucizumab and aflibercept treatments are presented in table below:

Table 6.2.1-2

Study drug and strength	Formulation identification	Lot numbers
Brolucizumab solution for IVT injection, 6 mg/50 µL	120852A	15-501537-1, 14-501526-1, 15-501555-1, 17-501646-1, 15-501588-1, 16-501602-1
Aflibercept solution for IVT injection, 2 mg/50 µL	122034	15-600312-1, 15-600319-1, 16-600320-1, 16-600323-1, 17-600325-1, 17-600326-1

Treatment masking, Subject Dosing, Study Treatment Administration, Concomitant and Prohibited Medications were the same as that employed in Study RTH258-C001.

Criteria for Evaluation	-same as Study RTH258-C001
Pharmacokinetics	-same as Study RTH258-C001
Safety Assessments	-same as Study RTH258-C001
Statistical Methods	-same as Study RTH258-C001
Efficacy Endpoints	-same as Study RTH258-C001
Statistical Analysis	-same as Study RTH258-C001

Interim analysis

No interim analysis prior to the primary analysis at Week 48 was planned or conducted for this study.

Protocol amendments

The study protocol was amended 3 times. These amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unmasking.

Compliance with Good Clinical Practices

This study was conducted per the principles of Good Clinical Practices (GCP).

Figure 6.2.1-2 Evaluation and Visit Schedule

Visit	Screening	V1/ Baseline	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Week	Day -14 to -2	Day 0	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit window (days)			± 3	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Informed consent ¹	X													
Demographics and Medical history	X													
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor for AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X ²												
VFQ-25 ³		X						X						X
General Physical Exam ⁴	X													X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ⁵	X													X
Lab Tests: Chemistry/Hematology/ Urinalysis ⁶	X				X									X
Blood Draw for ADA ⁶		X			X			X			X			X
Blood Draw for Systemic Brolucizumab ⁶		X			X			X			X			X
Blood Draw for Genetics ⁶		X												
BCVA ⁷	X ⁸	X ⁸	X	X	X ⁸	X	X	X ⁸	X	X	X ⁸	X	X	X ⁸
Complete Ophthalmic Exam ⁹	X ⁸	X	X	X	X	X	X	X	X	X	X	X	X	X ⁸
SD-OCT	X ⁸	X	X	X	X	X	X	X	X	X	X	X	X	X ⁸
FA ¹⁰	X ⁸				X									X ⁸
CF Photography	X ⁸				X									X ⁸
FAF ¹¹		X ¹¹			X ¹¹									X ¹¹

Figure 6.2.1-2 Evaluation and Visit Schedule (continued)

Visit	Screening	V1/ Baseline	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Week	Day -14 to -2	Day 0	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit window (days)			± 3	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Disease Activity Assessment						X	X		X	X		X	X	
Contact IRT	X	X	X	X		X	X	X	X	X	X	X	X	X
Administer Study Injection or Sham ¹² / Postinjection Assessment ¹³		X	X	X		X	X	X	X	X	X	X	X	X

Visit	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25/ Exit ¹⁴
Week	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
Visit window (days)	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Changes in Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Monitor for AEs	X	X	X	X	X	X	X	X	X	X	X	X
VFQ-25 ³						X						X
General Physical Exam ⁴												X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test ⁵												X
Lab Tests: Chemistry/Hematology/ Urinalysis ⁶												X
Blood Draw for ADA ⁶					X					X		(X) ¹⁵
Blood Draw for Systemic Brolocizumab ⁶					X					X		(X) ¹⁵
BCVA	X	X	X ⁸	X	X	X ⁸	X	X	X ⁸	X	X	X ⁸
Complete Ophthalmic Exam ⁹	X	X	X	X	X	X	X	X	X	X	X	X ⁸
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X ⁸
FA ¹⁰												X ⁸
CF Photography												X ⁸
Fundus Autofluorescence ¹¹												X ¹¹
Disease Activity Assessment	X	X		X	X		X	X		X	X	
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	
Administer Study Injection or Sham ¹² / Postinjection Assessment ¹³	X	X	X	X	X	X	X	X	X	X	X	

Figure 6.2.1-2 Evaluation and Visit Schedule (continued)

Visit	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25/ Exit ¹⁴
Week	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
Complete Exit Form												X

1. The informed consent form must have been signed/dated prior to performing any study procedures, including Screening procedures.
2. The inclusion/exclusion criteria must have been verified at Baseline, prior to assignment of study treatment.
3. Questionnaires were to be administered at those study centers where validated translations were available and where they were approved by the corresponding IEC/IRB. Questionnaires must have been administered prior to any examination.
4. All clinically significant findings were recorded as medical history or AEs, as appropriate.
5. Required for all female subjects of childbearing potential. Urine pregnancy tests were performed unless local regulations required a serum pregnancy test.
6. All blood draws and urine collections should have been performed prior to receiving the IVT or sham injection and prior to injection of fluorescein dye.
7. BCVA must have been performed at the Screening and at the Baseline Visit to qualify the subject.
8. Both eyes; all other assessments were study eye only.
9. Included slit-lamp exam, IOP measurement, and fundus exam. Dilation for the fundus exam was at the discretion of the Investigator.
10. Other FA assessments, done outside of the visit schedule, may have been performed at Investigator's discretion based on exam findings, observations, etc.
11. Fundus autofluorescence was performed at a subset of study centers.
12. Subjects were randomized to one of the following treatments: brolucizumab 6 mg or aflibercept 2 mg. Beginning at Week 16, when subjects did not receive an active injection, a sham injection was performed. The injection may have been performed at a later time, as long as it was within 7 days of the scheduled visit and within the visit window.
13. Regardless of whether the subject received an active or sham injection, the study eye was evaluated 0-5 minutes and 30 (± 15) minutes postinjection to ensure that the injection procedure and/or the study treatment did not endanger the health of the eye. This included an evaluation of central retinal artery perfusion via gross assessment of vision and measurement of IOP. Direct visualization to assess the central retinal artery, presence of retinal detachment and presence of new intraocular hemorrhage(s) might have been appropriate at the discretion of the Investigator and/or based on the results of gross assessment of vision and IOP measurement.
14. All exit procedures should have been followed, regardless of when the subject exited the study.
15. Blood draws for ADA and systemic brolucizumab were performed if the subject exited at or before Visit 23 / Week 88.

6.2.2. Study Results

Table 6.2.2-1 Subject Disposition Week 48 Analysis - All Enrolled Analysis Set

	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
All randomized	372 (100)	371 (100)
Randomized and treated	370 (99.5)	369 (99.5)
Completed Week 48	354 (95.2)	352 (94.9)
Discontinued the study prior to Week 48	18 (4.8)	19 (5.1)
Adverse event	5 (1.3)	1 (0.3)
Lack of Efficacy	0 (0.0)	2 (0.5)
Withdrawal by subject	9 (2.4)	7 (1.9)
Death	3 (0.8)	4 (1.1)
Lost to follow-up	0	4 (1.1)
Other reason	0	1 (0.3)
Discontinued the study treatment prior to Week 48	25 (6.7)	24 (6.5)
Adverse event	12 (3.2)	4 (1.1)
Lack of efficacy	1 (0.3)	2 (0.5)
Physician decision	1 (0.3)	1 (0.3)
Protocol violation	0	1 (0.3)
Withdrawal by subject	7 (1.9)	7 (1.9)
Death	3 (0.8)	4 (1.1)
Lost to follow-up	0	4 (1.1)
Other reason	1 (0.3)	1 (0.3)

Source: RTH258-C002 CSR, Table 14.1-1.1

All enrolled = Total number of subjects who signed informed consent. Percentages (%) are calculated based on "n" from "All randomized" category. The reason for discontinuation as given by the Investigator in the CRF. Study discontinuations are included in treatment discontinuation category. Completed Week 48 = Subjects have Week 48 visit. Early treatment discontinuation visit is based on subjects' last attended visit.

Reviewer's Comment: *Approximately 95% of subjects completed Week 48. Approximately 5% in both treatment groups discontinued study prior to Week 48 and approximately 7% discontinued study treatment prior to Week 48. Withdrawal by subject was the most common reason given for discontinuing the study. The most common reason for discontinuing the study treatment prior to Week 48 was adverse events in the brolucizumab 6 mg group and withdrawal by subject in the aflibercept group.*

Table 6.2.2-2 Subject Disposition Week 96 Analysis - All Enrolled Analysis Set

	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
All randomized	372 (100)	371 (100)
Randomized and treated	370 (99.5)	369 (99.5)
Completed Week 96	342 (91.9)	329 (88.7)
Discontinued the study prior to Week 96	30 (8.1)	42 (11.3)
Adverse event	9 (2.4)	4 (1.1)
Lack of efficacy	0	2 (0.5)
Physician decision	0	1 (0.3)
Withdrawal by subject	12 (3.2)	21 (5.7)
Death	4 (1.1)	7 (1.9)
Lost to follow-up	1 (0.3)	6 (1.6)
Other reason	4 (1.1)	1 (0.3)
Discontinued the study treatment prior to Week 96	43 (11.6)	52 (14.0)
Adverse event	20 (5.4)	9 (2.4)
Lack of efficacy	2 (0.5)	5 (1.3)
Physician decision	1 (0.3)	3 (0.8)
Protocol violation	0	1 (0.3)
Withdrawal by subject	10 (2.7)	20 (5.4)
Death	4 (1.1)	7 (1.9)
Lost to follow-up	1 (0.3)	6 (1.6)
Other reason	5 (1.3)	1 (0.3)

Source: RTH258-C002 CSR, Table 14.1-1.2_y2

All enrolled = Total number of subjects who signed informed consent. Percentages (%) are calculated based on “n” from “All randomized” category. The reason for discontinuation as given by the Investigator in the CRF. Study discontinuations are included in treatment discontinuation category. Completed Week 96 = Subjects have Week 96 visit. Early treatment discontinuation visit is based on subjects’ last attended visit.

Reviewer’s Comment: *Between 89-92% of subjects completed Week 96. Eight to eleven percent of subjects discontinued the study prior to Week 96 and 12-14% discontinued the study treatment prior to Week 96. The most common causes for these discontinuations in the brolucizumab 6 mg group were adverse events and withdrawal by subject.*

Table 6.2.2-3 Study and Treatment Discontinuations Prior to Week 48 Due to Serious Adverse Events and Death by Treatment Group - All Randomized Analysis Set

Reason for Discontinuation	Age / Sex	Subject Number	Last Study/ Treatment Day (Death Day)
Brolucizumab 6 mg			
AE – Anterior uveitis	83 F	(b) (6)	57
AE – Central retinal artery occlusion	79 F		28
AE – Endophthalmitis	75 M		254
AE – Panuveitis	81 F		112
AE – Panuveitis	87 F		140
AE – Panuveitis	74 F		141
AE – Progression to geographic atrophy	80 F		56
AE – Retinal detachment	77 F		225
AE – Retinal fibrosis	86 F		29
AE – Syncope	69 F		--
AE – Stroke	84 M		309
AE – Transient ischemic attack	75 F		113
AE – Retinal artery occlusion	79 F		156
AE – Retinal pigment epithelial tear	70 F		29
AE – Worsening AMD	83 M		60
AE – Worsening cardiovascular disease	77 M		323
AE – Metastatic cancer (unknown origin)	65 M		84
AE – Colon cancer	74 F		113
Death – Pulmonary edema	80 F		220 (283)
Death – Heart attack	80 F		58 (70)
Death – Cardiorespiratory failure	64 F		56 (79)
Aflibercept 2 mg			
AE – Retinal fibrosis	86 F	(b) (6)	315
AE – Syncope	94 F		--
AE – Worsening AMD	75 F		86
AE – Worsening AMD	83 M		225
Death – Cardiac arrest	82 F		302 (337)
Death – Cardiorespiratory failure	84 M		85 (108)
Death – Natural causes (vascular)	84 F		57 (59)
Death – Traumatic chest injury	77 M		113 (139)

Source: Study RTH258-C002 CSR, Listing 16.2.1-1.2, -1.4

Reviewer's Comment:

The most frequent serious adverse event leading to study or treatment discontinuation in the brolucizumab group was intraocular inflammation (uveitis or panuveitis).

Table 6.2.2-4 Protocol Deviations by Deviation Category (RAN) – Week 48 Analysis

	Brolucizumab 6 mg N=372 n (%)	Aflibercept 2 mg N=371 n (%)
Total number of subjects with at least one protocol deviation	43 (11.6)	43 (11.6)
Inclusion/ exclusion criteria not met	22 (5.9)	24 (6.5)
Deviation related to active treatment	17 (4.6)	13 (3.5)
Prohibited concomitant medication administered	3 (0.8)	2 (0.5)
Other	6 (1.6)	7 (1.9)

Source: RTH258-C002 CSR, Table 14.1-2.1

A subject with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category. A subject may have protocol deviations in more than one protocol deviation category. Percentages (%) are calculated based on N.

Deviations related to active treatment include subjects who were randomized but not treated, received wrong treatment, missed active treatment due to reason other than lack of efficacy or any safety event, received active treatment when schedule was for sham or were reassigned to q8w regimen although no disease activity was identified by the Investigator.

Table 6.2.2-5 Protocol Deviations and Analysis Restrictions leading to Exclusion from Analysis Sets (RAN) – Week 48 Analysis

Analysis Population/ Protocol Deviation or Analysis Restriction	Brolucizumab 6 mg N=372 n (%)	Aflibercept 2 mg N=371 n (%)
Excluded from Full Analysis Set (FAS)	2 (0.5)	2 (0.5)
Randomized but not treated	2 (0.5)	2 (0.5)
Excluded from Safety Analysis Set (SAF)	2 (0.5)	2 (0.5)
Randomized but not treated	2 (0.5)	2 (0.5)
Excluded from Per Protocol Analysis Set (PPS)	21 (5.6)	30 (8.1)
Protocol Deviation	8 (2.2)	15 (4.0)
Inclusion/ exclusion not met	4 (1.1)	6 (1.6)
Absence of confirmed active nAMD in the study eye	4 (1.1)	6 (1.6)
Deviation related to active treatment	4 (1.1)	8 (2.2)
Randomized but not treated	2 (0.5)	2 (0.5)
Missed active treatment at a single visit after loading for reasons other than lack of efficacy or any safety event	2 (0.5)	6 (1.6)
Prohibited concomitant medication	0	2 (0.5)
Early treatment/ study discontinuation	20 (5.5)	28 (7.8)
Other	1 (0.3)	0
Subject potentially unmasked	1 (0.3)	0
Analysis Restrictions	15 (4.0)	17 (4.6)
No valid BCVA assessment between Week 36 to 48	0	2 (0.5)
Early study discontinuation	10 (2.7)	11 (3.0)
Early treatment discontinuation	1 (0.3)	1 (0.3)
Missed active treatment during/after loading phase	4 (1.1)	4 (1.1)

Source: RTH258-C002 CSR, Table 14.1-2.3, Listing 16.2.2-1.2

Analysis restrictions due to lack of efficacy and/or safety will not result in exclusion from the PPS. A subject with multiple occurrences of a protocol deviation or analysis restriction within a given category is counted only once in that category. Percentages (%) are calculated based on N.

Table 6.2.2-6 Analysis Sets – Week 48 Analysis

Analysis Population	Screen failure/ Not randomized	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)	Overall n (%)
All Enrolled Analysis Set	305	372	371	1048
All Randomized Analysis Set (RAN)		372 (100)	371 (100)	743 (100)
Full Analysis Set (FAS)		370 (99.5)	369 (99.5)	739 (99.5)
Safety Analysis Set (SAF)		370 (99.5)	369 (99.5)	739 (99.5)
Per Protocol Analysis Set (PPS)		351 (94.4)	341 (91.9)	692 (93.1)

Source: RTH258-C002 CSR, Table 14.1-2.2

All enrolled = Total number of subjects who signed informed consent. Percentages (%) are based on “n” from All Randomized Analysis Set. Screen failures are those who were screened, but failed to meet all inclusion or met at least 1 exclusion criterion. All Enrolled Analysis Set includes subjects who signed an informed consent and were assigned to a subject number.

Table 6.2.2-7 Subject Demographics (FAS) – Week 48 Analysis

	Brolucizumab 6 mg N=370	Aflibercept 2 mg N=369
Age (years)		
N	370	369
Mean (SD)	74.8 (8.58)	75.5 (7.87)
Min, Median, Max	50, 75, 94	52, 76, 95
Age group, n(%)		
N	370	369
< 50 years	0	0
50-64 years	44 (11.9)	28 (7.6)
65-74 years	124 (33.5)	126 (34.1)
75-84 years	150 (40.5)	167 (45.3)
≥ 85 years	52 (14.1)	48 (13.0)
Sex, n(%)		
Male	160 (43.2)	157 (42.5)
Female	210 (56.8)	212 (57.5)
Race, n(%)		
N	370	369
White	340 (91.9)	341 (92.4)
Black or African American	1 (0.3)	0
American Indian	0	0
Asian	22 (5.9)	23 (6.2)
Native Hawaiian of Other Pacific Islander	0	0
Other	5 (1.4)	4 (1.1)

	Brolucizumab 6 mg N=370	Aflibercept 2 mg N=369
Multiple	2 (0.5)	1 (0.3)
Ethnicity, n(%)		
N	370	369
Hispanic/Latino	23 (6.2)	25 (6.8)
Not Hispanic or Latino	321 (86.8)	322 (87.3)
Not Reported	8 (2.2)	5 (1.4)
Unknown	18 (4.9)	17 (4.6)

Source: RTH258-C002 CSR Table 14.1-3.2
Percentages are calculated based on N.

Reviewer's Comment: Overall, the study population had a mean age of 75 years, was majority female (57%) and white (92%). These characteristics are consistent of the disease population.

Table 6.2.2-8 Baseline Ocular Characteristics (FAS) – Week 48 Analysis

Baseline Characteristic	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
Time since diagnosis of nAMD, n(%)		
N	369	369
< 1 month	136 (36.9)	139 (37.7)
1 – 3 months	191 (51.8)	197 (53.4)
> 3 months	42 (11.4)	33 (8.9)
Unilateral versus bilateral nAMD, n(%)		
N	370	369
Unilateral	268 (72.4)	255 (69.1)
Bilateral	102 (27.6)	114 (30.9)
BCVA (letters read)		
N	370	369
Mean (SD)	61.5 (12.59)	60.8 (12.93)
Min, Median, Max	22, 64, 78	23, 64, 79
BCVA (letters read), n(%)		
N	370	369
≤ 55 letters	102 (27.6)	107 (29.0)
56-70 letters	171 (46.2)	170 (46.1)
≥ 71 letters	97 (26.2)	92 (24.9)
CSFT-total (mcm)		
N	370	369
Mean (SD)	473.6 (171.39)	465.3 (151.21)

Baseline Characteristic	Brolucizumab 6 mg n (%)	Aflibercept 2 mg n (%)
Min, Median, Max	200, 433, 1192	206, 442, 1319
CSFT-total (mcm), n(%)		
N	370	369
< 400 mcm	148 (40.0)	130 (35.2)
≥ 400 mcm	222 (60.0)	239 (64.8)
Type of CNV, n(%)		
N	370	365
Predominantly classic	154 (41.6)	144 (39.5)
Minimally classic	33 (8.9)	34 (9.3)
Occult	183 (49.5)	187 (51.2)
Area of Lesion associated with CNV (mm²), n(%)		
N	370	369
Mean (SD)	2.6 (2.76)	2.9 (3.95)
Min, Median, Max	0.022, 1.5, 13.9	0, 1.6, 33.6
Presence of subretinal fluid, n(%)		
N	370	369
Present	251 (67.8)	368 (72.6)
Absent	119 (32.2)	101 (27.4)
Presence of intraretinal fluid/cyst, n(%)		
N	370	369
Present	149 (40.3)	139 (37.7)
Absent	221 (59.7)	230 (62.3)
Presence of SRF and/or IRF, n(%)		
N	370	369
Present	330 (89.2)	332 (90.0)
Absent	40 (10.8)	37 (10.0)
Presence of sub RPE fluid, n(%)		
N	370	369
Present	125 (33.8)	127 (34.4)
Absent	245 (66.2)	242 (65.6)

Source: RTH258-C002 CSR, Table 14.1-4.3, Table 14.2-33.3, and Table 14.2-34.1.

Percentages (%) are calculated based on N.

Occult is considered present if at least one of the 3 subtypes (Fibrovascular PED, Serous PED and Late Leakage) is present. "Predominantly classic" category includes both "Predominantly classic" and "Pure classic" subcategories.

Reviewer's Comment: *The treatment arms were generally well balanced with respect to baseline ocular characteristics for the study eye. The majority of subjects (71%) had unilateral nAMD at baseline with 90% diagnosed within ≤ 3 months prior to study entry. The mean*

baseline BCVA was 61 letters read and was comparable between treatment arms with 26% of the subjects with a BCVA \geq 71 letters.

Primary Efficacy Results

Table 6.2.2-9 Change from Baseline in Best Corrected Visual Acuity (Letters Read) Summary Statistics and ANOVA - Week 48 (FAS – LOCF)

	Brolucizumab 6 mg N=370	Aflibercept 2 mg N=369
Mean (SD)	6.9 (11.47)	7.6 (12.47)
SE	0.60	0.65
Median	8.0	8.0
Min, Max	-57, 38	-37, 50
95% CI for mean ¹	(5.8, 8.1)	(6.3, 8.9)
Pairwise ANOVA ²		
LS mean estimate (SE)	6.9 (0.61)	7.6 (0.61)
95% CI for LS mean	(5.7, 8.1)	(6.4, 8.8)
LS mean difference (Brolucizumab – Aflibercept)		
Difference (SE)	-0.7 (0.86)	
95% CI for treatment difference	(-2.4, 1.0)	
p-value for treatment difference (2-sided)	0.4199	

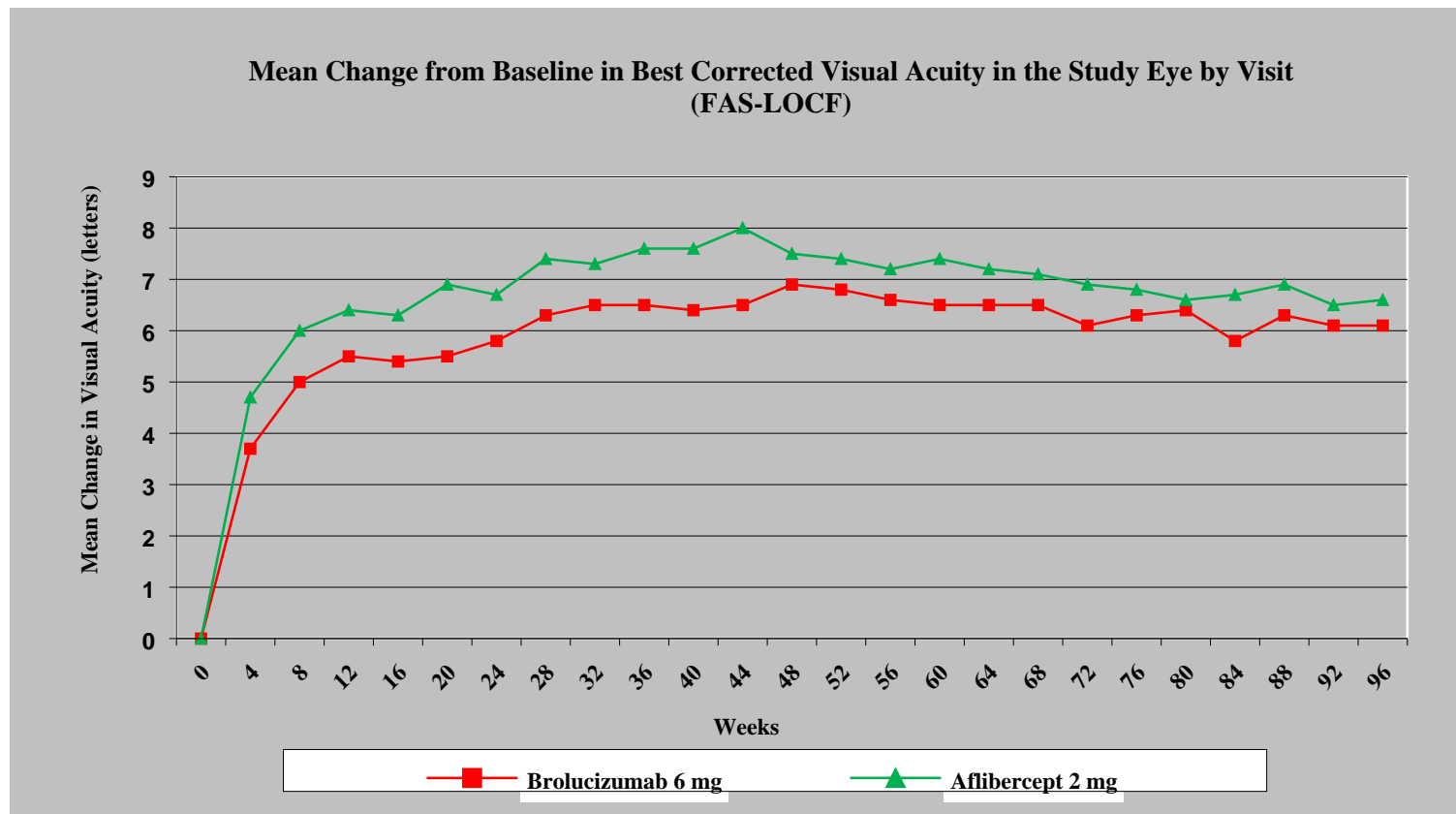
Source: RTH258-C002 CSR, Table 14.2-1.1

¹ 95% CI for the mean are based on t-distribution.

² Analyzed using ANOVA model with Baseline BCVA categories (≤ 55 , 56-70, ≥ 71 letters), age categories (< 75 , ≥ 75 years) and treatment as fixed effect factors. BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

Reviewer's Comment: *The LS mean difference between the brolucizumab 6 mg and aflibercept arms was -0.7 letter with a lower limit of the 95% confidence interval = -2.4.*

Figure 6.2.2-1



Sensitivity Analyses

Table 6.2.2-10 Change from Baseline in Best Corrected Visual Acuity (Letters Read) Summary Statistics and ANOVA - Week 48 (PPS – LOCF)

	Brolucizumab 6 mg N=351	Aflibercept 2 mg N=341
Descriptive Statistics		
Mean (SD)	7.0 (11.24)	7.8 (12.49)
SE	0.60	0.68
Median	8.0	8.0
Min, Max	-57, 38	-35, 50
95% CI for mean ¹	(5.8, 8.2)	(6.5, 9.1)
Pairwise ANOVA ²		
LS mean estimate (BRO6 vs AFL2)		
LS mean (SE)	7.0 (0.62)	7.8 (0.63)
95% CI for LS mean	(5.8, 8.2)	(6.6, 9.0)
LS mean difference (Brolucizumab – Aflibercept)		
Difference (SE)	-0.8 (0.88)	
95% CI for treatment difference	(-2.5, 1.0)	
p-value for treatment difference (2-sided)	0.3771	

Source: RTH258-C002 CSR, Table 14.2-1.2

¹ 95% CI for the mean are based on t-distribution.

² Analyzed using ANOVA model with Baseline BCVA categories (≤ 55 , 56-70, ≥ 71 letters), age categories (< 75 , ≥ 75 years) and treatment as fixed effect factors. BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

Reviewer's Comment: *The successful noninferiority findings using the FAS- LOCF were confirmed in the sensitivity analysis using the PPS – LOCF population.*

Additional sensitivity analyses for the primary endpoint using a MMRM model based on both the FAS and PPS confirmed the primary efficacy analysis using the FAS with LOCF.

Key Secondary Efficacy Results

Table 6.2.2-11 Change from Baseline in Best Corrected Visual Acuity (Letters Read) –Average from Week 36 through Week 48 Summary Statistics and ANOVA - Week 48 (FAS – LOCF)

	Brolucizumab 6 mg N=370	Aflibercept 2 mg N=369
Descriptive Statistics		
Mean (SD)	6.6 (11.10)	7.7 (11.81)
SE	0.58	0.61
Median	7.5	8.3
Min, Max	-58, 37	-38, 47
95% CI for mean ¹	(5.4, 7.7)	(6.6, 8.9)
Pairwise ANOVA ²		
LS mean estimate		
LS mean (SE)	6.5 (0.58)	7.7 (0.58)
95% CI for LS mean	(5.4, 7.7)	(6.6, 9.0)
LS mean difference (Brolucizumab – Aflibercept)		
Difference (SE)	-1.2 (0.82)	
95% CI for treatment difference	(-2.8, 0.5)	
p-value for treatment difference (2-sided)	0.1582	

Source: RTH258-C002 CSR, Table 14.2-2.1

¹ 95% CI for the mean are based on t-distribution.

² Analyzed using ANOVA model with Baseline BCVA categories (≤ 55 , 56-70, ≥ 71 letters), age categories (< 75 , ≥ 75 years) and treatment as fixed effect factors. BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

Reviewer's Comment: *This endpoint was consistent with the primary endpoint.*

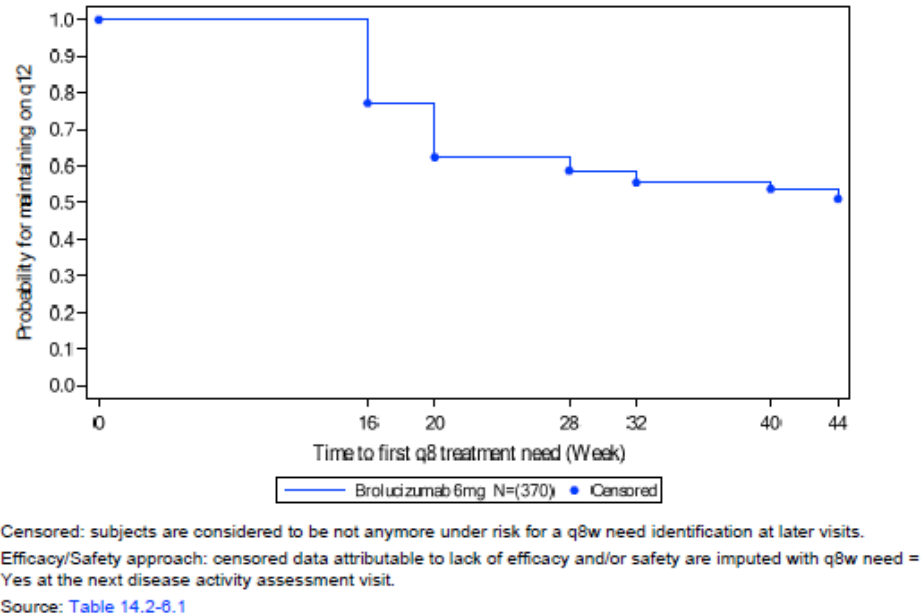
Table 6.2.2-12 Time-to-first q8w Treatment Need for Brolucizumab 6 mg Subjects by Disease Activity Assessment Visit (FAS – ‘Efficacy/Safety’ Approach)

Time	No. of subjects with first q8w need at visit	No. of subjects under risk at this visit	No. censored at the visit	Prob. of maintaining on q12w (survival)	95% CI for probability of maintaining on q12w
0	0	370	6	1.00	1.00, 1.00
16	83	364	9	0.77	0.73, 0.81
20	52	272	1	0.62	0.57, 0.67
28	13	219	6	0.59	0.53, 0.64
32	11	200	1	0.56	0.50, 0.61
40	6	188	4	0.54	0.48, 0.59
44	9	178	169	0.51	0.46, 0.56

Source: RTH258-C002 CSR, Table 14.2-6.1

Censored: Subjects are considered to be not anymore under risk for a q8w need identification at later visits.

Figure 6.2.2-2



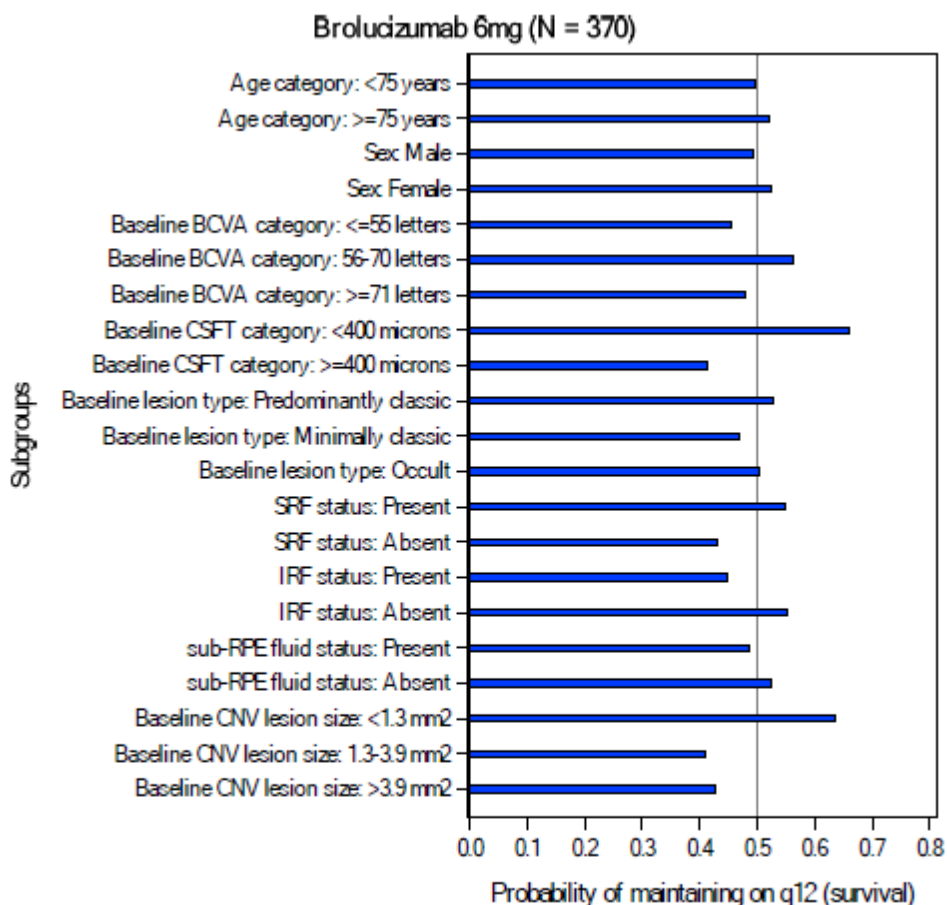
Reviewer's Comment: *The majority of the subjects who were switched to q8w dosing were identified at Week 16 and Week 20. Approximately 51% of subjects were maintained on the q12 week regimen.*

Q12w Treatment Status: Subgroup Analysis

Subgroup analyses for the proportion of subjects maintaining on q12w up to Week 44 revealed subject with smaller size lesions and less edema at baseline were more likely to continue on every 12-week dosing.

Figure 6.2.2-3

Time-to-First Q8w Treatment Need for Probability of Maintaining on Q12w at Week 44 for Brolucizumab 6 mg Subjects by Subgroups of Interest (FAS) - ‘Efficacy/Safety’ Approach



Censored: subjects are considered to be not anymore under risk for a q8 need identification at later visits.

Efficacy/Safety Approach: censored data attributable to lack of efficacy and/or safety are imputed with q8-need = Yes at the next disease activity assessment visit

6.3. Study CRTH258A2301E1 – A 24-week, double-masked, multicenter, two-arm extension study to collect safety and efficacy data on brolucizumab 6 mg drug product intended for commercialization in subjects with neovascular age-related macular degeneration who have completed the CRTH258A2301 study

6.3.1. Study Design

Study Objective: To collect data on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in subjects with nAMD previously treated in CRTH258A2301E1 study to support comparability to the brolucizumab 6 mg drug product used in Phase 3 clinical studies

Background:

To address a request a from the FDA to test the brolucizumab formulation intended for commercialization, subjects in the US who completed Study RTH258-C001 were offered the opportunity to participate in an extension study, CRTH258A2301E1. This extension study included subjects who could be enrolled within 12 weeks of completing Study RTH259-C001.

Related Endpoints:

By convention, all references to visits in the extension study were displayed as exWeekXX and visits in the core study were displayed as coWeekXX. Core Baseline and Extension Baseline were referred as coBL and exBL respectively. The related endpoints were as follows:

- Incidence and characteristics of treatment emergent adverse events
- Loss in Best-Corrected Visual Acuity (BCVA) of 15 letters or more from exBL at each post-exBL visit
- Change in BCVA from Baseline (exBL and coBL) at each post-baseline visit
- Q12w treatment status (1 injection every 12 weeks) at exWeek 24
- Change in central subfield thickness (CSFT) from Baseline (exBL and coBL) at each post-baseline visit
- Anti-drug antibodies (ADA) status at exBL, exWeek 8, exWeek 16 and exWeek 24.

Table 6.3.1-1 Principal Investigators

Alcon Site Number	Principal Investigator Site Address	Number of Subjects
2338	Neil Finnen Midwest Eye Institute Indianapolis, IN 46290	2
2627	Lawrence Singerman Retina Associates of Cleveland Cleveland, OH 44122	3
3943	Blake Cooper Retina Associates PA Shawnee Mission KS	1
3947	David Brown 6560 Fannin, Houston TX 77030	4

Clinical Review BLA 761125
Rhea A. Lloyd, MD
BEOVU (brolucizumab-dblb) injection

Alcon Site Number	Principal Investigator Site Address	Number of Subjects
6221	Ryan Rich * 2770 North Union Blvd., Colorado Springs, CO 80909	8
4046	Pravin Dugel 1101 E. Missouri Avenue, Phoenix, AZ 85014	2
4070	Sunil Gupta Retina Specialty Institute Pensacola, FL	3
4075	Todd Schneiderman Retina Center NW Silverdale, WA	1
5050	Andrew Antoszyk Charlotte Eye, Ear, Nose and Throat Associates Charlotte, NC	2
5101	Nicholas Chinskey New Jersey Retina Toms River, NJ	2
5447	Aleksandra Rachitskaya Cleveland Clinic Cole Eye Institute Cleveland, OH	2
5894	Joel Pearlman Retinal Consultants Medical Group Sacramento, CA	2
6222	Mark Wieland Northern California Retina Vitreous Associates Medical Group, Inc. Mountain View, CA	2
6226	Ashish Sharma National Ophthalmic Research Institute Ft. Myers, FL	1
6766	Nauman Chaudhry Retina Group of New England New London CT 06320	1
6803	Mark Michels Retina-Vitreous Association Incorporated Palm Beach Gardens FL	1
6808	Steven Rose Retina Associates of Western New York Rochester NY	1
6855	David Kenneth Scales Foresight Studies LLC San Antonio TX	2
6996	Jeffrey Moore Maine Eye Center Portland ME 04101	1
6997	Eric Guglielmo 427 South Bernard Spokane, WA 99204	4

Alcon Site Number	Principal Investigator Site Address	Number of Subjects
6999	Samantha Xavier Robert Feldman Florida Eye Clinic Altamonte Springs FL	3
5897	Adam Berger 2815 Lakeland Hills Blvd, Suite 200 Winter Haven, FL 33805	2
6154	H. Logan Brooks Southern Vitreoretinal Associates Tallahassee, FL	1
7020	Maria Berrocal San Juan Health Centre, Dr. Berrocal and Associate San Juan PR	2
7031	Philip Falcone Connecticut Retina Consultants Bridgeport CT 06606	1
7043	Joseph Khawly Retina & Vitreous of Texas Houston TX 77025	2
7051	Brian Joondeph Colorado Retina Associates Golden CO	2
7057	John Choi Chesapeake Retina Centers Waldorf MD	1
7066	David DiLoreto University of Rochester Flaum Eye Institute Rochester NY	2
7068	William Freeman 9415 Campus Point Drive La Jolla, CA 92093-0706	4
7069	Mohammed Hajee Ocean County Retina Toms River NJ 08755	5
7070	G. Robert Hampton Retina Vitreous Surgeons Syracuse NY	1
7071	Gregory Cohen Sierra Eye Associates Reno NV	3
7080	Juan Rubio Retina Associates of South Texas PA San Antonio TX	1
7082	Chander Samy Ocala Research Institute Ocala FL	1
7087	Allen Thach Retina Consultants of Nevada Henderson NV	1

Alcon Site Number	Principal Investigator Site Address	Number of Subjects
7116	Melvin Chen Sarasota Retina Institute Research Foundation Sarasota FL	1
7124	Calvin Mein Retinal Consultants of San Antonio San Antonio TX	2
7132	Jay Prensky Pennsylvania Retina Specialists Camp Hill, PA	3
7134	Michael Rauser Loma Linda University Eye Institute Loma Linda CA	2
7142	Sam Mansour Virginia Retina Center Warrenton VA	1
7146	Carl Danzig Rand Eye Institute Deerfield FL	3
7160	Haroon Chaudhry Eye Care Associates of Cincinnati Inc. DBA Apex Eye Fairfield OH	1
7204	Michael Elman Elman Retina Group Baltimore MD	1
7207	Bryan Schwent Retina Institute of Virginia Richmond VA	2
7287	Hani Salehi-Had Atlantis Eye Care Huntington Beach CA	1
7290	Michael Cassell Sabates Eye Center Research Division Leawood KS	1
7301	Santosh Patel Retina Specialists Plano TX	1
7336	Gawain Dyer San Antonio Eye Center San Antonio TX	2
7342	James Earl Retina Specialists of Idaho PLLC Boise ID	3
7344	Arghavan Almony Carolina Eye Associates PA Southern Pines NC	1
7353	John Carlson Retinal Consultants of Southern CA Redlands CA	1
7354	Grant Janzen Retina Research Institute of Texas Abilene TX	6

Alcon Site Number	Principal Investigator Site Address	Number of Subjects
7355	Cecilia Sanchez Texan Eye Austin TX	1
7358	Soraya Rofagha East Bay Retina Consultants Oakland CA	1
7360	Everton Arrindell Tennessee Retina PC Nashville TN	1
7376	Andres Emanuelli Emanuelli Research & Development Center Arecibo PR00612	9
7426	Patrick Williams Texas Retina Associates Fort Worth TX	5
7493	William Wirostko The Eye Institute: Medical College of Wisconsin Milwaukee WI	3
7515	Evelyn Fu Cascade Eye and Skin Centers University Place WA	1
7631	Ghassan Ghorayeb West Virginia Eye Institute Morgantown WV	2
7693	Peter Win Win Retina Arcadia Ca	2
7704	Sumit Bhatia Gailey Eye Clinic Bloomington IL	3
7733	Sugat Patel Midwest Retina Dublin OH	1
7737	Pamela Weber Island Retina Shirley NY	3
7765	Kamlesh Ramaiya Eye Associates of New Mexico Albuquerque NM 87109	4
7778	Stephen Tate New Vision Eye Center Vero Beach FL	2

* Clinical study site inspection performed by the Office of Scientific Investigations as part of Study RTH258-C001.

Overall Design:

This was a 24-week, double-masked, multicenter, two-arm extension study of RTH258-C001, which only enrolled subjects at US sites. The study was designed to collect data on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in nAMD subjects. Enrollment of subjects who were treated with aflibercept in the core study ensured that

the conduct of both studies remained double-masked in a seamless fashion and until the end of each study.

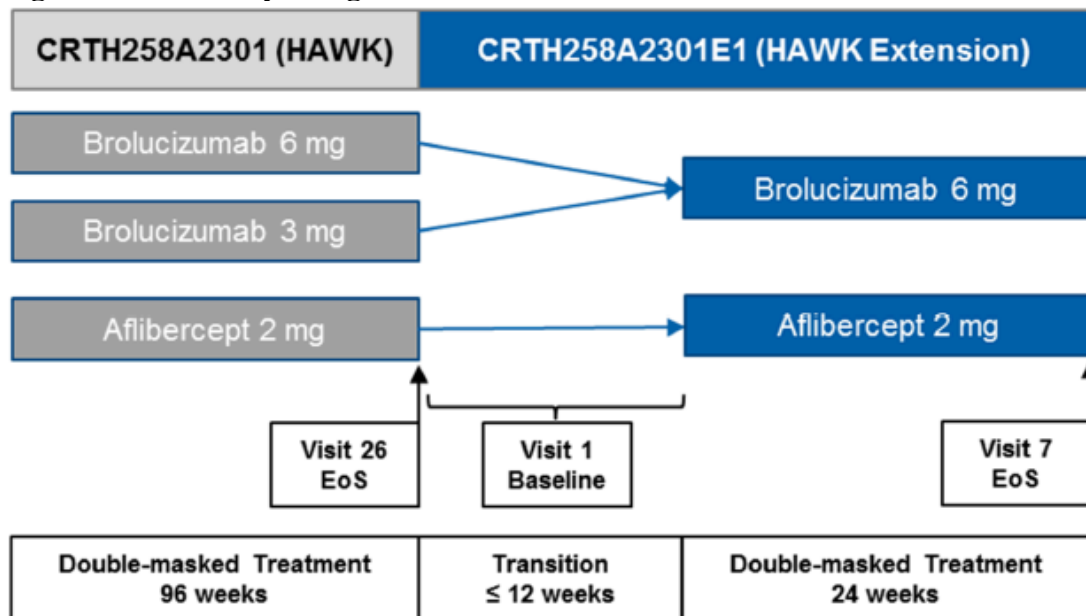
Subjects who had completed the 96-week core study RTH258-C001, regardless of the treatment group (brolucizumab 3 mg, brolucizumab 6 mg or aflibercept 2 mg) were eligible for inclusion in the extension provided Visit 26/Week 96 in the core study was ≤ 12 weeks from Baseline visit in the extension study. Subjects who were treated with aflibercept during the core study continued to receive aflibercept in the extension study in order to maintain masking. Subjects who were treated with brolucizumab 3 mg or 6 mg in the core study received brolucizumab 6 mg [formulation intended for commercialization] in the extension study. At the Baseline visit, subjects signed an informed consent and were evaluated for study eligibility based on inclusion/exclusion criteria.

Baseline visit

If the subject could directly rollover from the core to the extension study, Baseline visit of the extension study could occur on the same day as the Visit 26/Week 96 of the core study. If the subject already completed Visit 26/Week 96 in the core study, Baseline visit of the extension study occurred as soon as possible and no later than 12 weeks after Visit 26/Week 96 of the core study.

Enrolled subjects received three IVT injections of either brolucizumab 6 mg or aflibercept 2 mg according to the dosing schedule. This extension study consisted of 7 study visits at 4-week intervals, labeled Visit 1/ Baseline to Visit 7/ EoS over a period of 24 weeks. The study eye was the same eye that received brolucizumab or aflibercept study treatment in the core study.

Figure 6.3.1-1 Study Design



Diagnosis and Main Criteria for Inclusion

The study population was planned to consist of male and female subjects who completed the core CRTH258A2301 study. Approximately 75 to 100 subjects were expected to be enrolled in approximately 70 centers in the United States.

The main inclusion criteria were:

- The subject had completed the core study, as defined by providing assessments at the Visit 26/ Week 96, within ≤ 12 weeks of Baseline visit of the extension study.

The main exclusion criteria were:

- Subject discontinued the treatment or the core study prematurely at any time.
- Subject received standard of care treatment for nAMD after completion of the core study.
- Any of the following treatments received after completion of the core study: investigational treatment for nAMD in the study eye, intraocular periocular injections of steroids in the study eye, systemic anti-VEGF therapy.
- Stroke or myocardial infarction within the 3 months of Baseline visit of the extension study.

Test and Reference Therapies

Brolucizumab 6 mg drug product intended for commercialization was used in this study. It was supplied to the Investigators in single use, sterile glass vials. Aflibercept was obtained as commercially available, single use glass vials, sourced by Novartis or the study site. The batch and formulation numbers of brolucizumab and aflibercept treatments are presented below.

The batch number for brolucizumab 6 mg was 2020589.

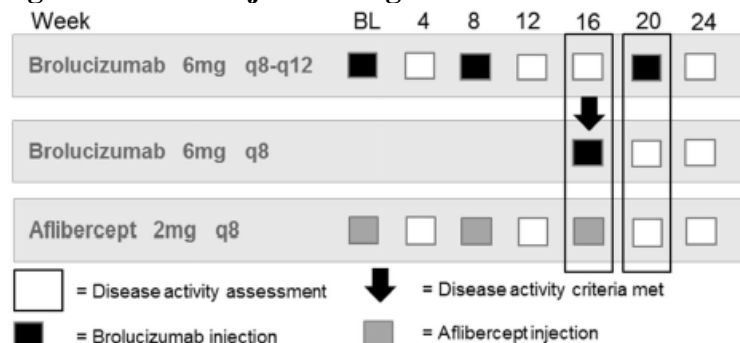
Treatment arms

Depending on the treatment arm assignment in the core study, subjects were assigned at Visit 1/ Baseline to one of the two treatment arms:

- Arm 1: brolucizumab 6 mg – subjects treated with brolucizumab 3 mg or brolucizumab 6 mg in the core study. All subjects received IVT injection at Baseline and exWeek 8 and, depending on disease activity as assessed by the investigator, at exWeek 16 or exWeek 20.
- Arm 2: aflibercept 2 mg – subjects treated with aflibercept 2 mg in the core study. All subjects received IVT injection at Baseline, exWeek 8 and exWeek 16.

Treatment Masking and Study Drug Handling were the same as in Study RTH258-C001.

Figure 6.3.1-2 Subject Dosing



Disease activity assessment

Disease activity was assessed by the masked investigator at Visit 5/ exWeek 16 and Visit 6/ exWeek 20. The investigators applied their own expert judgement when assessing disease activity, i.e., q8w treatment need. Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with exWeek 12 was provided as guidance. Study treatment dose adjustments were not permitted, although adjustments to the treatment regimen were allowed. Specifically, if disease activity was identified by the masked Investigator, the subject was assigned to receive active injections q8w, rather than q12w.

Sham injection

At Visit 5/ exWeek 16 or Visit 6/ exWeek 20, a sham injection was administered to maintain masking. For the sham injection, the tip of an injection syringe (the hub without a needle) was used. Study treatment dose adjustments were not permitted. Rescue treatment was not permitted in the study eye. Treatment with medications approved for nAMD was allowed in the fellow eye at the discretion of the Investigator and in accordance with the administration procedures established at the study center.

Criteria for Evaluation

Efficacy Assessments consisted of BCVA using ETDRS testing charts and spectral domain-optical coherence tomography (SD-OCT).

Pharmacokinetics

Serum samples for the analysis of systemic brolocizumab levels and anti-drug antibodies (immunogenicity) were collected at Baseline (exBL) and at Week 8, Week 16, and Week 24. Neutralizing antibodies (nAb) were assessed in the pre-dose samples from all subjects receiving brolocizumab and in the post-dose samples of brolocizumab subjects with induced or boosted integrated ADA status.

Statistical Methods

Analysis Sets

The Extension Safety Set included all subjects who enter this extension study and receive at least one injection of study treatment in this extension study. The Extension Safety Set was used for

the descriptive analyses and listings related to both efficacy and safety for the brolucizumab treatment arm and for the listings for the aflibercept treatment arm.

Subjects were reported under the treatment group they were randomized to in the core study (brolucizumab 6 mg, brolucizumab 3 mg, aflibercept 2 mg). Note: In the core study, subjects in the safety set were analyzed according to the treatment group from which they received the majority of treatments up to and including Week 44. All subjects received the majority of their treatments according to the randomization during this time period in the core study.

Efficacy

No formal hypothesis testing was planned for this study.

BCVA was summarized for the study eye. The number and percentage of subjects with a loss in BCVA of 15 letters or more from exBL at each post-exBL visit were presented. Descriptive statistics for change from baseline (exBL and coBL) in BCVA to each post-baseline study visit were presented as well. BCVA assessments after start of alternative anti-VEGF treatment in the study eye were censored and imputed by the last value prior to start of this alternative treatment (LOCF).

For CSFT, descriptive statistics for change from baseline (exBL and coBL) to each post-baseline study visit were presented.

The estimate for the proportion of subjects with a positive q12w treatment status at exWeek 24 was derived from Kaplan Meier time-to-event analyses for the event 'first q8w-need'. The outcome of the Kaplan-Meier analysis was presented graphically by the estimated probability for maintaining on q12w over time, i.e., each DAA visit.

Safety

The incidence and characteristics of treatment emergent AEs during the extension study were displayed and compared to the corresponding numbers during the last 6 months of the core study (as a reference) on the same population. The number and percentage of subjects presenting at least one AE starting during the last 6 months of the core study and one new AE (for the same Preferred Term) starting during the extension study were summarized as well.

Compliance with Good Clinical Practices

This study was conducted per the principles of Good Clinical Practices (GCP).

Figure 6.3.1-3 Evaluation and Visit Schedule

Visit number	1/ Baseline ^a	2	3	4	5	6	7/ EoS ^l
Week	Day 1	4	8	12	16	20	24
Visit window (days)		+/- 7	+/- 7	+/- 7	+/- 7	+/- 7	+/- 7
Informed consent ^b	X						
Inclusion/Exclusion Criteria	X						
Demographics	X						
Medical History	X ^c						
Urine Pregnancy Test ^d	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X ⁿ	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Chemistry/ Hematology/ Urinalysis ^{ef}	X						X
Anti-Drug Antibodies (ADA)	X		X		X		X
Systemic brolucizumab exposure	X		X		X		X
BCVA ^h	X	X	X	X	X	X	X
Slit-lamp and Fundus Exam ^f	X ^o	X	X	X	X	X	X ^o
Intraocular Pressure (IOP)	X ^o	X	X	X	X	X	X ^o
Optical Coherence Tomography ^j	X ^o	X	X	X	X	X	X ^o
Color Fundus Photography ^{fi}	X						X
Access IRT	X		X		X	X	
Disease Activity Assessment					X	X	
IVT injection ^m and post-injection assessment ^g	X		X		X ⁱ	X ^k	

^a – Visit 1/ Baseline of CRTH258A2301E1 can occur on the same day as the subject's last visit in RTH258-C001 (Visit 26/ Week 96) but no later than 12 weeks after Visit 26/ Week 96 of RTH258-C001
^b – ICF must have been obtained prior to any study specific procedure
^c – When Baseline visit of the extension study did not occur on the same day as the last visit in the core study, medical conditions which started and/or ended after the last visit in the core and before the baseline visit in the extension study were recorded
^d – Women of childbearing potential only. Urine pregnancy tests were performed unless local regulations require a serum pregnancy test
^e – All blood draws were performed prior to receiving the IVT injection
^f – These assessments were source documentation only and were not to be entered into the CRF
^g – The study eye was evaluated within 5 minutes and approximately 30 minutes post injection to ensure that the injection procedure and/or the investigational product had not endangered the health of the eye
^h – Both eyes at all visits
ⁱ – Local assessments (no central reading center)
^j – Only if subject assigned to q8w
^k – Only if subject assigned to q12w
^l – All procedures should have been followed, regardless of when the subject exited the study
^m – At selected sites, the conduct of IVT injections were observed by an external study team member to ensure compliance with the proposed commercial instruction for use
ⁿ – Adverse Events which were ongoing at the subject's last visit in RTH258-C001 and at the baseline visit in the extension study were to be recorded and entries in the extension study database had to match those in the core study database as appropriate
^o – Both eyes; all other assessments were study eye only

6.3.2. Study Results

Disposition of Subjects

Table 6.3.2-1 Brolucizumab Subject Disposition - (All Enrolled Brolucizumab Subjects)

	Brolucizumab 6 mg – 3mg in Core study n (%)	Brolucizumab 6 mg – 6mg in Core study n (%)
All enrolled	62	45
All enrolled and treated	62	45
Completed exWeek 24	61 (98.4)	45 (100)
Discontinued study prior to exWeek 24	1 (1.6)	0
Death	1 (1.6)	0
Discontinued study treatment prior to exWeek 24	2 (3.2)	0
Death	1 (1.6)	0
Lack of efficacy	1 (1.6)	0

Source: RTH258A2301E1 CSR, Table 14.1-1.1

Percentages (%) are calculated based on “n” from “All enrolled and treated” category. The reason for discontinuation as given by the Investigator in the CRF. Study discontinuations are included in treatment discontinuation category. Completed exWeek 24 = Subject has extension Week 24 visit. Early treatment discontinuation visit is derived based on subjects’ last attended visit.

Reviewer’s Comment: *Ninety-nine percent of subjects completed Week 24 of the Extension study (exWeek24). There were two study discontinuations prior to exWeek 24 due to death and lack of efficacy.*

Table 6.3.2-2 Protocol Deviations and Analysis Restrictions (All Enrolled Subjects)

	Brolucizumab 6 mg – 3mg in Core study n (%)	Brolucizumab 6 mg – 6mg in Core study n (%)
N	62	45
Subjects with at least one PD or AR	8 (12.9)	9 (20.0)
Subjects with at least one PD	5 (8.1)	7 (15.6)
Inclusion/ exclusion not met	0	1 (2.2)
Withdrawal criteria met but subject not withdrawn	0	0
Deviation related to active treatment	5 (8.1)	6 (13.3)
Subject entered the study > 12 weeks after completion of the core study	0	1 (2.2)
Subject did not have disease activity but received active treatment	4 (6.5)	5 (11.1)
Subject missed active treatment for reasons other than lack of efficacy or any safety event	1 (1.6)	1 (2.2)
Prohibited concomitant medication administered	0	0

	Brolucizumab 6 mg – 3mg in Core study n (%)	Brolucizumab 6 mg – 6mg in Core study n (%)
Other	0	0
Subjects with at least one AR	3 (4.8)	2 (4.4)
Early study termination due to reasons other than lack of efficacy/ safety	1 (1.6)	0
Early treatment discontinuation due to lack of efficacy	1 (1.6)	0
Missed active treatment for reasons other than lack of efficacy or related safety event or PD (=TRT05)	2 (3.2)	2 (4.4)

Source: RTH258A2301E1 CSR, Table 14.1-1.4, Table 14.1-1.5

A subject with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category. A subject may have protocol deviations in more than one protocol deviation category. Percentages (%) are calculated based on N. Deviations related to active treatment include subjects who were reassigned to q8w regimen although the Investigator identified no disease activity or subjects who missed active treatment due to reason other than lack of efficacy or any safety event.

Table 6.3.2-3 Subject Demographics (Extension Safety Set)

	Brolucizumab 6 mg – 3mg in Core study n (%)	Brolucizumab 6 mg – 6mg in Core study n (%)
Age at exBL (years)		
N	62	45
Mean (SD)	81.0 (9.14)	80.0 (7.93)
Min, Median, Max	52, 82, 98	57, 81, 96
Age group at exBL, n(%)		
N	62	45
< 50 years	0	0
50-64 years	3 (4.8)	2 (4.4)
65-74 years	13 (21.0)	8 (17.8)
75-84 years	20 (32.3)	22 (48.9)
≥ 85 years	26 (41.9)	13 (28.9)
Age at coBL (years)		
N	62	45
Mean (SD)	79.0 (9.15)	78.1 (7.91)
Min, Median, Max	50, 80, 96	55, 79, 94
Age group at coBL, n(%)		
N	62	45
< 50 years	0	0
50-64 years	3 (4.8)	2 (4.4)
65-74 years	16 (25.8)	10 (22.2)
75-84 years	24 (38.7)	25 (55.6)

	Brolucizumab 6 mg – 3mg in Core study n (%)	Brolucizumab 6 mg – 6mg in Core study n (%)
≥ 85 years	19 (30.6)	8 (17.8)
Sex, n(%)		
Male	17 (27.4)	21 (46.7)
Female	45 (72.6)	24 (53.3)
Race, n(%)		
N	62	45
White	59 (95.2)	44 (97.8)
Black or African American	1 (1.6)	0
American Indian or Alaskan Native	0	0
Asian	1 (1.6)	1 (2.2)
Native Hawaiian or Other Pacific Islander	0	0
Other	1 (1.6)	0
Ethnicity, n(%)		
N	62	45
Hispanic/Latino	7 (11.3)	4 (8.9)
Not Hispanic or Latino	55 (88.7)	40 (88.9)
Not Reported	0	1 (2.2)
Unknown	0	0

Source: RTH258A2301E1 CSR Table 14.1-3.1

N = Number of subjects with an assessment. n = Number of subjects with assessment meeting the criterion for the given categorical variables. Percentages are calculated based on n. coBL = core study baseline; exBL = extension study baseline.

Reviewer's Comment: *Overall, the study population had a mean age of 80 years, was majority female (61%) and white (96%). Across the treatment groups, there were imbalances by gender (brolucizumab 6 mg-3mg in core study were 72% female and the 6 mg – 6mg in core study was 53% female), and by age distribution (i.e., 75-84 years and ≥ 85 years).*

Table 6.3.2-4 Extension Baseline Ocular Characteristics for the Study Eye (Extension Safety Set)

Extension Baseline Characteristic	Brolucizumab 6 mg – 3mg in Core study n (%)	Brolucizumab 6 mg – 6mg in Core study n (%)
BCVA (letters read)		
N	62	45
Mean (SD)	64.7 (17.36)	65.8 (18.82)
Min, Median, Max	25, 68, 93	12, 72, 88
BCVA (letters read), n(%)		
N	62	45
≤ 55 letters	16 (25.8)	11 (24.4)
56-70 letters	18 (29.0)	9 (20.0)
≥ 71 letters	28 (45.2)	25 (55.6)
CSFT-total (mcm)		
N	62	45
Mean (SD)	274.5 (70.41)	296.8 (91.85)
Min, Median, Max	141, 273, 468	120, 273, 558
CSFT-total (mcm), n(%)		
N	62	45
< 400 mcm	56 (90.3)	39 (86.7)
≥ 400 mcm	6 (9.7)	6 (13.3)

Source: RTH258A2301E1 CSR Table 14.1-4.1

N = Number of subjects with an assessment. Percentages are calculated based on n.

Reviewer's Comment: *The mean BCVA at Extension study baseline (exBL) was 65.2 letters read (range: 12-93) compared to 60.7 letters read (range: 25-85) at Core study baseline (coBL) which corresponds to an increase in mean BCVA of 4.5 letters from the coBL.*

Table 6.3.2-5 Other Baseline Characteristics (Extension Safety Set)

Baseline Characteristic	Brolucizumab 6 mg – 3mg in Core study n (%)	Brolucizumab 6 mg – 6mg in Core study n (%)	Brolucizumab 6 mg - Overall n (%)
N	62	45	107
Length of transition period (weeks)			
Mean (SD)	4.8 (4.15)	4.2 (3.98)	4.6 (4.07)
Min, Median, Max	0, 4, 12	0, 5, 13	0, 4, 13
Length of transition period, n(%)			
0 Days	16 (25.8)	17 (37.8)	33 (30.8)
1 Day - ≤ 4 weeks	14 (22.6)	5 (11.1)	19 (17.8)
> 4 Weeks - ≤ 8 Weeks	18 (29.0)	17 (37.8)	35 (32.7)

Baseline Characteristic	Brolucizumab 6 mg – 3mg in Core study n (%)	Brolucizumab 6 mg – 6mg in Core study n (%)	Brolucizumab 6 mg - Overall n (%)
> 8 Weeks - ≤ 12 Weeks	14 (22.6)	5 (11.1)	19 (17.8)
> 12 Weeks	0	1 (2.2)	1 (0.9)
Treatment interval related to the transition period* (weeks)			
Mean (SD)	10.7 (4.66)	10.2 (4.21)	10.5 (4.46)
Min, Median, Max	3, 11, 21	3, 10, 20	3, 11, 21
Treatment interval related to the transition period*, n(%)			
≤ 4 Weeks	4 (6.5)	7 (15.6)	11 (10.3)
> 4 Weeks - ≤ 8 Weeks	20 (32.3)	8 (17.8)	28 (26.2)
> 8 Weeks - ≤ 12 Weeks	14 (22.6)	15 (33.3)	29 (27.1)
> 12 Weeks - ≤ 16 Weeks	18 (29.0)	12 (26.7)	30 (28.0)
> 16 Weeks	6 (9.7)	3 (6.7)	9 (8.4)
Final Treatment status in core study, n(%)			
q8w Interval	40 (64.5)	35 (77.8)	75 (70.1)
q12w Interval	22 (35.5)	10 (22.2)	32 (29.9)
Treatment interval based on final core q12w/q8w status vs treatment interval related to the transition period#, n(%)			
≤ 4 Weeks	43 (69.4)	31 (68.9)	74 (69.2)
> 4 Weeks	19 (30.6)	14 (31.1)	33 (30.8)

Source: RTH258A2301E1 CSR Table 14.1-4.3

n = Number of subjects with assessment meeting the criterion for the given categorical variables.

N = Number of subjects with an assessment. Percentages are calculated based on n.

Transition period: time period between the End of Study visit (EoS) of the core study and the first visit of the extension study.

* Time between last active treatment in the study eye in the core study and baseline (=first active treatment in the study eye in the extension study).

Treatment intervals based on final q12w/q8w status in core study versus treatment interval related to the transition period/

Reviewer's Comment: *The transition period between End of the Core study (coWeek 96 visit) and the Baseline visit for the Extension study (exBL visit) was on average 4.6 weeks long and ranged from 0 to 13 weeks. Most subjects (81.3%) were enrolled in the extension study within 8 weeks from completion of the core study. Approximately one-third of subjects (31%) enrolled in the extension study at the time of the coWeek 96 visit and had no transition period between the core and extension studies.*

Table 6.3.2-6 Best Corrected Visual Acuity (Letters Read): Summary Statistics of Change from exBL to exWeek 24 and coWeek 96 for the Study Eye (Extension Safety Set – LOCF)

		Brolucizumab 6 mg – 3mg in Core study n (%)			Brolucizumab 6 mg – 6mg in Core study n (%)		
Visit	Statistics	exBL	Visit	Change	exBL	Visit	Change
coWeek 96	n	62	62	62	45	45	45
	Mean	64.7	64.6	-0.1	65.8	66.7	0.9
	SD	17.36	18.34	4.84	18.82	18.60	2.74
	SE	2.20	2.33	0.61	2.81	2.77	0.41
	Min	25	18	-24	12	15	-5
	Med	68.0	70.0	0.0	72.0	72.0	0.0
	Max	93	93	12	88	88	7
exWeek 24	n	62	62	62	45	45	45
	Mean	64.7	62.7	-2.0	65.8	66.1	0.3
	SD	17.36	19.82	8.17	18.82	19.05	6.79
	SE	2.20	2.52	1.04	2.81	2.84	1.01
	Min	25	3	-34	12	18	-14
	Med	68.0	68.0	-0.5	72.0	74.0	0.0
	Max	93	94	21	88	93	19

Source: RTH258A2301E1 CSR, Table 14.2-1.1

Change = Visit -exBL

n for 'Change' is the number of subjects with a value for both exBL and the specific visit.

BCVA assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

Reviewer's Comment: *There was no clinically significant change in BCVA between the Core Study Week 96 visit (coWeek 96) and the Extension Study Baseline visit (exBL). There was also no clinically significant change in BCVA between the Extension Study Baseline visit (exBL) and the Extension Study Week 24 (End of Study) visit. Thus, the change in the formulation of brolucizumab 6 mg from Studies RTH258-C001 and RTH258-C002 compared to that in the Extension Study CRTH2582301E1 had no clinically relevant effect on the mean change in BCVA.*

Table 6.3.2-7 Central Subfield Thickness-Total (µm): Summary Statistics of Change from exBL to coWeek 96 and exWeek 24 for the Study Eye (Extension Safety Set – LOCF)

		Brolucizumab 6 mg – 3mg in Core study n (%)			Brolucizumab 6 mg – 6mg in Core study n (%)		
Visit	Statistics	exBL	Visit	Change	exBL	Visit	Change
coWeek 96	n	62	62	62	45	45	45
	Mean	274.5	281.8	7.3	296.8	294.1	-2.6
	SD	70.4	83.1	58.8	91.9	84.4	55.5
	Min	141	172	-127	120	149	-137
	Med	273.0	272.5	2.5	273.0	284.0	-1.0
	Max	468	616	263	558	497	134
exWeek 24	n	62	62	62	45	45	45
	Mean	274.5	254.8	-19.8	296.8	272.2	-24.6
	SD	70.4	63.9	37.7	91.9	71.9	42.1
	Min	141	136	-161	120	135	-138
	Med	273.0	255.0	-9.0	273.0	259.0	-11.0
	Max	468	454	38	558	472	80

Source: RTH258A2301E1 CSR, Table 14.2-4.1

Change = Visit -exBL

n for 'Change' is the number of subjects with a value for both exBL and the specific visit.

CSFT assessments after start of alternative anti-VEGF treatment in the study eye are censored and imputed by the last value prior to start of this alternative treatment.

Reviewer's Comment: *The reduction in Central Subfield Thickness-Total (CSFT_{tot}) observed at the end of the core study (coWeek96) was maintained throughout this extension study. Further slight decreases in CSFT_{tot} were observed at all post exBL visits with mean change in CSFT_{tot} from exBL of -21.8mcm at exWeek 24. No relevant differences between core treatment groups were observed. The time course of CSFT_{tot} changes reflects the treatment pattern, i.e., with CSFT_{tot} reductions seen at exBL and exWeek 8, study visits when all subjects received active injection.*

Thus, the change in the formulation of brolucizumab 6 mg from Studies RTH258-C001 and RTH258-C002 compared to that in the Extension Study CRTH2582301E1 had no clinically relevant effect on Central Subfield Thickness-Total.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The data from three (RTH258-C001, RTH258-C002 and CTRH2582301E1) studies contained in this submission establishes the efficacy of brolucizumab ophthalmic solution, 6 mg/ 0.05 mL administered by intravitreal injection every 28 days x 3 and then every 8-12 weeks for the treatment of age-related macular degeneration.

8. Review of Safety

8.1. Safety Review Approach

The review focuses on the safety database from Studies RTH258-C001 and RTH258-C002 which have:

- A study duration of at least 96 weeks
- A treatment group with brolucizumab 6 mg/ 50mcL, 3xq4w intravitreal injections (monthly loading) during the first 12 weeks followed by q12w/q8w.

Supportive safety data are provided from three phase 2 studies (C-12-006, C-13-001, and RTH258-E003) and a Phase 1 study (C-10-083).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 8.2.1-1 Exposure to Study Drug from Baseline to Week 96

Extent of Exposure	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358	Brolucizumab 6 mg N=730	Aflibercept 2 mg N= 729
Number of injections, n(%)			
N	358	730	729
Mean (SD)	10.5 (2.55)	10.5 (2.59)	11.7 (2.82)
Min- Median-Max	2, 10, 13	1, 10, 13	1, 13, 14
1	0	4 (0.5)	10 (1.4)
2	3 (0.8)	6 (0.8)	6 (0.8)
3	8 (2.2)	20 (2.7)	12 (1.6)
4	6 (1.7)	10 (1.4)	15 (2.1)
5	11 (3.1)	13 (1.8)	10 (1.4)
6	6 (1.7)	13 (1.8)	13 (1.8)

Extent of Exposure	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358	Brolucizumab 6 mg N=730	Aflibercept 2 mg N= 729
7	5 (1.4)	12 (1.6)	11 (1.5)
8	9 (2.5)	12 (1.6)	9 (1.2)
9	12 (3.4)	24 (3.3)	13 (1.8)
10	122 (34.1)	268 (36.7)	13 (1.8)
11	27 (7.5)	54 (7.4)	24 (3.3)
12	42 (11.7)	80 (11.0)	59 (8.1)
13	107 (29.9)	214 (29.3)	533 (73.1)
14	0	0	1 (0.1)

Source: Summary of Clinical Safety, Appendix 1 – Table 1.2-1 RTHP2

n = number of subjects with non-missing assessments

N= number of subjects with non-missing assessment meeting the criterion for the given categorical variable.

Percentages are based on n.

NOTE: A brolucizumab 3 mg treatment group was included in Study RTH258-C001 only.

Reviewer's Comment: *The mean number of intravitreal injections was similar for each treatment group.*

Table 8.2.1-2 Subject Disposition

Disposition	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Treated	358 (100)	730 (100)	729 (100)
Completed study without permanently discontinuing study drug	297 (83.0)	622 (85.2)	600 (82.3)
Discontinued study drug	61 (17.0)	108 (14.8)	129 (17.7)
Withdrawal by subject	24 (6.7)	46 (6.3)	42 (5.8)
Adverse event	14 (3.9)	32 (4.4)	22 (3.0)
Death	9 (2.5)	10 (1.4)	19 (2.6)
Lost to follow-up	1 (0.3)	6 (0.8)	12 (1.6)
Other reason	1 (0.3)	6 (0.8)	12 (1.6)
Lack of efficacy	4 (1.1)	3 (0.4)	9 (1.2)
Progressive disease	4 (1.1)	3 (0.4)	8 (1.1)
Physician decision	3 (0.8)	3 (0.4)	8 (1.1)
Protocol deviation	1 (0.3)	1 (0.1)	3 (0.4)

Source: Summary of Clinical Safety, Appendix 1 – Table 1.2-2 RTHP2

The reason for discontinuation was given by the Investigator in the Ecrf. Reasons are sorted by descending frequency in the pooled brolucizumab 6 mg group, the RTH258-C001 brolucizumab 3 mg group, then the pooled aflibercept 2 mg group.

Completed subjects are those who completed the study without permanently discontinuing study drug.

A brolucizumab 3 mg treatment group was included in study RTH258-C001 only.

Reviewer's Comment: *Eighty-two to eighty-five percent of subjects completed studies RTH258-C001 and RTH258-C002 without permanently discontinuing the study drug. Overall, 16.4% of subjects discontinued study drug with the most common reasons for discontinuation being "withdrawal by subject" (6.2% of subjects overall) and "adverse event" (3.7% of subjects overall).*

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat.

8.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

Adverse events for the 96-week study duration which included brolucizumab 6 mg / 0.05 mL administered intravitreally in three monthly (every 28-day) doses followed by an every 12-week/q 8-week regimen are included. Adverse events were categorized as ophthalmic and systemic.

8.3.3. Routine Clinical Tests

Clinical laboratory parameters were as expected for the subject population under study. No clinically significant differences between treatment groups were observed for any of the analyzed laboratory parameters.

8.4. Safety Results

8.4.1. Deaths

Table 8.4.1-1 Deaths

Country/ Center. Patient Number	Age/ Sex	Cause of Death	Last Injection Day/ Death Day
Study RTH258-C001			
Brolucizumab 3 mg			
(b) (6)	73 F	Lung cancer	537 / 593
	90 M	Influenza Pneumonia	585 / 667
	81 M	Cardiac arrest	398 / 442
	84 F	Unknown	225 / 272
	83 M	Pneumonia / Sepsis	449 / 507
	87 M	Cerebrovascular accident	563 / 591
	91 F	Transient ischemic attack	55 / 121
	80 F	Malnourishment	139 / 154
	84 M	Suicide (opioid, other pain med overdose)	192/ 244
Brolucizumab 6 mg			
(b) (6)	82 M	Non-small cell lung cancer	420 / 473
	74 M	Emphysema worsening	225 / 477
	79 F	Atherosclerotic heart disease	555 / 626
	94 M	Cerebrovascular accident	106 / 192
	77 F	Sepsis	393 / 466
	85 F	Cerebrovascular accident	202 / 230
	85 F	Stage 4 lung cancer	232 / 325
	65 M	Cardiac arrest	220 / 270
Aflibercept 2 mg			
(b) (6)	78 M	H1N1 influenza	277 / 308
	74 F	Unknown cause	452 / 469
	77 M	Unknown cause	511 / 589
	93 M	Aortic stenosis	110 / 117
	89 F	Acute respiratory failure	56 / 99
	86 M	Cardiac arrest	447 / 473
	75 M	Cardiac arrest	225 / 250
	78 F	Metastatic pancreatic cancer	456 / 512
	79 M	Myocardial infarction	1 / 20
	67 F	Malignant neoplasm	397 / 492

(b) (6)	82 F	COPD exacerbation, pneumonia, respiratory failure	113 / 180
	79 F	Cardio-respiratory arrest	620 / 653
Study RTH258-C002			
Brolucizumab 6 mg			
(b) (6)	80 F	Pulmonary edema	220 / 283
	80 F	Myocardial infarction	58 / 70
	64 F	Cardiopulmonary failure	56 / 79
	88 M	Internal hemorrhage	394 / 481
Aflibercept 2 mg			
(b) (6)	77 M	Traumatic chest injury	113 / 139
	84 F	Unknown cause	57 / 59
	84 M	Cardiopulmonary failure	57 / 108
	76 M	Unknown cause	561 / 607
	81 M	Renal failure	616 / 678
	91 F	Unknown cause	499 / 571
	82 F	Pneumonia	280 / 373

Source: Summary of Clinical Safety, Appendix 1 – Table 2.1-2.3 RTHP2

NOTE: A brolucizumab 3 mg treatment group was included in Study RTH258-C001 only.

Reviewer's Comment: *The deaths which occurred during the studies are consistent with the age and past medical history of the subjects enrolled.*

8.4.2. Serious Adverse Events

Table 8.4.2-1 Serious Ocular Adverse Events

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Number of subjects with at least one SAE	6 (1.7)	25 (3.4)	11 (1.5)
Uveitis ^a	1 (0.3)	7 (1.0)	0
Endophthalmitis	3 (0.8)	4 (0.5)	1 (0.1)
Retinal artery occlusion	3 (0.8)	0	1 (0.1)
Uveitis	1 (0.3)	5 (0.7)	0
Visual acuity reduced	0	2 (0.3)	3 (0.4)
Retinal detachment	1 (0.3)	2 (0.3)	2 (0.3)
Retinal artery thrombosis	0	2 (0.3)	0
Retinal pigment epithelial tear	0	2 (0.3)	0
Retinal tear	0	2 (0.3)	1 (0.1)

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Cataract subcapsular	0	0	1 (0.1)
Dry age-related macular degeneration	0	0	1 (0.1)
Macular hole	0	1 (0.1)	1 (0.1)
Anterior chamber inflammation	0	1 (0.1)	0
Blindness	0	1 (0.1)	0
Cataract	0	1 (0.1)	0
Cataract, traumatic	0	1 (0.1)	0
Dacryocystitis	0	1 (0.1)	0
Retinal artery embolism	0	1 (0.1)	0
Retinal depigmentation	0	1 (0.1)	0
Retinopathy proliferative	0	1 (0.1)	0
Vitritis	0	1 (0.1)	0

Source: Summary of Clinical Safety, Appendix 1 – Table 2.1-2.1 RTHP2

a Uveitis = preferred terms; uveitis, anterior chamber inflammation, and vitritis

A subject with multiple occurrences of a SAE for a preferred term is counted only once for that preferred term. Preferred terms are presented by maximum incidence across the RTH258-C001 brolucizumab 3 mg, pooled brolucizumab 6mg and pooled aflibercept 2 mg treatment groups. MedDRA Version 20.1 has been used for reporting.

A brolucizumab 3 mg treatment group was included in study RTH258-C001 only.

Reviewer's Comment: *The serious ocular adverse events reported were generally consistent with the underlying condition and the intravitreal injection procedure.*

More subjects in the pooled brolucizumab 6 mg group experienced serious ocular adverse events. Seven subjects in the pooled brolucizumab 6 mg group experienced intraocular inflammation adverse events (uveitis, anterior chamber inflammation, vitritis) compared with 1 subject in the brolucizumab 3 mg group and no subjects in the aflibercept group.

Table 8.4.2-2 Serious Non-Ocular Adverse Events by Preferred Term Occurring in At Least 2 Subjects in Any Treatment Group

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Number of subjects with at least one SAE	87 (24.3)	153 (21.0)	194 (26.6)
Pneumonia	7 (2.0)	12 (1.6)	17 (2.3)
Coronary artery disease	6 (1.7)	1 (0.1)	3 (0.4)
Atrial fibrillation	4 (1.1)	5 (0.7)	2 (0.3)
Cardiac failure congestive	4 (1.1)	6 (0.8)	5 (0.7)

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Cholelithiasis	4 (1.1)	3 (0.4)	2 (0.3)
Hyponatremia	4 (1.1)	2 (0.3)	1 (0.1)
Urinary tract infection	4 (1.1)	3 (0.4)	3 (0.4)
Chronic obstructive pulmonary disease	1 (0.3)	8 (1.1)	5 (0.7)
Cerebrovascular accident	3 (0.8)	4 (0.5)	7 (1.0)
Influenza	3 (0.8)	0	1 (0.1)
Sepsis	3 (0.8)	5 (0.7)	2 (0.3)
Syncope	3 (0.8)	5 (0.7)	5 (0.7)
Transient ischemic attack	3 (0.8)	2 (0.3)	4 (0.5)
Acute myocardial infarction	2 (0.6)	2 (0.3)	1 (0.1)
Bile duct stone	2 (0.6)	0	1 (0.1)
Chronic kidney disease	2 (0.6)	0	1 (0.1)
Delirium	2 (0.6)	0	0
Dementia	2 (0.6)	1 (0.1)	1 (0.1)
Osteoarthritis	2 (0.6)	2 (0.3)	3 (0.4)
Pubis fracture	2 (0.6)	0	1 (0.1)
Pulmonary embolism	2 (0.6)	1 (0.1)	3 (0.4)
Pyelonephritis	2 (0.6)	0	0
Cardiac failure	1 (0.3)	2 (0.3)	4 (0.5)
Femur fracture	0	4 (0.5)	4 (0.5)
Benign prostatic hyperplasia	0	4 (0.5)	1 (0.1)
Lower limb fracture	0	4 (0.5)	0
Myocardial infarction	1 (0.3)	4 (0.5)	3 (0.4)
Arrhythmia	0	2 (0.3)	3 (0.4)
Bronchitis	1 (0.3)	1 (0.1)	3 (0.4)
Cardiac arrest	1 (0.3)	1 (0.1)	3 (0.4)
Femoral neck fracture	1 (0.3)	1 (0.1)	3 (0.4)
Intestinal obstruction	1 (0.3)	0	3 (0.4)
Non-cardiac chest pain	1 (0.3)	1 (0.1)	3 (0.4)
Subdural hematoma	1 (0.3)	1 (0.1)	3 (0.4)
Nephrolithiasis	1 (0.3)	3 (0.4)	2 (0.3)
Prostate cancer	0	3 (0.4)	1 (0.1)
Pulmonary edema	1 (0.3)	3 (0.4)	2 (0.3)
Respiratory failure	0	3 (0.4)	2 (0.3)
Septic shock	0	3 (0.4)	0

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Cerebral hemorrhage	1 (0.3)	2 (0.3)	0
Cholecystitis, acute	1 (0.3)	2 (0.3)	1 (0.1)
Hip fracture	1 (0.3)	0	2 (0.3)
Neoplasm malignant	1 (0.3)	0	2 (0.3)
Abdominal hernia	0	0	2 (0.3)
Anemia	0	1 (0.1)	2 (0.3)
Angina pectoris	0	2 (0.3)	2 (0.3)
Carotid artery stenosis	0	0	2 (0.3)
Cerebrovascular disorder	0	0	2 (0.3)
Deep vein thrombosis	0	1 (0.1)	2 (0.3)
Diffuse large B-cell lymphoma	0	0	2 (0.3)
Fall	0	2 (0.3)	2 (0.3)
Gastric adenoma	0	0	2 (0.3)
Hematuria	0	0	2 (0.3)
Humerus fracture	0	0	2 (0.3)
Intervertebral disc protrusion	0	0	2 (0.3)
Ischemic stroke	0	2 (0.3)	2 (0.3)
Osteomyelitis	0	0	2 (0.3)
Pyrexia	0	0	2 (0.3)
Rectal hemorrhage	0	2 (0.3)	2 (0.3)
Respiratory tract infection	0	0	2 (0.3)
Rib fracture	0	2 (0.3)	2 (0.3)
Spinal fracture	0	0	2 (0.3)
Acute kidney injury	0	2 (0.3)	0
Atrial flutter	0	2 (0.3)	0
Back pain	0	2 (0.3)	1 (0.1)
Constipation	0	2 (0.3)	0
Gastroenteritis	0	2 (0.3)	0
Inguinal hernia	0	2 (0.3)	1 (0.1)
Invasive ductal breast carcinoma	0	2 (0.3)	0
Joint dislocation	0	2 (0.3)	0
Large intestinal polyp	0	2 (0.3)	1 (0.1)
Metastatic neoplasm	0	2 (0.3)	0
Non-small cell lung cancer	0	2 (0.3)	1 (0.1)
Pancreatitis	0	2 (0.3)	0

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Pneumothorax	0	2 (0.3)	1 (0.1)

Source: Summary of Clinical Safety, Appendix 1 – Table 2.1-2.3

RTHP2

A subject with multiple occurrences of a SAE for a preferred term is counted only once for that preferred term. Preferred terms are presented by maximum incidence across the RTH258-C001 brolucizumab 3 mg, pooled brolucizumab 6mg and pooled aflibercept 2 mg treatment groups. MedDRA Version 20.1 has been used for reporting.

A brolucizumab 3 mg treatment group was included in study RTH258-C001 only.

Reviewer's Comment: *Serious non-ocular adverse events occurred with similar frequency across all treatment groups. The most frequently reported serious non-ocular adverse event was pneumonia which had similar incidence across all treatment groups. Serious non-ocular adverse events reported in ≥ 5 subjects in the pooled brolucizumab group were chronic obstructive pulmonary disease, congestive heart failure, atrial fibrillation, sepsis, and syncope.*

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Less than 2% of subjects in each treatment group experienced at least one non-ocular adverse event that led to permanent discontinuation of study drug. The most frequently reported preferred terms, each reported for 3 subjects overall, were ischemic stroke (2 pooled brolucizumab 6 mg group subjects and 1 subject in the pooled aflibercept 2 mg group) and dementia (1 subject in each treatment group).

Table 8.4.3-1 Ocular Adverse Events in the Study Eye which Led to Permanent Study Drug Discontinuation

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Number of subjects with at least one SAE	11 (3.1)	21 (2.9)	16 (2.2)
Endophthalmitis	3 (0.8)	1 (0.1)	1 (0.1)
Uveitis	1 (0.3)	6 (0.8)	0
Retinal artery occlusion	2 (0.6)	0	0
Visual acuity reduced	0	0	3 (0.4)
Eye inflammation	1 (0.3)	0	0
Glaucoma	1 (0.3)	0	0
Hyphema	1 (0.3)	0	0
Retinal hemorrhage	1 (0.3)	0	1 (0.1)
Subretinal fluid	1 (0.3)	0	0
Visual field defect	1 (0.3)	0	0

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Dry age-related macular degeneration	0	0	2 (0.3)
Retinal pigment epithelial tear	0	1 (0.1)	2 (0.3)
Visual impairment	0	1 (0.1)	2 (0.3)
Iritis	0	2 (0.3)	0
Retinal artery thrombosis	0	2 (0.3)	0
Neovascular age-related macular degeneration	0	0	1 (0.1)
Retinal detachment	0	1 (0.1)	1 (0.1)
Retinal fibrosis	0	0	1 (0.1)
Retinal function test abnormal	0	0	1 (0.1)
Vitritis	0	1 (0.1)	1 (0.1)
Age-related macular degeneration	0	1 (0.1)	0
Anterior chamber inflammation	0	1 (0.1)	0
Blindness	0	1 (0.1)	0
Retinal artery embolism	0	1 (0.1)	0
Retinal perivascular sheathing	0	1 (0.1)	0
Retinal tear	0	1 (0.1)	0
Retinopathy proliferative	0	1 (0.1)	0

Source: Summary of Clinical Safety, Appendix 1 – Table 2.1-1.7 RTHP2

A subject with multiple occurrences of a SAE for a preferred term is counted only once for that preferred term. Preferred terms are presented by maximum incidence across the RTH258-C001 brolucizumab 3 mg, pooled brolucizumab 6mg and pooled aflibercept 2 mg treatment groups. MedDRA Version 20.1 has been used for reporting.

A brolucizumab 3 mg treatment group was included in study RTH258-C001 only.

Reviewer's Comment: *Similar proportions of subjects across treatment groups experienced at least 1 adverse event in the study eye leading to permanent discontinuation of the study drug.*

The most frequently reported ocular adverse events which led to permanent study drug discontinuation which was reported more frequently in the brolucizumab 6 mg group was uveitis.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Table 8.4.4-1 Ocular Adverse Events Occurring in at Least 2% of Study Eyes

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Number of subjects with at least one AE	217 (60.6)	390 (53.4)	372 (51.0)
Conjunctival hemorrhage	39 (10.9)	46 (6.3)	51 (7.0)
Visual acuity reduced	32 (8.9)	53 (7.3)	54 (7.4)
Eye pain	28 (7.8)	30 (4.1)	40 (5.5)
Cataract	18 (5.0)	31 (4.2)	56 (7.7)
Vitreous floaters	26 (7.3)	37 (5.1)	21 (2.9)
Vitreous detachment	24 (6.7)	29 (4.0)	24 (3.3)
Dry eye	20 (5.6)	28 (3.8)	37 (5.1)
Posterior capsule opacification	16 (4.5)	21 (2.9)	16 (2.2)
Vision blurred	16 (4.5)	14 (1.9)	12 (1.6)
Intraocular pressure increased	15 (4.2)	26 (3.6)	30 (4.1)
Visual impairment	15 (4.2)	10 (1.4)	17 (2.3)
Retinal hemorrhage	14 (3.9)	30 (4.1)	23 (3.2)
Blepharitis	8 (2.2)	25 (3.4)	17 (2.3)
Conjunctivitis	3 (0.8)	24 (3.3)	11 (1.5)
Punctate keratitis	11 (3.1)	10 (1.4)	17 (2.3)
Eye irritation	10 (2.8)	13 (1.8)	12 (1.6)
Macular fibrosis	10 (2.8)	8 (1.1)	5 (0.7)
Retinal pigment epithelial tear	5 (1.4)	20 (2.7)	8 (1.1)
Visual field defect	9 (2.5)	8 (1.1)	4 (0.5)
Foreign body sensation	8 (2.2)	5 (0.7)	13 (1.8)
Lenticular opacities	7 (2.0)	13 (1.8)	16 (2.2)
Dry age-related macular degeneration	7 (2.0)	12 (1.6)	7 (1.0)
Lacrimation increased	7 (2.0)	7 (1.0)	8 (1.1)
Pooling of Like Terms			
Decreased visual acuity (includes visual acuity reduced, vision blurred and visual impairment)	63 (17.6%)	77 (10.5%)	83 (11.4%)
Cataract (cataract and lenticular opacities)	25 (7.0%)	44 (6.0%)	72 (9.9%)

Source: Summary of Clinical Safety, Appendix 1 – Table 2.1-1.1RTHP2

A subject with multiple occurrences of a SAE for a preferred term is counted only once for that preferred term. Preferred terms are presented by maximum incidence across the RTH258-C001 brolucizumab 3 mg, pooled brolucizumab 6mg and pooled aflibercept 2 mg treatment groups. MedDRA Version 20.1 has been used for reporting.

A brolucizumab 3 mg treatment group was included in study RTH258-C001 only.

Reviewer's Comment: *The adverse event rates were approximately the same between pooled brolucizumab 6 mg group and pooled aflibercept group.*

Table 8.4.4-2 Non-Ocular Adverse Events Occurring in at Least 2% of Study Eyes

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Number of subjects with at least one AE	300 (83.8)	565 (77.4)	569 (78.1)
Nasopharyngitis	44 (12.3)	80 (11.0)	75 (10.3)
Urinary tract infection	41 (11.5)	42 (5.8)	57 (7.8)
Hypertension	32 (8.9)	53 (7.3)	47 (6.4)
Back pain	25 (7.0)	30 (4.1)	43 (5.9)
Influenza	17 (4.7)	41 (5.6)	47 (6.4)
Bronchitis	12 (3.4)	36 (4.9)	43 (5.9)
Cough	20 (5.6)	24 (3.3)	25 (3.4)
Pneumonia	17 (4.7)	39 (5.3)	32 (4.4)
Arthralgia	19 (5.3)	28 (3.8)	33 (4.5)
Fall	18 (5.0)	13 (1.8)	14 (1.9)
Nausea	17 (4.7)	13 (1.8)	15 (2.1)
Sinusitis	17 (4.7)	12 (1.6)	17 (2.3)
Upper respiratory tract infection	17 (4.7)	24 (3.3)	29 (4.0)
Osteoarthritis	14 (3.9)	28 (3.8)	16 (2.2)
Pain in extremity	14 (3.9)	24 (3.3)	13 (1.8)
Anxiety	13 (3.6)	8 (1.1)	13 (1.8)
Atrial fibrillation	13 (3.6)	13 (1.8)	24 (3.3)
Anemia	12 (3.4)	12 (1.6)	22 (3.0)
Diarrhea	11 (3.1)	24 (3.3)	19 (2.6)
Headache	10 (2.8)	24 (3.3)	21 (2.9)
Constipation	11 (3.1)	18 (2.5)	15 (2.1)
Gastroesophageal reflux disease	11 (3.1)	9 (1.2)	8 (1.1)
Insomnia	11 (3.1)	7 (1.0)	13 (1.8)
Cystitis	9 (2.5)	22 (3.0)	8 (1.1)
Blood urea increased	10 (2.8)	3 (0.4)	11 (1.5)
Blood pressure increased	9 (2.5)	11 (1.5)	20 (2.7)
Contusion	7 (2.)	15 (2.1)	19 (2.6)
Coronary artery disease	9 (2.5)	4 (0.5)	4 (0.5)
Dizziness	9 (2.5)	13 (1.8)	15 (2.1)
Dyspnea	9 (2.5)	6 (0.8)	9 (1.2)

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%)	Brolucizumab 6 mg N=730 n(%)	Aflibercept 2 mg N= 729 n(%)
Laceration	9 (2.5)	5 (0.7)	6 (0.8)
Chronic obstructive pulmonary disease	6 (1.7)	18 (2.5)	16 (2.2)
Hypercholesterolemia	5 (1.4)	17 (2.3)	12 (1.6)
Benign prostatic hyperplasia	8 (2.2)	11 (1.5)	9 (1.2)
Gamma-glutamyltransferase increased	8 (2.2)	12 (1.6)	11 (1.5)
Arthritis	4 (1.1)	16 (2.2)	16 (2.2)
Syncope	6 (1.7)	15 (2.1)	14 (1.9)
Asthenia	7 (2.0)	3 (0.4)	5 (0.7)
Blood uric acid increased	7 (2.0)	4 (0.5)	6 (0.8)
Depression	7 (2.0)	7 (1.0)	11 (1.5)
Hematoma	7 (2.0)	2 (0.3)	5 (0.7)
Vomiting	7 (2.0)	9 (1.2)	9 (1.2)

Source: Summary of Clinical Safety, Appendix 1 – Table 2.1-1.3RTHP2

A subject with multiple occurrences of a SAE for a preferred term is counted only once for that preferred term. Preferred terms are presented by maximum incidence across the RTH258-C001 brolucizumab 3 mg, pooled brolucizumab 6mg and pooled aflibercept 2 mg treatment groups. MedDRA Version 20.1 has been used for reporting.

A brolucizumab 3 mg treatment group was included in study RTH258-C001 only.

Reviewer's Comment: *There were no significant differences between groups in non-ocular adverse events.*

8.4.5. Laboratory Findings

No notable trends or clinically significant changes between treatment groups were observed for any of the analyzed laboratory parameters.

8.4.6. Vital Signs

No clinically relevant changes from Baseline to Week 96 were observed in any pooled treatment group for pre-dose systolic blood pressure, pre-dose diastolic blood pressure and pre-dose pulse rate.

8.4.7. Electrocardiograms (ECGs)

Electrocardiograms were not performed during Studies RTH258-C001, RTH258-C002 or CRTH2582301E1. Electrocardiograms which were performed in a Phase 1 study in healthy volunteers did not demonstrate any significant effect.

8.4.8. QT

QT studies were not performed during the clinical development of brolucizumab.

8.4.9. Immunogenicity

Pre-treatment antibodies have been detected in drug-naïve subjects for a variety of biotechnology-derived therapeutic proteins including single-chain antibodies. The pre-treatment incidence of anti-brolucizumab antibodies was 35-52%. After dosing with brolucizumab for 88 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 23-25% of subjects.

In the absence of a placebo-treatment (sham treatment) arm, aflibercept-treated subjects were assessed for anti-brolucizumab antibodies in an effort to understand the natural variability in ADA status and titers over time. However, the anti-brolucizumab antibody assay was developed and validated to detect anti-brolucizumab antibodies in serum from subjects treated with brolucizumab and was not designed to assay subjects treated with aflibercept. Samples from aflibercept-treated subjects were not tested for presence of nAb in RTH258-C001 and RTH258-C002 studies. Blood samples collected from aflibercept-treated patients in all studies were not screened for anti-aflibercept antibodies.

The existence of pre-existing anti-brolucizumab antibodies, whether neutralizing or not, did not have an impact on the efficacy of brolucizumab. Similarly, there was no clear, or consistent, evidence of an impact of treatment-emergent anti-brolucizumab antibodies on efficacy.

Study RTH258-C001

Table 8.4.9-1 Anti-Drug Antibody (ADA) and Neutralizing Antibody (nAb): Frequency distribution of pre-dose ADA and pre-dose nAb Status (SAF – Observed)

	Brolucizumab 3 mg (N=358) n/M (%)	Brolucizumab 6 mg (N=107) n/M (%)	Aflibercept 2 mg (N=360) n/M (%)
ADA Status			
Negative	217/356 (61.0)	231/357 (64.7)	223/354 (63.0)
Positive	139/356 (39.0)	126/357 (35.3)	131/354 (37.0)
nAb Status			
Negative	314/356 (88.2)	342/357 (95.8)	
Positive	42/356 (11.8)	15/357 (4.2)	

Source: RTH258C001 CSR Table 11-38

n = Number of subjects satisfying the condition. M = Total number of subjects with ADA/nAb data.

ADA Status: Negative: No titer value at pre-dose; Positive = Positive titer value at pre-dose. nAb was only assessed for brolucizumab treated subjects.

Table 8.4.9-2 Anti-Drug Antibody (ADA): Frequency Distribution of Integrated ADA Status (SAF - Observed)

Integrated ADA Status	Brolucizumab 3 mg (N=358) n/M (%)	Brolucizumab 6 mg (N=360) n/M (%)
Up to Week 48		
ADA negative or ADA positive with no boost	265/356 (74.4)	281/353 (79.6)
Induced or Boosted	91/356 (25.6)	72/353 (20.4)
Induced (ADA negative at predose)	66/217 (30.4)	61/231 (26.4)
Boosted (ADA positive at predose)	25/139 (18.0)	11/126 (8.7)

Integrated ADA Status	Brolucizumab 3 mg (N=358) n/M (%)	Brolucizumab 6 mg (N=360) n/M (%)
Missing ADA at Pre-dose	2	3
Missing post-dose ADA while Pre-dose ADA available	0	4
Up to Week 88		
ADA negative or ADA positive with no boost	248/356 (69.7)	266/354 (75.1)
Induced or Boosted	108/356 (30.3)	87/354 (24.6)
Induced (ADA negative at predose)	77/217 (35.5)	71/231 (30.7)
Transient	28/217 (12.9)	36/231 (15.6)
Persistent	49/217 (22.6)	35/231 (15.2)
Boosted (ADA positive at predose)	31/139 (22.3)	16/126 (12.7)
Transient	11/139 (7.9)	6/126 (4.8)
Persistent	20/139 (14.4)	10/126 (7.9)
Missing ADA at Pre-dose	2	3
Missing post-dose ADA while Pre-dose ADA available	0	3

Source: RTH258C001 CSR Table 11-40

N= Number of subjects satisfying the condition.

M = Total number of subjects with a Pre-dose and at least one post-dose ADA data available.

Study RTH258-C002

Table 8.4.9-3 Anti-Drug Antibody (ADA) and Neutralizing Antibody (nAb): Frequency distribution of pre-dose ADA and pre-dose nAb Status (SAF – Observed)

	Brolucizumab 6 mg (N=370) n/M (%)	Aflibercept 2 mg (N=369) n/M (%)
ADA Status		
Negative	169/354 (47.7)	198/358 (55.3)
Positive	185/354 (52.3)	160/358 (44.7)
nAb Status		
Negative	249/354 (70.3)	
Positive	105/354 (29.7)	

Source: RTH258C002 CSR Table 11-38

n = Number of subjects satisfying the condition. M = Total number of subjects with ADA/nAb data.

ADA Status: Negative: No titer value at pre-dose; Positive = Positive titer value at pre-dose. nAb was only assessed for brolucizumab treated subjects.

Table 8.4.9-4 Anti-Drug Antibody (ADA): Frequency Distribution of Integrated ADA Status (SAF - Observed)

Integrated ADA Status	Brolucizumab 6 mg (N=370) n/M (%)
Up to Week 48	

Integrated ADA Status	Brolucizumab 6 mg (N=370) n/M (%)
ADA negative or ADA positive with no boost	285/351 (81.2)
Induced or Boosted	66/351 (18.8)
Induced (ADA negative at predose)	47/169 (27.8)
Boosted (ADA positive at predose)	19/185 (10.3)
Missing ADA at Pre-dose	16
Missing post-dose ADA while Pre-dose ADA available	3
Up to Week 88	
ADA negative or ADA positive with no boost	270/351 (76.9)
Induced or Boosted	81/351 (23.1)
Induced (ADA negative at predose)	57/169 (33.7)
Transient	34/169 (20.1)
Persistent	23/169 (13.6)
Boosted (ADA positive at predose)	24/185 (13.0)
Transient	14/185 (7.6)
Persistent	10/185 (5.4)
Missing ADA at Pre-dose	16
Missing post-dose ADA while Pre-dose ADA available	3

Source: RTH258C002 CSR Table 11-40

N= Number of subjects satisfying the condition.

M = Total number of subjects with a Pre-dose and at least one post-dose ADA data available.

Among subjects with treatment-emergent antibodies, a higher number of intraocular inflammation events were observed. The clinical significance of anti-brolucizumab antibodies on safety is unclear.

To obtain greater clarity on the clinical relevance of the immunogenicity status of subjects in the Phase 3 studies, an Information Request was sent to the Applicant on May 31, 2019. The Applicant submitted a response on June 20, 2019.

Refer to the Clinical Pharmacology review for further details.

Reviewer's Comment: *The BCVA outcomes in the brolucizumab and aflibercept groups were similar regardless of the immunogenicity status (ADA, nAb, transient/persistent ADA, boosted/induced ADA).*

Overall, in brolucizumab-treated patients, ADA status had no consistent impact on the BCVA outcome. Moreover, in all analyses, robust BCVA gains from baseline were observed that are comparable to the results in patients treated with aflibercept.

8.5. Analysis of Submission-Specific Safety Issues

Table 8.5-1 Ocular Adverse Events in the Study Eye of Potential Relevance to Intravitreal Anti-VEGF

Category / Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%) [Eyes]	Brolucizumab 6 mg N=730 n(%) [Eyes]	Aflibercept 2 mg N= 729 n(%) [Eyes]
Number of subjects with at least one AE	59 (16.5) [96]	105 (14.4) [161]	86 (11.8) [110]
Intraocular inflammation	16 (4.5) [25]	32 (4.4) [44]	6 (0.8) [10]
Endophthalmitis	4 (1.1) [4]	5 (0.7) [5]	1 (0.1) [1]
Intraocular pressure increased	18 (5.0) [33]	28 (3.8) [4.1]	33 (4.5) [44]
Hypersensitivity	11 (3.1) [11]	18 (2.5) [22]	19 (2.6) [20]
Retinal pigment epithelial tear	5 (1.4) [6]	20 (2.7) [20]	8 (1.1) [9]
Glaucoma	5 (1.4) [5]	4 (0.5) [4]	9 (1.2) [9]
Arterial thromboembolic events	4 (1.1) [5]	9 (1.2) [9]	3 (0.4) [3]
Retinal arterial occlusive events	04 (1.1) [5]	6 (0.8) [6]	1 (0.1) [1]
Venous thromboembolic events	3 (0.8) [3]	0	0
Vitreous hemorrhage	1 (0.3) [1]	1 (0.1) [1]	3 (0.4) [3]
Hypertension *	1 (0.3) [1]	0	0
Non-ocular hemorrhage **	0	0	2 (0.3) [2]
Traumatic cataract	0	1 (0.1) [1]	0

Source: Module 2.7.4 Summary of Clinical Safety, Table 2-29

AEs with start date on or after the date of first study drug administration are counted. AEs with a start date on or after the start date of treatment with an alternative anti-VEGF are not included.

E= number of events. A subject with multiple occurrences of an AE for a category is counted only once for that category in column n. All events are counted in column E.

Categories are identified using Novartis search definition (RTH258 Case Retrieval Strategy). Categories are presented by maximum incidence across the RTH258-C001 brolucizumab 3 mg, pooled brolucizumab 6 mg and pooled aflibercept 2 mg treatment arms.

MedDRA Version 20.1 has been used for reporting.

A brolucizumab 3 mg treatment group was included in study RTH258-C001 only.

* Preferred term: retinopathy hypertensive

** Preferred term: contusion

Reviewer's Comment: Overall, there was no significant difference in the incidence of ocular adverse events of potential relevance to intravitreal anti-VEGF for the study eye except for intraocular inflammation. Adverse events categorized under intraocular inflammation were reported with a higher incidence in the brolucizumab treatment groups compared to the aflibercept 2 mg group.

Table 8.5-2 Arterial Thromboembolic Events (ATEs)

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%) [E]	Brolucizumab 6 mg N=730 n(%) [E]	Aflibercept 2 mg N= 729 n(%) [E]
Number of subjects with at least one ATE	21 (5.9) [25]	33 (4.5) [34]	34 (4.7) [36]
Retinal artery occlusion	4 (1.1) [5]	3 (0.4) [3]	1 (0.1) [1]
Transient ischemic attack	4 (1.1) [7]	5 (0.7) [5]	5 (0.7) [5]
Cerebrovascular accident	3 (0.8) [3]	4 (0.5) [4]	8 (1.1) [8]
Acute myocardial infarction	2 (0.6) [2]	2 (0.3) [2]	1 (0.1) [1]
Myocardial infarction	2 (0.6) [2]	4 (0.5) [4]	3 (0.4) [3]
Carotid artery occlusion	1 (0.3) [1]	0	3 (0.4) [3]
Retinal artery embolism	1 (0.3) [1]	3 (0.4) [4]	0
Arterial occlusive disease	1 (0.3) [1]	0	0
Cerebral infarction	1 (0.3) [1]	1 (0.1) [1]	0
Hemorrhagic cerebral infarction	1 (0.3) [1]	0	0
Peripheral arterial occlusive disease	1 (0.3) [1]	1 (0.1) [1]	2 (0.3) [2]
Cerebrovascular disorder	0	1 (0.1) [1]	2 (0.3) [2]
Ischemic stroke	0	2 (0.3) [2]	2 (0.3) [2]
Retinal artery thrombosis	0	2 (0.3) [2]	0
Amaurosis fugax	0	1 (0.1) [1]	1 (0.1) [1]
Blindness transient	0	0	1 (0.1) [2]
Cardiac ventricular thrombosis	0	0	1 (0.1) [1]
Cerebrovascular insufficiency	0	0	1 (0.1) [1]
Lacunar infarction	0	0	1 (0.1) [1]
Peripheral artery occlusion	0	0	1 (0.1) [1]
Visual acuity reduced transiently	0	1 (0.1) [1]	1 (0.1) [1]
Amaurosis	0	1 (0.1) [1]	0
Cerebral ischemia	0	1 (0.1) [1]	0
Coronary artery occlusion	0	1 (0.1) [1]	0
Hemiparesis	0	1 (0.1) [1]	0
Number of subjects with ≥ 1 ATE in the study eye	4 (1.1) [5]	9 (1.2) [9]	3 (0.4) [3]
Number of subjects with ≥ 1 non-ocular ATE	16 (4.5) [19]	22 (3.0) [23]	30 (4.1) [31]
Pooling of Like Terms			
Amaurosis *	0	3 (0.4) [3]	3 (0.4) [4]
Myocardial infarction **	4 (1.1) [4]	6 (0.8) [6]	4 (0.5) [4]
Stroke ***	5 (1.4) [5]	9 (1.2) [9]	13 (1.8) [14]

Source: Module 2.7.4 Summary of Clinical Safety, Table 2-33

AEs with start date on or after the date of first study drug administration are counted. AEs with a start date on or after the start date of treatment with an alternative anti-VEGF are not included.

E= number of events. A subject with multiple occurrences of an AE for a category is counted only once for that category in column n. All events are counted in column E.

Preferred terms are presented by maximum incidence across the RTH258-C001 brolucizumab 3 mg, pooled brolucizumab 6 mg and pooled aflibercept 2 mg treatment arms. MedDRA Version 20.1 has been used for reporting.

A brolucizumab 3 mg treatment group was included in study RTH258-C001 only.

* Preferred terms: amaurosis fugax, blindness transient, visual acuity reduced transiently, amaurosis

** Preferred terms: acute myocardial infarction and myocardial infarction

*** Preferred terms: cerebrovascular accident, cerebral infarction, hemorrhagic cerebral infarction, cerebrovascular disorder, ischemic stroke, cerebrovascular insufficiency, cerebral ischemia.

Reviewer's Comment: *Overall, the incidence of arterial thromboembolic events was similar across the treatment groups.*

Table 8.5-3 Intraocular Inflammation Adverse Events in the Study Eye by Preferred Term

Preferred term	RTH258-C001	Pooled	
	Brolucizumab 3 mg N=358 n(%) [E]	Brolucizumab 6 mg N=730 n(%) [E]	Aflibercept 2 mg N= 729 n(%) [E]
Number of subjects with at least one intraocular inflammation AE	16 (4.5) [25]	32 (4.4) [44]	6 (0.8) [10]
Uveitis	5 (1.4) [7]	11 (1.5) [11]	1 (0.1) [1]
Iritis	3 (0.8) [3]	9 (1.2) [14]	2 (0.3) [4]
Vitritis	3 (0.8) [3]	3 (0.4) [4]	3 (0.4) [3]
Anterior chamber inflammation	2 (0.6) [2]	3 (0.4) [3]	0
Eye inflammation	2 (0.6) [2]	1 (0.1) [1]	0
Iridocyclitis	2 (0.6) [3]	3 (0.4) [3]	1 (0.1) [1]
Keratic precipitates	2 (0.6) [3]	0	0
Anterior chamber cell	0	3 (0.4) [3]	0
Chorioretinitis	1 (0.3) [1]	2 (0.3) [2]	0
Retinal vasculitis	1 (0.3) [1]	0	0
Anterior chamber flare	0	2 (0.3) [3]	0
Vitreous haze	0	0	1 (0.1) [1]

Source: Module 2.7.4 Summary of Clinical Safety, Table 2-34

AEs with start date on or after the date of first study drug administration are counted. AEs with a start date on or after the start date of treatment with an alternative anti-VEGF are not included.

E= number of events. A subject with multiple occurrences of an AE for a category is counted only once for that category in column n. All events are counted in column E.

AEs are identified using the RTH258 Case Retrieval Strategy. Preferred terms are presented by maximum incidence across the RTH258-C001 brolucizumab 3 mg, pooled brolucizumab 6 mg and pooled aflibercept 2 mg treatment arms. MedDRA Version 20.1 has been used for reporting.

A brolucizumab 3 mg treatment group was included in study RTH258-C001 only.

Reviewer's Comment: *A larger proportion of subjects in the brolucizumab treatment groups experienced an intraocular inflammation adverse event compared to the aflibercept treatment groups.*

8.6. Safety Analyses by Demographic Subgroups

No clinically significant differences in adverse events were identified related to age (< 65 and ≥

65 years of age) or gender. Because of the low numbers of patients of different races, it is difficult to discern differences or commonalities in adverse events. The disease does not commonly occur outside the Caucasian or Asian population.

8.7. Specific Safety Studies/Clinical Trials

None.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Because of the negligible systemic absorption of brolucizumab ophthalmic solution after intravitreal administration, no carcinogenicity studies were conducted.

8.8.2. Human Reproduction and Pregnancy

This drug has not been tested in pregnant women.

8.8.3. Pediatrics and Assessment of Effects on Growth

This drug has not been tested in pediatric patients.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Brolucizumab is not a narcotic and does not have abuse potential.

8.9. Safety in the Postmarket Setting

Brolucizumab is not a marketed drug product. There are no Postmarketing data to report.

8.10. Integrated Assessment of Safety

On May 6, 2019, the Applicant submitted the 120-day Safety Update report. All supporting clinical safety and efficacy study information were submitted with the original application. Study CTRH258AUS04 (MERLIN), a Phase 3 a study to evaluate the safety and efficacy of brolucizumab dosed monthly in patients with neovascular AMD is ongoing. No new safety signals have been identified for brolucizumab in this study as of April 4, 2019.

The safety database contained in this submission supports the relative safety of brolucizumab ophthalmic solution, 6 mg/ 0.05 mL administered by intravitreal injection every 28 days x 3 and then every 8-12 weeks for the treatment of age-related macular degeneration.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

See the labeling recommendations in Section 13.3.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12. Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

13. Appendices

13.1. References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

13.2. Financial Disclosure

Clinical Investigator Financial Disclosure Review Template

Application Number: BLA 761125
Submission Date(s): February 7, 2019
Applicant: Novartis Pharmaceuticals Corporation
Product: BEOVU (brolucizumab injection) 120 mcg/mL

Reviewer: Rhea A. Lloyd, MD
Date of Review: July 1, 2019
Covered Clinical Studies (Name and/or Number):
RTH258-C12-006
RTH258-C001
RTH258-C002
CRTH2582301E1

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: RTH258-C12-006 46 investigators RTH258-C001 212 investigators RTH258-C002 147 investigators CRTH2582301E1 68 investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): RTH258-C12-006 3 investigators		

RTH258-C001	9 investigators
RTH258-C002	37 investigators
CRT2582301E1	3 investigators

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 37

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in sponsor of covered study: 0

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>None</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

13.3. Labeling Review

Following is the applicant's draft labeling submitted on February 7, 2019, with recommended revisions.

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/

RHEA A LLOYD
09/09/2019 07:23:42 AM

WILLIAM M BOYD
09/09/2019 07:46:51 AM