CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 761125
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Indication:	Treatment of neovascular (wet) age-related macular degeneration
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1 EXECUTIVE SUMMARY

The Applicant seeks approval of brolucizumab intravitreal injection for the treatment of neovascular (wet) age-related macular degeneration (nAMD). Brolucizumab is an inhibitor of vascular endothelial growth factor (VEGF) that plays a key role in neovascularization process.

The Applicant conducted two pivotal efficacy studies: RTH258-C00**1** (HAWK) and RTH258-C00**2** (HARRIER). These studies are hereafter referred to as Study 1 and Study 2, respectively.

Studies 1 and 2 have similar designs. They are two-year, multi-center, randomized, double-masked, active-controlled, and noninferiority (NI) studies. Study 1 was conducted in North America, Latin America, Japan, Australia, New Zealand, and Israel, whereas Study 2 was conducted in European Union (EU), Middle East, Asia, and Russia. In Study 1, a total of 1082 subjects with nAMD were randomized in a 1:1:1 ratio to brolucizumab 3mg arm, brolucizumab 6mg arm, or aflibercept 2mg arm. In Study 2, a total of 743 subjects with nAMD were randomized in a 1:1 ratio to brolucizumab 6mg arm or aflibercept 2mg arm. For all arms, treatment was initiated with 3 monthly loading injections at Weeks 0, 4, and 8. After the loading injections, the aflibercept 2mg arm received injections every 8 weeks (q8w) up to Week 88. The brolucizumab arms received injections every 12 weeks (q12w) up to Week 92; however, if the investigators determined that q8w treatment was needed during the study, subjects received injections every 8 weeks thereafter up to Week 92.

The primary efficacy endpoint of the two studies is the change in best-corrected visual acuity (BCVA) from baseline to Week 48. The protocol-defined NI margin for the primary endpoint is 4-letters, which is acceptable from the reviewer's statistical perspective. The primary endpoint is analyzed using a pairwise analysis of variance (ANOVA) model including treatment, baseline BCVA categories (≤55, 56-70, or ≥71 letters), and age categories (<75, or ≥75 years) as factors. In Study 1, the multiple tests are performed in a sequential manner: brolucizumab 6mg vs. aflibercept 2mg and then brolucizumab 3mg vs. aflibercept 2mg.

The study patients' age ranged from 50 to 97 years with a mean of 77 years in Study 1 and from 50 to 95 years with a mean of 75 years in Study 2. The proportion of female patients was higher than the proportion of male patients: 57% vs 43% in both studies. The majority (81% in Study 1 and 92% in Study 2) of the patients were white people. The baseline BCVA ranged from 16 to 85 letters in Study 1 and from 22 to 79 letters in Study 2 with a mean of 61 letters in both studies.

For both studies, the estimates of the mean change in BCVA from baseline to Week 48 are comparable between the brolucizumab 6mg and aflibercept 2mg arms: 6.61 letters vs. 6.78 letters in Study 1 and 6.91 letters vs. 7.61 letters in Study 2 (Table 1). The estimated treatment difference (brolucizumab 6mg - aflibercept 2mg) is -0.16 [95% CI: (**-2.13**, 1.80)] in Study 1 and -0.70 [95% CI: (**-2.39**, 1.00)] in Study 2. The lower bounds of the 95% confidence intervals for the treatment differences are larger than the prespecified NI margin of -4 letters, which demonstrates statistical noninferiority of brolucizumab 6mg to aflibercept 2mg.

Table 1: Primary analysis results for the mean change in BCVA from baseline to Week 48 (FAS [1])

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg (N=358)	**Brolucizumab 6mg (N=360)**	**Aflibercept 2mg (N=360)**	**Brolucizumab 6mg (N=370)**	**Aflibercept 2mg (N=369)**
Baseline BCVA (letters)					
Mean (SD)	61.0 (13.6)	60.8 (13.7)	60.0 (13.9)	61.5 (12.6)	60.8 (12.9)
Median	64.5	64.0	63.0	64.0	64.0
Min, Max	23, 85	23, 85	16, 83	22, 78	23, 79
Mean change in BCVA					
LS mean (SE) [2]					
BRO 3 mg vs. AFL 2mg	6.14 (0.69)		6.77 (0.69)		
BRO 6 mg vs. AFL 2mg		6.61 (0.71)	6.78 (0.71)	6.91 (0.61)	7.61 (0.61)
Difference in LS means	-0.62	**-0.16**		**-0.70**	
95% CI for Difference	(-2.54, 1.29)	**(-2.13, 1.80)**		**(-2.39, 1.00)**	
Noninferiority p-value	0.0003	<.0001		<.0001	

[1] FAS: full analysis set including all randomized subjects who received at least 1 injection of study treatment; the last available observation (LAO) prior to start of alternative anti-VEGF treatments was used if a subject received alternative anti-VEGF treatments; missing values were imputed by the LAO prior to missed assessments.
[2] LS Mean: least squares mean; SE: standard error; BRO: brolucizumab; AFL: aflibercept; CI: confidence interval.
Source: Table 14.2-1.1 of the clinical study reports for Study 1 and Study 2. This table was produced by the reviewer.

Most of the BCVA improvement observed at Week 48 was maintained through Week 96 (see Figure 2 in Section 3.2.4.1). The estimated mean change in BCVA from baseline to Week 96 are comparable between the brolucizumab 6mg and aflibercept 2mg arms: 5.9 letters vs. 5.3 letters in Study 1 and 6.1 letters vs. 6.6 letters in Study 2.

Subjects in the brolucizumab arms were allowed to switch from q12w dosing schedule to q8w dosing schedule during the study if the investigators determined that q8w treatment was needed based on the protocol-defined disease activity criteria. Within the brolucizumab 6mg arm, the estimated probability that a subject remained on q12w dosing schedule at Week 48 is 0.56 [95% CI: (0.50, 0.61)] for Study 1 and 0.51 [95% CI: (0.46, 0.56)] for Study 2 (these probabilities are estimated by Kaplan-Meier analyses of time to first q8w-need). Thus, approximately half of the subjects in the brolucizumab 6mg arms were able to remain on the q12w dosing schedule up to Week 48. At Week 96, this probability is 0.45 [95% CI: (0.40, 0.51)] for Study 1 and 0.39 [95% CI: (0.33, 0.44)] for Study 2.

In terms of rate of 'responders' who are defined as subjects with BCVA gain of ≥ 15 letters at Week 48, the brolucizumab 6mg arm in Study 1 shows slightly better performance than the aflibercept 2mg arm: 33.6% vs. 25.4%. However, in Study 2, the two arms show similar performance: 29.3% vs. 29.9%. In terms of rate of 'non-responders' who are defined as subjects with BCVA loss of ≥ 15 letters at Week 48, the two arms show similar performance for both studies: 6.4% vs. 5.5% in Study 1 and 3.8% vs. 4.8% in Study 2.

In terms of anatomical parameters, the brolucizumab 6mg arm shows numerically larger reduction in central subfield thickness and lower proportion of subjects with intra- or sub-retinal fluid at Week 48 compared to those in the aflibercept 2mg arm. See Section 3.2.4.3 for details.

Regarding safety, the incidence rates of adverse events are comparable between the brolucizumab 6mg arm and aflibercept 2mg arm. No notable imbalance in the AE profile between the two arms is observed. However, the reviewer defers to the medical reviews for a comprehensive safety evaluation.

In summary, the reviewer concludes that this application provides adequate statistical evidence of efficacy to support an approval of brolucizumab 6mg intravitreal injection for the treatment of nAMD.

2 INTRODUCTION

This section provides an overview of the application, a summary of the clinical studies selected for review, and information on data sources for review.

2.1 Overview

The Applicant seeks approval of brolucizumab intravitreal injection for the treatment of neovascular (wet) age-related macular degeneration.

Age-related macular degeneration (AMD) is a leading cause of vison loss among people of age 50 or older (https://nei.nih.gov/health/maculardegen/armd_facts). AMD can be classified into two forms: non-neovascular (dry) form or neovascular (wet) form. Neovascular AMD (nAMD) is characterized by the growth of abnormal blood vessels (neovascularization) behind the retina. These abnormal blood vessels leak blood and fluid into the retina, which results in thickening of the retina (retinal edema). The key symptom of nAMD is blurred central vision. Without treatment, most affected eyes will have poor central vision within 1 year.

Vascular endothelial growth factor (VEGF) is known to play a key role in the neovascularization process. Thus, anti-VEGF treatments inhibiting VEGF signaling pathways have been used to halt the growth of neovascular legions and resolve retinal edema in patients with nAMD. Anti-VEGF treatments currently approved for the treatment of nAMD include ranibizumab 0.5mg (Lucentis®) and aflibercept 2mg (Eylea®).

2.1.1 Class and Indication

Per the Applicant, brolucizumab (also referred to as RTH258) is an inhibitor of VEGF factor A (VEGF-A), preventing binding to its receptors VEGFR1 and VEGFR2. The Applicant expects a prolonging duration of action for brolucizumab as it provides a molar dose approximately 12-fold higher than aflibercept 2mg and 22-fold higher than ranibizumab 0.5mg. The indication that the Applicant seeks is the treatment of nAMD.

2.1.2 History of Drug Development

IND 112023 for brolucizumab was opened on April 18, 2011 by Alcon Research, Ltd (Alcon). (b) (4) in connection with IND 112023 (\\CDSESUB1\evsprod\IND112023\0106).

The initial code name for brolucizumab was ESBA1008. Alcon conducted Phase 1 and Phase 2 studies of ESBA1008. On May 8, 2013, a Type B End-of-Phase 2 meeting was held to discuss a Phase 3 development program of ESBA1008. In the meeting package, Alcon proposed to conduct two confirmatory noninferiority (NI) studies in nAMD patients: one comparing ESBA1008 to aflibercept and the other comparing ESBA1008 to (b) (4) The DTOP disagreed with several aspects of the proposed study designs in the protocol synopses. See the DARRTS entry on 06/07/2013 for details.

After modifying study designs, Alcon submitted the initial protocols for the two confirmatory studies:

- Study RTH258-C001: 2-year NI study comparing RTH258 (brolucizumab) to aflibercept
- Study RTH258-C002: 2-year NI study comparing RTH258 to (b) (4)

Note that the code name for brolucizumab was changed from ESBA1008 to RTH258. Alcon requested a Special Protocol Assessment (SPA) for Study RTH258-C002. The Agency issued a no-agreement letter on 12/18/2014. For the statistical review of the SPA by the former reviewer, Dr. Zhuang, see the DARRTS entry on 12/17/2014. No further SPA was submitted by either Alcon or the current Applicant.

Reviewer's note: The reviewer was not able to find any updated protocol for Study RTH258-C002 in DARRTS since the SPA. However, the amendments and final protocol for Study RTH258-C002 can be found in this BLA submission (Appendix 16.1.1 of the clinical study report for Study RTH258-C002). Although Alcon initially proposed an active comparator of (b) (4) *for Study RTH258-C002, it had been changed to aflibercept later. Thus, for both pivotal studies, the active comparator was aflibercept.*

For Study RTH258-C001, the Applicant's proposal for an NI margin in the initial protocol was 4 letters. Regarding this proposal, the DTOP stated that "the Division would be willing to accept a non-inferiority margin of 3.5 letters when comparing RTH 258 to Eylea q8 weeks" (see the DARRTS entry on 04/07/2015). A Type C meeting was held on September 1, 2015 to discuss an NI margin for Study RTH258-C001. For details of the meeting discussion, see the DARRTS entry on 09/23/2015. The NI margin stated in the final protocol and statistical analysis plan (SAP) is 4-letters.

Reviewer's note: The former statistical reviewer, Dr. Zhuang, considered the NI margin of 4 letters acceptable from a statistical perspective (see the DARRTS entries on 01/02/2015 and 08/25/2015). This reviewer agrees with the former reviewer's perspective. See Appendix J for the reviewer's assessment of the NI margin.

On September 20, 2017, a Type C meeting was held to discuss the proposed comparability program between Phase 3 and commercial materials. At the meeting, the Applicant indicated that they are considering an extension study of the Phase 3 studies which would roll over remaining patients to receive the commercial product. The DTOP recommended that as many patients as possible be rolled over into the extension study. As a result, the Applicant completed an extension study of RTH258-C001 with a total of 150 patients. No formal statistical hypothesis testing was conducted for this study.

On March 6, 2018, the Applicant requested a Type C meeting with the Agency to seek inputs for the preparation of a planned BLA. The meeting package included the statistical analysis plans (SAPs) for the two pivotal Phase 3 studies. This reviewer considered them acceptable. See the DARRTS entry on 05/16/2018 for the statistical review of the SAPs.

On August 27, 2018, a Type B pre-BLA meeting was held to discuss the presentation of the BLA submission as well as questions regarding the need for Advisory Committee Meeting and patient reported outcome. This reviewer considered the proposed presentation of clinical data package acceptable. For the questions regarding the patient reported outcomes, we deferred to the medical review team. See the DARRTS entry on 09/16/2018 for details of the meeting discussion.

2.1.3 Specific Studies Reviewed

Under IND 112023, the following clinical studies were completed:

- C-10-083 (SEE): Phase 1 dose escalating study (N=194)
- C-12-006 (OSPREY): Phase 2 efficacy and safety study (N=90)
- RTH258-C001 (HAWK): Phase 3 efficacy and safety study (N=1082)
- RHT258-C002 (HARRIER): Phase 3 efficacy and safety study (N=743)
- CRTH258A2301E1: Extension study of RTH258-C001 (N=150)

This review focuses on the two pivotal Phase 3 studies, HAWK and HARRIER, which are hereafter referred to as Study 1 and Study 2, respectively. A summary of the two studies is presented in Table 2. Note that Study CRTH258A2301E1 was conducted to provide data with the intended commercial product. A subgroup of 150 subjects who completed Study 1 participated in Study CRTH258A2301E1. No formal statistical hypothesis tests were performed in Study CRTH258A2301E1.

Table 2: Summary of specific studies reviewed

Study ID	**Study RTH258-C001 (HAWK)**	**Study RTH258-C002 (HARRIER)**
Design	Phase 3, multi-center, randomized, double-masked, active-controlled, efficacy (non-inferiority) and safety study	
Duration	96 weeks (92 weeks of treatment + 4 weeks follow-up)	
Treatment/ Sample Size	Brolucizumab 3mg/ 360 Brolucizumab 6mg/ 361 Aflibercetp 2mg/ 361	Brolucizumab 6mg/ 372 Aflibercetp 2mg/ 371
Primary Endpoint	**Change in Best-Corrected Visual Acuity (BCVA) from baseline to Week 48**	
Key Secondary Endpoints	- Average change in BCVA from baseline over the period Week 36 through 48. - q12w treatment status at Week 48 for subjects randomized to brolucizumab - q12w treatment status at Week 48 for subjects who are randomized to brolucizumab and have no q8-need during the first q12 cycle	
Study Population	- Age 50 years or older with active choroidal neovascularization (CNV) lesions secondary to AMD in the study eye - BCVA between 78 and 23 letters in the study eye - Treatment naïve for AMD	

Source: reviewer's summary based on the clinical study reports.

2.2 Data Sources

The data sources for this review include protocols, statistical analysis plans (SAPs), clinical study reports (CSRs), the summary of clinical efficacy (SCE), the summary of clinical safety (SCS), and the datasets for the respective studies.

The CSRs can be found at the following locations:

- Study 1: \\CDSESUB1\evsprod\BLA761125\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\n-amd\5351-stud-rep-contr\rth258-c001
- Study 2: \\CDSESUB1\evsprod\BLA761125\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\n-amd\5351-stud-rep-contr\rth258-c002

The protocol and SAP for each study can be found in Appendix 16.1.1 and Appendix 16.1.9 of each CSR. The Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) can be found at \\CDSESUB1\evsprod\BLA761125\0001\m2\27-clin-sum .

The datasets are submitted in the formats of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) in electronic submission. The datasets can be located at \\CDSESUB1\evsprod\BLA761125\0001\m5\datasets. This location also includes the SAS programs used to generate tables and figures for the efficacy and safety results in the CSRs.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No major issues were identified regarding the quality and integrity of the submitted SDTM and ADaM datasets. The data quality control/assurance procedures are properly documented in the CSRs.

The datasets are well organized. The Applicant's primary efficacy results are reproducible using the ADaM datasets. In general, using SDTM and ADaM datasets, the reviewer is able to conduct the necessary analyses without complex manipulations.

3.2 Evaluation of Efficacy

This section evaluates the efficacy results of Study1 and Study 2.

3.2.1 Study Design and Endpoints

Study Design

Study 1 (HAWK) and Study 2 (HARRIER) have similar design. They are two-year, Phase 3, multicenter, randomized, double-masked, active-controlled, noninferiority study comparing the efficacy and safety of brolucizumab intravitreal (IVT) injections versus aflibercept IVT injections in subjects with nAMD. Study 1 was conducted in North America, Latin America, Japan, Australia, New Zealand, and Israel, whereas Study 2 was conducted in EU, Middle East, Asia, and Russia.

In Study 1, a total of 1082 subjects were randomized in a 1:1:1 ratio to brolucizumab 3mg arm (N=360), brolucizumab 6mg arm (N=361), or aflibercept 2mg arm (N=361). In Study 2, a total of 743 subjects were randomized in a 1:1 ratio to brolucizumab 6mg arm (N=372) or aflibercept 2mg arm (N=371).

Reviewer's note: The countries (the number of study centers) participated in each study are as follows:

- *Study 1: Argentina (1), Australia (12), Canada (13), Colombia (5), Israel (10), Japan (34), Mexico (4), New Zealand (3), Panama (1),* ***USA (130)***
- *Study 2: 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), Vietnam (2)*

The key inclusion criteria for both studies are as follows:

- ≥ 50 years of age
- Active choroidal neo-vascularization (CNV) lesions secondary to AMD that affected the central subfield (including retinal angiomatous proliferation lesions with a CNV component) in the study eye
- Total area of CNV (including both classic and occult components) must have comprised >50% of the total lesion area in the study eye
- Intra- and/or subretinal fluid affecting the central subfield of the study eye
- BCVA between 78 and 23 letters, inclusive, in the study eye

For all treatment arms, treatment was initiated with 3 monthly loading injections at Weeks 0, 4, and 8. After the loading phase, the injection schedule differed between the brolucizumab arms and aflibercept arm as follows:

- Aflibercept 2 mg arm: subjects received injections every 8 weeks (q8w) up to Week 88.
- Brolucizumab arms: subjects received injections every 12 weeks (q12w) up to Week 92. However, if disease activity was identified during the study, subjects received injections every 8 weeks (q8w) thereafter up to Week 92.

To establish an identical monthly injection schedule across the treatment arms for masking purpose, sham injections were administered when treatment injections were not administered.

Disease activity was assessed by masked investigators. Disease activity criteria (Table 3) were given in the protocols as guidance for disease activity assessment (DAA); however, the masked investigators made the final decision.

In Study 1, disease activity was assessed at Week 16 and at the scheduled q12w treatment visits (Weeks 20, 32, 44, 56, 68, 80 and 92). In Study 2, additional assessments were performed at 8 weeks after every scheduled q12w brolucizumab injection, i.e., assessments were made at Weeks 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, and 92 (14 assessments). Per the CSR of Study 2, the additional assessments were based on European health authority feedback. Figure 1 depicts

drug administration and disease activity assessment schedule in Studies 1 and 2. See Appendix A for the schedule of visits and assessment.

Table 3: Disease activity criteria in Phase 3 protocols

Table 2-1 Guidance criteria for disease activity assessment in Phase III study protocols

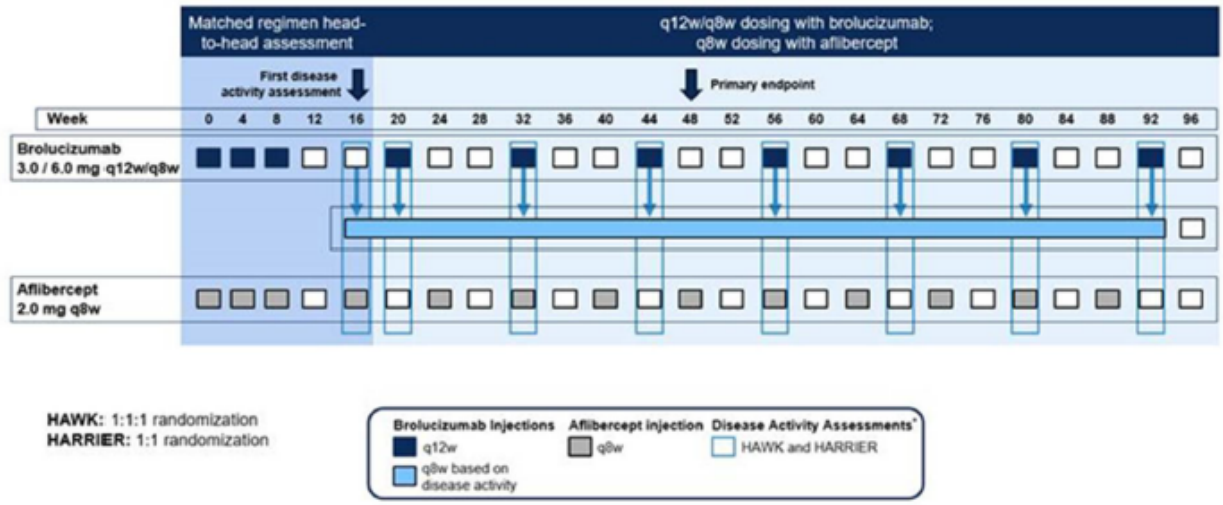
At Week	Criterion
Week 16	Decrease in BCVA of ≥ 5 letters compared with Baseline
	Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75µm compared with Week 12
	Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with Week 12
	New or worse IRC/IRF compared with Week 12
Weeks 20, 28 [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

[a] Study RTH258-C002 only
[b] Assessed by anatomical parameters, e.g., CSFT or IRF

Source: Table 2-1 of the Summary of Clinical Efficacy (SCE).

Figure 1: Drug administration and disease activity assessment schedule

Figure 2-2 Drug administration and disease activity assessment schedule in studies RTH258-C001 and RTH258-C002



Note: Study RTH258-C002 had additional disease activity assessment at Weeks 28, 40, 52, 64, 76, and 88.

Source: Figure 2-2 of the Summary of Clinical Efficacy (SCE).

Reviewer's notes on the planned number of injections:

1. *The primary endpoint was evaluated at Week 48 prior to any drug administration at this visit. Thus, the total number of planned injections per subject prior to the evaluation of the primary endpoint is as follows:*

a. *Aflibercept arms: 7 (Weeks 0, 4, 8, 16, 24, 32, and 40)*

b. *Brolucizumab arms: 6 (Weeks 0, 4, 8, 20, 32, and 44)*

Thus, prior to the evaluation of the primary endpoint, the subjects in the aflibercept arm will receive one more planned injection of study drug than the subjects in the two brolucizumab arms if the subjects in the brolucizumab arms are treated with the q12w regimen.

As presented in Section 3.2, within the brolucizumab 6mg arm, the proportion of subjects who remained on the q12w treatment schedule until Week 48 was about 50% for both studies. Within the brolucizumab 3mg arm in Study 1, this proportion was also about 50%.

2. *The planned number of injections up to Week 96 is 13 for the aflibercept arms and 10 for the brolucizumab arms. The proportion of subjects who remained on the q12w treatment schedule until Week 96 was about 35~40% for the two brolucizumab arms.*

Efficacy Endpoints

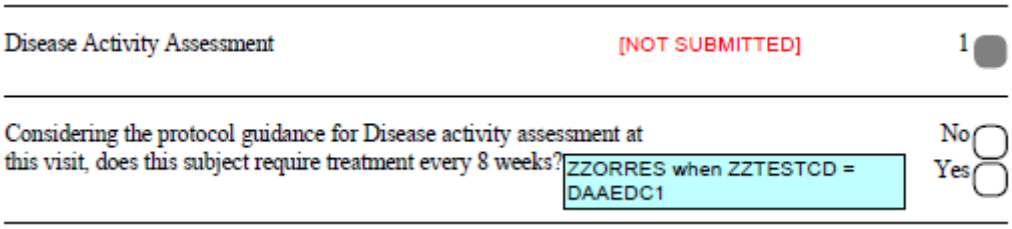
Table 4 summarizes the efficacy endpoints in the two pivotal studies.

Table 4: Efficacy endpoints in Study 1 (HAWK) and Study 2 (HARRIER)

Primary	• **change in BCVA from baseline to Week 48**
Key Secondary	• Average change in BCVA from baseline over the period Week 36 through Week 48. For each subject, this endpoint is defined as the average of the changes from baseline to Weeks 36, 40, 44, and 48. • q12w treatment status at Week 48 for subjects randomized to brolucizumab • q12w treatment status at Week 48 for subjects who are randomized to brolucizumab and have no q8w-need during the first q12 cycle (Week 16, Week 20)
Additional Secondary	• BCVA change from baseline to each postbaseline visit • Proportion of subjects with BCVA gain of ≥ 15 letters from baseline to each visit [1] • Proportion of subjects with BCVA loss of ≥ 15 letters from baseline to each visit • Change in central subfield thickness (CSFT) from baseline to Weeks 16, 48, and 96 • Proportion of subjects with intra-retinal fluid (IRF) and/or sub-retinal fluid (SRF) at Weeks 16, 48, and 96 • Proportion of subjects with sub-RPE (subretinal pigment epithelium) fluid at Weeks 16, 48, and 96 • Proportion of subjects with disease activity at Week 16

[1] Note: In this review, a subject with BCVA gain of ≥ 15 letters from baseline is referred to as a 'responder'. Subjects with BCVA of ≥ 84 letters are also considered as responders as planned in the SAPs.

The q12w treatment status (positive/negative) at Week 48 is derived from all disease activity assessments conducted prior to Week 48. More specifically, at each disease activity assessment (DAA) visit, the masked investigators evaluated whether each subject required treatment every 8 weeks (q8w-need) or not as shown below:



Source: Page 86 of the annotated case report form (ACRF) of Study RTH258-C001

In general, the q12w treatment status at Week 48 was considered positive if all performed DAAs prior to Week 48 showed no q8w-need. If one or more assessments showed q8-need, the q12w status was considered negative. For handling of missing DAAs and intercurrent events that can affect the q12w treatment status evaluation, see Section 3.2.2.

Note that the two pivotal studies had more than 20 additional secondary efficacy endpoints and more than 10 exploratory efficacy endpoints. See Appendix B for all additional secondary and exploratory efficacy endpoints. Among them, this review focuses on the secondary endpoints listed in Table 4. (b) (4) The reviewer also considers that evaluation of these endpoints regarding BCVA and anatomical parameters may be informative for efficacy conclusion.

3.2.2 Statistical Methodologies

This section primarily focuses on describing statistical methodologies for analyzing the primary and key secondary efficacy endpoints. Statistical methodologies for analyzing additional secondary endpoints are also briefly described.

Analysis populations

The SAPs define the following analysis sets:

- The full analysis set (FAS) includes all randomized subjects who receive at least one IVT injection of the study treatment. The FAS serves as the primary analysis set for all efficacy analyses.
- Supportive analyses of the primary and secondary endpoints are performed on the per-protocol set (PPS). PPS is a subset of the FAS and excludes subjects with protocol deviations and analysis restrictions that are expected to majorly affect the validity of the assessment of efficacy at Week 48 including the followings: lack of compliance (including missed treatments and treatment misallocation), missing data, prohibited concomitant medication and deviation from inclusion/exclusion criteria. Per the SAPs,

discontinuation from treatment due to lack of efficacy and/or safety does not constitute a reason for exclusion from the PPS.

- Safety analysis set includes all subjects who received at least one IVT injection. Subjects in the safety analysis set are analyzed according to the first treatment received. This analysis set is used for all safety analyses.

Analysis of the primary and first key secondary efficacy endpoints

Recall that the primary and first key secondary endpoints are as follows:

- **Primary: change in BCVA from baseline to Week 48**
- First key secondary: average change in BCVA from baseline over the period Week 36 through Week 48.

The SAP-defined primary analysis methods for these two endpoints are Analysis of Variance (ANOVA) models. The ANOVA models include treatment, baseline BCVA categories (≤55, 56-70, or ≥71 letters), and age categories (<75, or ≥75 years) as factors. In Study 1, the ANOVA models are fitted separately for the following two comparisons: brolucizumab 3mg vs. aflibercept 2mg and brolucizumab 6mg vs. aflibercept 2mg.

Least square (LS) means and 95% CIs for the treatment difference (brolucizumab - aflibercept) are obtained from the ANOVA models. Noninferiority of brolucizumab to aflibercept is tested using the 95% CIs with the NI margin of 4 letters. In Study 1, the multiple tests arising from the multiple comparisons are performed sequentially in the following order as specified in the SAP:

1. brolucizumab 6 mg vs. aflibercept 2 mg in the primary endpoint
2. brolucizumab 6 mg vs. aflibercept 2 mg in the first key secondary endpoint.
3. brolucizumab 3 mg vs. aflibercept 2 mg in the primary endpoint
4. brolucizumab 3 mg vs. aflibercept 2 mg in the first key secondary endpoint.

Per the SAPs, missing data are imputed using last observation carried forward (LOCF) method in the primary analysis. For subjects with no postbaseline value, the baseline values are carried forward. For subjects who discontinued treatment but continued the study, the BCVA values are censored at the time the subjects started alternative anti-VEGF treatments. Censored data are "imputed" by the last available BCVA values prior to receiving alternative anti-VEGF treatments.

Reviewer's comments:

1. *The SAPs states that the censored data are "imputed" by the observations prior to receiving alternative anti-VEGF treatments. It appears that the Applicant views the censored data as missing data. However, the reviewer does not agree with this perspective. Censoring and using the last observation prior to censoring is one way of handling the intercurrent event of receiving alternative anti-VEGF treatments. The reviewer does not consider the censored data as missing data.*

2. *The primary analysis was conducted essentially for the change in BCVA from baseline up to the last visit prior to study treatment discontinuation before Week 48. Thus, the estimand addressed by this analysis is an example of 'while-on-treatment' strategy (see the ICH E9 Addendum: Estimands and Sensitivity Analysis in Clinical Trials).*

3. *The NI margin of 4 letters is acceptable from the reviewer's perspective. See Appendix J for the reviewer's assessment of the NI margin.*

To assess robustness of the primary analysis results of the primary endpoint, the following supportive analyses are performed as planned in the SAPs:

- ANOVA using the PPS with LOCF for missing/censored values: the ANOVA model in this supportive analysis is the same as that in the primary analysis.
- Mixed model repeated measures (MMRM) using the FAS or PPS: the MMRM model includes treatment, visit, baseline BCVA category, age category, and treatment by visit interactions as factors. An unstructured covariance matrix is used to model the within-subject error. For subjects who discontinued treatment but continued the study, the BCVA values are censored at the time the subjects started alternative anti-VEGF treatments. Censored or missing data are not imputed.

In addition to these supportive analyses, the reviewer conducts the following supportive analysis:

- ANOVA using the FAS with observed data: the same ANOVA model in the primary analysis is used. Unlike the primary analysis, however, for subjects who received alternative anti-VEGF treatments prior to Week 48, their observed BCVA values at Week 48 are used if they were collected.

Reviewer's note: The above supportive analysis is conducted for the observed BCVA change at Week 48 regardless of treatment discontinuation. Thus, under the assumption of missing at complete random for subjects who had missing data at Week 48, the estimand addressed by this supportive analysis is an example of 'treatment-policy' strategy (see the ICH E9 Addendum: Estimands and Sensitivity Analysis in Clinical Trials).

Analysis of the second and third key secondary efficacy endpoints

Recall that the second and third key secondary endpoints are as follows:

- q12w treatment status at Week 48 for subjects who are randomized to brolucizumab
- q12w treatment status at Week 48 within subjects who are randomized to brolucizumab and have no q8w-need during the first q12 cycle (Week 16, Week 20)

No hypothesis tests are planned in the SAPs for these q12w treatment status endpoints. The SAP-defined primary analysis method for these endpoints is the Kaplan-Meier analysis of time to the first 'q8w-need' event.

Recall that the q12w status is considered positive at a postbaseline visit if all performed DAAs prior to that visit show no q8-need. In the primary Kaplan-Meier analysis, handling of various intercurrent events and censoring are as follows:

- Rule 1: If the following intercurrent events are attributable to lack of efficacy and/or adverse events, the q12w status at the next DAA visit is considered negative (i.e., 'q8-need = yes'): early treatment/study discontinuation, use of forbidden concomitant medication, procedures and/or other deviation from treatment schedule (e.g., due to a missed visit/treatment).
- Rule 2: If the above intercurrent events and missing data are attributable to reasons other than lack of efficacy and/or adverse events, the q12w status is censored.

Reviewer's note: Briefly speaking, in the above approach, the intercurrent events due to lack of efficacy/safety lead to negative q12w status while the intercurrent events due to reasons other than lack of efficacy/safety lead to censoring of q12w status. The reviewer finds this approach reasonable.

The primary Kaplan-Meier analysis with the above rules is referred to as the 'efficacy/safety' approach in the CSRs. Subjects without any valid DAA are considered censored at baseline. For defining the subset of subjects having no identified q8w-need during the first q12 cycle (Week 16 and Week 20), a valid Week 20 DAA is required (i.e., a subject with no valid Week 20 DAA is excluded from this subset). However, missing Week 16 assessment is considered as no q8w-need. Various supportive analyses for the q12w status endpoints are also performed as planned in the SAPs. See Appendix G for details of the supportive analyses.

Analysis of the additional secondary efficacy endpoints

In Study 1, formal hypothesis tests were performed for some of the additional secondary endpoints as planned in the SAPs (see Appendix C). However, Study 2 had no plan to perform a formal hypothesis test for any of the additional secondary endpoints.

The additional secondary endpoints are analyzed as follows:

- BCVA change from baseline to each postbaseline visit: the same ANOVA model as the one for the primary endpoint.
- Change in central subfield thickness (CSFT) from baseline to Weeks 16, 48, and 96: ANOVA model including treatment, baseline CSFT categories (<400, ≥400 μm), and age categories (<75, ≥75 years) as factors.
- Binary endpoints: logistic regression with baseline status (see below) and age categories (<75, ≥75 years) as factors. The baseline status is defined as follows:
    - Baseline BCVA category (≤55, 56-70, or ≥71 letters) for the proportion of subjects with BCVA gain or loss of ≥ 15 letters
    - Baseline fluid status (yes or no) for the proportion of subjects with fluid
    - No baseline status is included in the model for the proportion of subjects with disease activity.

Based on the logistic regression model, an estimated proportion for each treatment arm and difference in proportions are obtained as follows:

Step A: Consider all possible subgroups that can be generated by the baseline factors in the logistic regression model. Compute an estimated proportion within each subgroup for each treatment arm. For example, consider the logistic regression model for the proportion of subjects with fluid. Let π_{ijk} be the estimated proportion of subjects with fluid for the treatment arm i (i = a or b) within the subgroup of subjects who have baseline fluid status j (j = 0 or 1) and belong to age group k (k= <75 or ≥75). In addition, let n_{jk} be the number of subjects in this subgroup.

Step B: The estimated proportion for each treatment arm (say, π_i) is obtained by the weighted average of π_{ijk} over all baseline factors (j and k) with the weights proportional to the subgroup sample sizes (n_{jk}).

Step C: Difference in proportions between the arms is estimated by $\pi_b - \pi_a$.

The SAP-defined method to compute a 95% confidence interval (CI) for difference in proportions is a delta method. However, as stated in the CSRs, there was a change in the final method for the calculation of the confidence intervals. The 95% confidence intervals reported in the CSRs were computed by using a bootstrap method. Per the Applicant's submitted SAS codes, the bootstrap method was performed as follows:

1. Generate 1000 bootstrap datasets from the FAS. Each dataset has the same number of subjects in the FAS.
2. For each dataset, fit a logistic regression and estimate proportion for each treatment arm and difference in proportions as described above (Steps A to C). Let $\pi_{a,r}$, $\pi_{b,r}$, and $d_r = \pi_{b,r} - \pi_{a,r}$ (r=1, … ,1000) be the estimated proportions and difference in the proportions from the r-th bootstrap dataset.
3. Finally, a 95% confidence interval for difference in proportions is computed as (d_{FAS} - $Q_{0.025}$, d_{FAS} + $Q_{0.975}$) where d_{FAS} is the estimated difference in proportions from the FAS and $Q_{0.025}$ ($Q_{0.975}$) is the 0.025^{th} (0.975^{th}) percentile of the 1000 estimated differences in proportions (d_1, …, d_{1000}).

Reviewer's comment:

1. *Regarding the delta method for computing 95% CIs for difference in proportions, the SAPs do not include any mathematical or computing details. Thus, the reviewer developed own codes for implementing the delta method and applied them to the binary endpoints. In the reviewer's delta method approach, the proportions and difference in the proportions were estimated in the same manner as described above (Steps A to C). Only difference from the bootstrap method is that the variance of the estimator for difference in proportions was obtained through the delta method instead of the bootstrap procedure. The 95% CIs estimated from the delta method were very similar to those estimated from the bootstrap method. Given relatively sufficient sample sizes of the pivotal studies, it appears that the estimated variance of the estimator for difference in proportions are similar between the two methods. See Appendix I for details.*

2. *The reviewer also calculated 95% CIs based on unadjusted analyses using the 2-sample tests for the difference in proportions. In terms of width of the 95% CIs, the unadjusted analyses and the adjusted analyses (by the logistic regression) performed similarly: the*

widths of the 95% CIs were very similar between the unadjusted and adjusted analyses. In terms of point estimation, it does not appear that the adjusted analyses provided consistently favorable results for the brolucizumab arm compared to the unadjusted analyses. See Appendix I for details.

For these additional secondary endpoints, missing values are handled using the LOCF approach described for the primary efficacy endpoint.

3.2.3 Subject Disposition, Demographic, and Baseline Characteristics

Subject disposition and primary reasons for study discontinuation at Week 48 (the primary efficacy time point) are summarized in Table 5. In general, the proportion of subjects who completed Week 48 is comparable between the brolucizumab 6mg arm and aflibercept 2mg arm: 92.2% vs. 90.6% in Study 1 and 95.2% vs. 94.9% in Study 2.

In Study 1, 7 subjects (1.9%) in the brolucizumab 6mg arm and 8 subjects (2.2%) in the aflibercept 2mg arm discontinued the study prior to Week 48 due to adverse events. Discontinuations related to efficacy were reported under the categories of 'lack of efficacy' and 'progressive disease'. No subject in either the brolucizumab 6mg arm and aflibercept 2mg arm discontinued the study prior to Week 48 due to lack of efficacy or progressive disease.

In Study 2, 5 subjects (1.3%) in the brolucizumab 6mg arm and 1 subject (0.3%) in the aflibercept 2mg arm discontinued the study prior to Week 48 due to adverse events. Two subjects (0.5%) in the aflibercept 2mg arm discontinued the study prior to Week 48 due to lack of efficacy while no brolucizumab-treated subject discontinued the study due to lack of efficacy.

None of the deaths up to Week 48 were suspected by the investigators to be related to study treatment.

Table 5: Subject disposition (Week 48), n (%)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg	**Brolucizumab 6mg**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Aflibercept 2mg**
Randomized	**360 (100)**	**361 (100)**	**361 (100)**	**372 (100)**	**371 (100)**
Full Analysis Set	**358 (99.4)**	**360 (99.7)**	**360 (99.7)**	**370 (99.5)**	**369 (99.5)**
Subjects Completed Week 48					
Yes	**334 (92.8)**	**333 (92.2)**	**327 (90.6)**	**354 (95.2)**	**352 (94.9)**
No	**26 (7.2)**	**28 (7.8)**	**34 (9.4)**	**18 (4.8)**	**19 (5.1)**
Adverse Event	6 (1.7)	7 (1.9)	8 (2.2)	5 (1.3)	1 (0.3)
Death	4 (1.1)	3 (0.8)	6 (1.7)	3 (0.8)	4 (1.1)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Lost to Follow-Up	1 (0.3)	2 (0.6)	3 (0.8)	0 (0.0)	4 (1.1)
Physician Decision	2 (0.6)	1 (0.3)	4 (1.1)	0 (0.0)	0 (0.0)
Progressive Disease	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Withdrawal by Subject	10 (2.8)	15 (4.2)	11 (3.0)	9 (2.4)	7 (1.9)
Other	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg	**Brolucizumab 6mg**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Aflibercept 2mg**
Treatment Discontinuation prior to Week 48	**31 (8.6)**	**37 (10.2)**	**46 (12.7)**	**25 (6.7)**	**24 (6.5)**
Adverse Event	8 (2.2)	11 (3.0)	8 (2.2)	12 (3.2)	4 (1.1)
Death	4 (1.1)	3 (0.8)	6 (1.7)	3 (0.8)	4 (1.1)
Lack of Efficacy	0 (0.0)	0 (0.0)	3 (0.8)	1 (0.3)	2 (0.5)
Lost to Follow-Up	1 (0.3)	2 (0.6)	3 (0.8)	0 (0.0)	4 (1.1)
Physician Decision	2 (0.6)	1 (0.3)	5 (1.4)	1 (0.3)	1 (0.3)
Progressive Disease	3 (0.8)	0 (0.0)	7 (1.9)	0 (0.0)	0 (0.0)
Protocol Deviation	1 (0.3)	1 (0.3)	2 (0.6)	0 (0.0)	1 (0.3)
Withdrawal by Subject	10 (2.8)	19 (5.3)	11 (3.0)	7 (1.9)	7 (1.9)
Other	2 (0.6)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)

Source: Table 14.1-1.1 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

Within the FAS of Study 1, 36 subjects in the brolucizumab 6mg arm and 45 subjects in the aflibercept 2mg arm discontinued the study treatment prematurely prior to Week 48. In Study 2, the number of such subjects within the FAS was 23 in the brolucizumab 6mg arm and 22 in the aflibercept 2mg arm. The reviewer examined time profile of BCVA for two subgroups of these subjects: (1) patients who completed Week 48 visit and (2) patients who did not complete Week 48 visit (see Appendix K). The reviewer did not find any notable difference in the BCVA profiles between the completers and non-completers among the subjects who discontinued the study treatment prematurely. Note that the number of the completers who discontinued the study treatment prematurely prior to Week 48 is 26 in Study 1 and 12 in Study 2. Among these completers, 17 subjects (17/26; 65%) in Study 1 and 7 subjects (7/12; 58%) in Study 2 received alternative anti-VEGF treatments prior to Week 48.

Subject disposition and primary reasons for study discontinuation at Week 96 are summarized in Table 6. In general, the proportion of subjects who completed the study is comparable between the brolucizumab 6mg arm and aflibercept 2mg arm: 84.2% vs. 82.3% in Study 1 and 91.9% vs. 88.7 % in Study 2. The proportion of subjects who discontinued the study due to adverse events is also comparable between the two arms: 2.2% vs. 3.3% in Study 1 and 2.4% vs. 1.1% in Study 2. For each study, only 2 subjects discontinued the study due to lack of efficacy.

None of the deaths during the study were suspected by the investigators to be related to study treatment except one case in the brolucizumab 3mg arm: this subject experienced a serious adverse event with a fatal outcome (cerebrovascular accident) in the second year of the study.

Table 6: Subject disposition (Week 96), n (%)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg	**Brolucizumab 6mg**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Aflibercept 2mg**
Randomized	**360 (100)**	**361 (100)**	**361 (100)**	**372 (100)**	**371 (100)**
Full Analysis Set	**358 (99.4)**	**360 (99.7)**	**360 (99.7)**	**370 (99.5)**	**369 (99.5)**
Subjects Completed Week 96					
Yes	**310 (86.1)**	**304 (84.2)**	**297 (82.3)**	**342 (91.9)**	**329 (88.7)**

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg	**Brolucizumab 6mg**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Aflibercept 2mg**
No	**50 (13.9)**	**57 (15.8)**	**64 (17.7)**	**30 (8.1)**	**42 (11.3)**
Adverse Event	9 (2.5)	8 (2.2)	12 (3.3)	9 (2.4)	4 (1.1)
Death	9 (2.5)	7 (1.9)	12 (3.3)	4 (1.1)	7 (1.9)
Lack of Efficacy	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.5)
Lost to Follow-Up	1 (0.3)	5 (1.4)	6 (1.7)	1 (0.3)	6 (1.6)
Physician Decision	2 (0.6)	2 (0.6)	8 (2.2)	0 (0.0)	1 (0.3)
Progressive Disease	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Withdrawal by Subject	26 (7.2)	34 (9.4)	23 (6.4)	12 (3.2)	21 (5.7)
Other	1 (0.3)	1 (0.3)	0 (0.0)	4 (1.1)	1 (0.3)
Treatment Discontinuation prior to Week 96	**63 (17.5)**	**68 (18.8)**	**80 (22.2)**	**43 (11.6)**	**52 (14.0)**
Adverse Event	14 (3.9)	13 (3.6)	14 (3.9)	20 (5.4)	9 (2.4)
Death	9 (2.5)	6 (1.7)	12 (3.3)	4 (1.1)	7 (1.9)
Lack of Efficacy	4 (1.1)	1 (0.3)	4 (1.1)	2 (0.5)	5 (1.3)
Lost to Follow-Up	1 (0.3)	5 (1.4)	6 (1.7)	1 (0.3)	6 (1.6)
Physician Decision	3 (0.8)	2 (0.6)	10 (2.8)	1 (0.3)	3 (0.8)
Progressive Disease	4 (1.1)	3 (0.8)	8 (2.2)	0 (0.0)	0 (0.0)
Protocol Deviation	1 (0.3)	1 (0.3)	2 (0.6)	0 (0.0)	1 (0.3)
Withdrawal by Subject	25 (6.9)	36 (10.0)	23 (6.4)	10 (2.7)	20 (5.4)
Other	2 (0.6)	1 (0.3)	1 (0.3)	5 (1.3)	1 (0.3)

Source: Table 14.1-1.2 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

In the primary efficacy analysis, the BCVA values at Week 48 are censored for the subjects who received alternative anti-VEGF treatments prior to Week 48. As shown in Table 7, the proportion of subjects who received alternative anti-VEGF treatments prior to Week 48 is very low: 0.8% ~ 3.6% in Study 1 and 1.4% in Study 2. Thus, the reviewer expects that the impact of censoring for these subjects on the primary efficacy results would be minimal.

Table 7: Number of subjects who received alternative anti-VEGF treatments

	Study 1			Study 2	
	Brolucizumab 3mg	**Brolucizumab 6mg**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Aflibercept 2mg**
Full Analysis Set	N = 358	N = 360	N = 360	N = 370	N = 369
Alternative anti-VEGF prior to Week 48					
Yes	3 (0.8)	4 (1.1)	13 (3.6)	5 (1.4)	5 (1.4)
No	355 (99.2)	356 (98.9)	347 (96.4)	365 (98.6)	364 (98.6)
Alternative anti-VEGF prior to Week 96					
Yes	9 (2.5)	8 (2.2)	18 (5.0)	10 (2.7)	8 (2.2)
No	349 (97.5)	352 (97.8)	342 (95.0)	360 (97.3)	361 (97.8)

† This table was produced by the reviewer.

Baseline demographic characteristics are summarized in Table 8. In general, the baseline demographic characteristics are similar between the treatment groups within each study. No notable imbalance is observed between the brolucizumab arms and aflibercept arm. The mean age is 76~77 in Study 1 and 75~76 in Study 2. In terms of sex, the proportion of female is slightly higher than that of male in both studies. In terms of race, most subjects are White (79%~84% in Study 1 and 91%~92% in Study 2). Most subjects identify themselves as neither Hispanic nor Latino.

Table 8: Baseline demographics (Full Analysis Set)

	Study 1			Study 2	
	Brolucizumab 3mg	**Brolucizumab 6mg**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Aflibercept 2mg**
Full Analysis Set	N = 358	N = 360	N = 360	N = 370	N = 369
Age (years)					
Mean (SD)	76.7 (8.3)	76.7 (8.9)	76.2 (8.8)	74.8 (8.6)	75.5 (7.9)
Median	78.0	78.0	77.0	75.0	76.0
Min, Max	50, 96	51, 97	51, 96	50, 94	52, 95
Sex, n (%)					
Female	210 (58.7)	205 (56.9)	194 (53.9)	210 (56.8)	212 (57.5)
Male	148 (41.3)	155 (43.1)	166 (46.1)	160 (43.2)	157 (42.5)
RACE, n (%)					
White	302 (84.4)	285 (79.2)	287 (79.7)	340 (91.9)	341 (92.4)
Asian	44 (12.3)	61 (16.9)	53 (14.7)	22 (5.9)	23 (6.2)
Black †	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)
American Indian ††	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Other	9 (2.5)	9 (2.5)	17 (4.7)	5 (1.4)	4 (1.1)
Multiple	1 (0.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Ethnicity, n (%)					
Hispanic or Latino	32 (8.9)	29 (8.1)	40 (11.1)	23 (6.2)	25 (6.8)
Not Hispanic or Latino	323 (90.2)	329 (91.4)	319 (88.6)	321 (86.8)	322 (87.3)
Not Reported	1 (0.3)	1 (0.3)	0 (0.0)	8 (2.2)	5 (1.4)
Unknown	2 (0.6)	1 (0.3)	1 (0.3)	18 (4.9)	17 (4.6)

† Black or African American; ††American Indian or Alaska Native
Source: Table 14.1-3.2 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

Baseline disease and ocular characteristics are summarized in Table 9. In general, the brolucizumab 6mg arm and aflibercept 2mg arm are comparable in terms of baseline disease and ocular characteristics. No notable differences between the two groups are observed.

Table 9: Baseline disease and ocular characteristics (Full Analysis Set)

	Study 1			Study 2	
	Brolucizumab 3mg	**Brolucizumab 6mg**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Aflibercept 2mg**
Full Analysis Set	N = 358	N = 360	N = 360	N = 370	N = 369
Previous Treatment for AMD					
Treated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Study 1			Study 2	
	Brolucizumab 3mg	**Brolucizumab 6mg**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Aflibercept 2mg**
Treatment Naive	358 (100.0)	360 (100.0)	360 (100.0)	370 (100.0)	369 (100.0)
Baseline BCVA (letters)					
Mean (SD)	61.0 (13.6)	60.8 (13.7)	60.0 (13.9)	61.5 (12.6)	60.8 (12.9)
Median	64.5	64.0	63.0	64.0	64.0
Min, Max	23, 85	23, 85	16, 83	22, 78	23, 79
Baseline BCVA Category					
<=55 letters	109 (30.4)	101 (28.1)	116 (32.2)	102 (27.6)	107 (29.0)
>=71 letters	111 (31.0)	102 (28.3)	91 (25.3)	97 (26.2)	92 (24.9)
56-70 letters	138 (38.5)	157 (43.6)	153 (42.5)	171 (46.2)	170 (46.1)
CSFT (µm) †					
Mean (SD)	466.6 (167.4)	463.1 (166.6)	457.9 (146.4)	473.6 (171.4)	465.3 (151.2)
Median	426.5	416.5	425.0	433.5	442.0
Min, Max	168, 1392	217, 1204	215, 1082	200, 1192	206, 1319
CSFT Category					
<400 µm	157 (43.9)	157 (43.6)	146 (40.6)	148 (40.0)	130 (35.2)
>=400 µm	201 (56.1)	203 (56.4)	214 (59.4)	222 (60.0)	239 (64.8)
Area of CNV † within a Lesion (mm^2)					
Mean (SD)	4.5 (4.7)	4.6 (4.1)	4.4 (3.7)	2.6 (2.8)	2.9 (3.9)
Median	3.2	3.4	3.7	1.5	1.6
Min, Max	0, 28	0, 20	0, 19	0, 14	0, 34
Type of CNV Group					
Minimally Classic	32 (8.9)	39 (10.8)	34 (9.4)	33 (8.9)	34 (9.2)
Occult	204 (57.0)	208 (57.8)	209 (58.1)	183 (49.5)	187 (50.7)
Predominantly Classic	122 (34.1)	113 (31.4)	116 (32.2)	154 (41.6)	144 (39.0)

† CSFT: Central Sub-Field Thickness; CNV: Choroidal Neo-Vascularization.
Source: Table 14.1-4.3 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

3.2.4 Results and Conclusions

Section 3.2.4.1 provides the efficacy results regarding BCVA change. Section 3.2.4.2 presents the proportion of subjects who remained on q12w treatment schedule through Week 96. Section 3.2.4.3 provides the efficacy results of anatomical parameters: CSFT change from baseline and fluid status. The reviewer's efficacy conclusion is provided in Section 3.2.4.4.

3.2.4.1 Change from Baseline in BCVA

Table 10 presents the primary analysis results of the primary efficacy endpoint: change from baseline in BCVA to Week 48. The two pivotal studies demonstrated that brolucizumab 6mg is noninferior to aflibercept 2mg with the NI margin of 4 letters. Specifically, in Study 1, the estimated mean BCVA change from baseline to Week 48 by the ANOVA model is 6.61 letters and 6.78 letters for the brolucizumab 6mg arm and aflibercept 2mg arm, respectively. In Study 2, it is 6.91 letters and 7.61 letters for the brolucizumab 6mg arm and aflibercept 2mg arm, respectively. The treatment difference (brolucizumab 6mg - aflibercept 2mg) is -0.16 [95% CI: (-**2.13**, 1.80)] in Study 1 and -0.70 [95% CI: (-**2.39**, 1.00)] in Study 2. The lower bounds of the 95% CIs for the treatment differences are larger than -4 letters, which demonstrates statistical noninferiority of brolucizumab 6mg to aflibercept 2mg. In Study 1, brolucizumab 3mg is also

noninferior to aflibercept 2mg: 6.14 letters vs. 6.77 letters. The treatment difference between the brolucizumab 3mg arm and aflibercept 2mg arm is -0.62 [95% CI: (**-2.54**, 1.29)]. See Figure 2 for a graphical presentation of the mean change in BCVA from baseline over time.

Table 10: Primary analysis results for mean change in BCVA from baseline to Week 48 (FAS with LAO[1])

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg (N=358)	**Brolucizumab 6mg (N=360)**	**Aflibercept 2mg (N=360)**	**Brolucizumab 6mg (N=370)**	**Aflibercept 2mg (N=369)**
Baseline BCVA					
Mean (SD)	61.0 (13.6)	60.8 (13.7)	60.0 (13.9)	61.5 (12.6)	60.8 (12.9)
Median	64.5	64.0	63.0	64.0	64.0
Min, Max	23, 85	23, 85	16, 83	22, 78	23, 79
BCVA change from baseline					
A. Descriptive Statistics					
Number of LAO [2]	34	38	50	21	24
Mean (SD)	5.94 (13.49)	6.42 (14.40)	6.97 (13.16)	6.93 (11.47)	7.60 (12.47)
Median	7	8	8	8	8
Min, Max	-57, 51	-69, 52	-57, 54	-57, 38	-37, 50
B. Pairwise ANOVA [3]					
LS Mean (SE)					
BRO 3 mg vs. AFL 2mg	6.14 (0.69)		6.77 (0.69)		
BRO 6 mg vs. AFL 2mg		6.61 (0.71)	6.78 (0.71)	6.91 (0.61)	7.61 (0.61)
LS Mean Difference	**-0.62**	**-0.16**		**-0.70**	
95% CI	**(-2.54, 1.29)**	**(-2.13, 1.80)**		**(-2.39, 1.00)**	
NI p-value	0.0003	<.0001		<.0001	

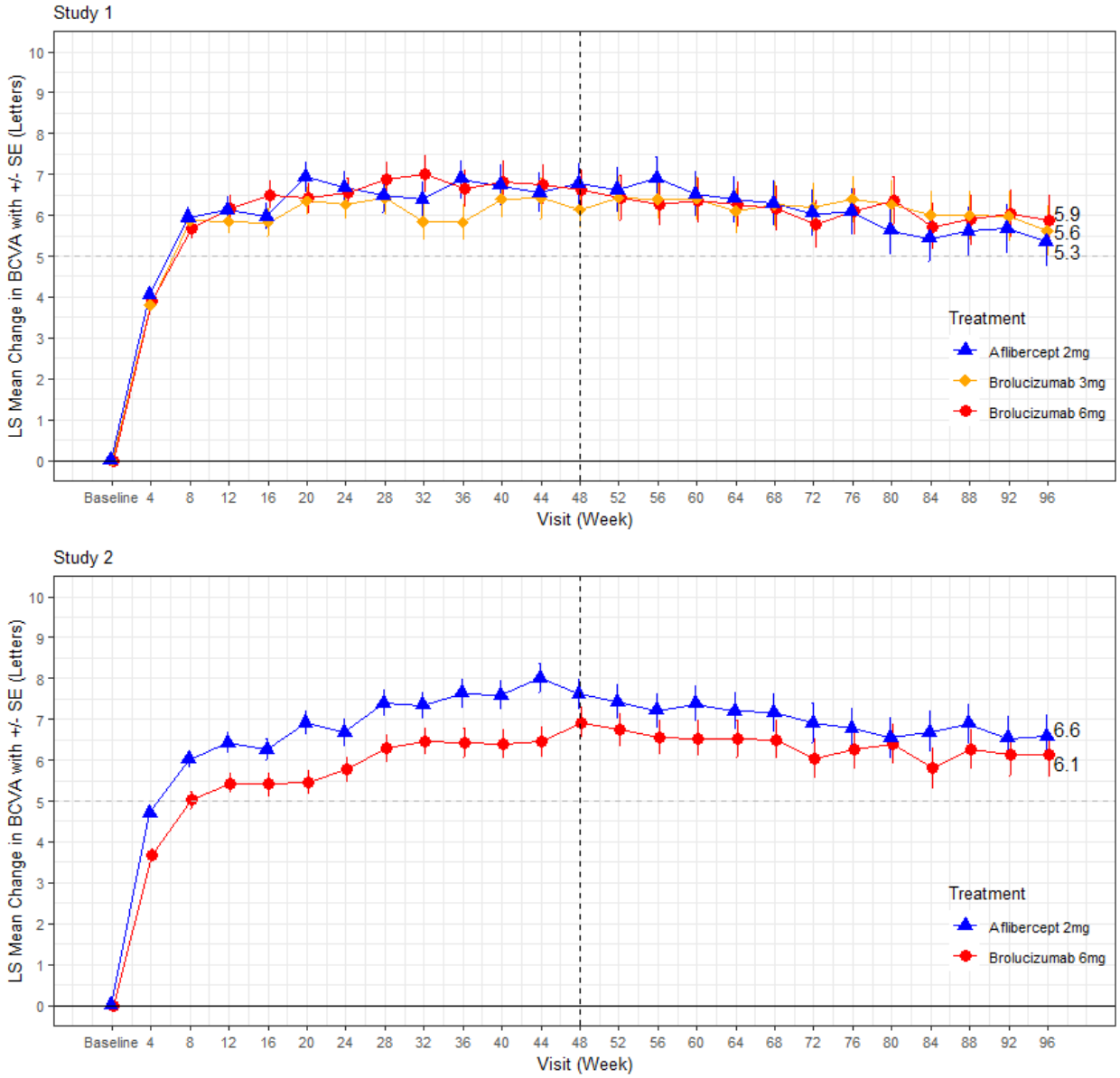
[1] FAS: full analysis set including all randomized subjects who received at least 1 injection of study treatment;
LAO: the last available observation (LAO) prior to start of alternative anti-VEGF treatments was used if a subject received alternative anti-VEGF treatments. Missing values were also imputed by the LAO prior to missed assessments.
[2] Number of subjects who's the LAO other than Week 48 values were used in the analysis.
[3] LS Mean: Least squares mean; SE: Standard error; BRO: Brolucizumab; AFL: Aflibercept; CI: confidence interval.
Source: Table 14.2-1.1 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

In the reviewer's supportive analysis where the censoring was not applied to the subjects who received alternative anti-VEGF treatments prior to Week 48 (Table 27 of Appendix D), the treatment difference (brolucizumab 6mg - aflibercept 2mg) is -0.02 [95% CI: (**-2.00**, 1.96)] in Study 1 and -0.63 [95% CI: (**-2.32**, 1.05)] in Study 2. Although the treatment differences in this supportive analysis are slightly smaller (about 0.1 letter) than those in the primary analysis, the impact of the censoring for subjects with alternative anti-VEGF treatments on the primary efficacy results appears minimal.

The results of a supportive analysis performed on the PPS can be found in Table 28 of Appendix D. The results of this supportive analysis are consistent with the primary analysis results. Specifically, in this supportive analysis, the treatment difference (brolucizumab 6mg - aflibercept 2mg) is -0.29 [95% CI: (**-2.38**, 1.79)] and -0.78 [95% CI: (**-2.51**, 0.95)] in Study 1 and Study 2, respectively. Further supportive results by the MMRM models can be found in Table 29 and Table 30 of Appendix D. The supportive results by the MMRM models are also consistent with the primary efficacy results.

Figure 2 depicts the mean change in BCVA from baseline over time (up to 96 weeks). The mean change at each visit is estimated by fitting the same ANOVA model for the primary endpoint separately at each visit. In Study 1, all three treatment groups show similar patterns over time in terms of BCVA change. In Study 2, the aflibercept 2mg group shows slightly larger BCVA improvement than that observed in the brolucizumab 6mg group. However, it appears that the difference between the two groups becomes smaller after 1 year. See Table 31 - Table 33 in Appendix D for numerical summaries of these mean changes in BCVA over time.

Figure 2: Mean change in BCVA[1] from baseline by visits (FAS with LAO [2])

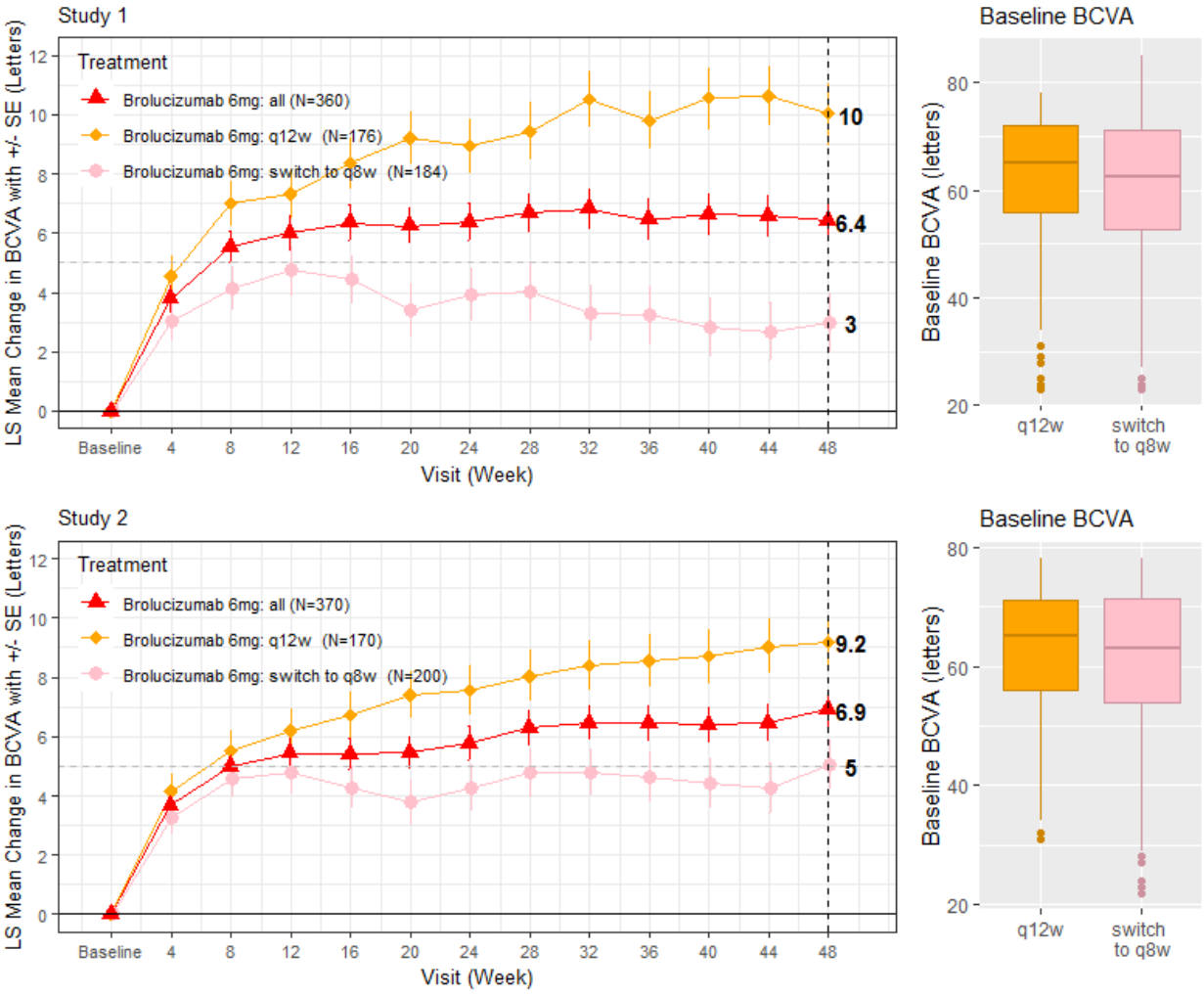


[1] The mean changes were obtained by fitting ANOVA model separately at each time point. The ANOVA model included treatment, baseline BCVA categories, and age categories.
[2] LAO: the last available observation (LAO) prior to start of alternative anti-VEGF treatments was used if a subject received alternative anti-VEGF treatments. Missing values were also imputed by the LAO prior to missed assessments.
Source: Figure 3-2 of the Summary of Clinical Efficacy. Figure was produced by the reviewer.

Recall that the subjects in the brolucizumab arms received injections every 12 weeks (q12w). However, if disease activity was identified during the study, they received injections every 8 weeks (q8w) thereafter. Figure 3 depicts mean change in BCVA from baseline over time (up to 48 weeks) by the following three groups:

- Entire brolucizumab 6mg group (referred to as 'Brolucizumab 6mg: all' in the figure)
- Group A: subgroup of subjects in the brolucizumab 6mg arm who remained on q12w treatment up to Week 48 (referred to as 'Brolucizumab 6mg: q12w' in the figure)
- Group B: subgroup of subjects in the brolucizumab 6mg arm who switched to q8w treatment prior to Week 48 (referred to as 'Brolucizumab 6mg: switch to q8w' in the figure)

Figure 3: Mean change from baseline in BCVA by q12w treatment status (FAS with LAO[2]) [1]



[1] The group 'Brolucizumab 6mg: q12w' is the subgroup of subjects in the brolucizumab 6mg arm who remained on q12w treatment up to Week 48. The group 'Brolucizumab 6mg: switch to q8w' is the subgroup of subjects in the brolucizumab 6mg arm who switched to q8w treatment within Week 48.
[2] LAO: the last available observation (LAO) prior to start of alternative anti-VEGF treatments was used if a subject received alternative anti-VEGF treatments. Missing values were also imputed by the LAO prior to missed assessments.
Figure was produced by the reviewer.

The number of subjects in Group A (the number of subjects in the brolucizumab 6mg arm who remained on q12w treatment up to Week 48) was 176 (49%) in Study 1 and 170 (46%) in Study 2. For Figure 3, subjects with any missing DAAs and subjects with over-treatment (more active injections than q8w schedule) were considered as subjects who switch to q8w treatment. This approach is referred to as the 'conservative approach' in the CSRs. See Section 3.2.4.2 and Appendix G for further evaluation of these proportions.

As in Figure 3, Group A (yellow) shows better BCVA improvement than that for Group B (pink). Such difference between these two subgroups are somewhat expected. Subjects in Group A did not experience a BCVA loss of ≥ 5 letters within Week 48 to remain on the q12w schedule. On the other hand, most subjects in Group B experienced a BCVA loss of ≥ 5 letters and thus switched to q8w dosing schedule.

Table 11 summarizes baseline ocular characteristics in the brolucizumab 6mg arm by the q12w status at Week 48. On average, the subgroup of subjects who switched to the q8w dosing schedule tends to have numerically worse baseline ocular characteristics compared to those for the subgroup of subjects who remained on the q12w dosing schedule as follows:

(1) BCVA: 59.4 vs. 62.3 in Study 1 and 60.2 vs. 63.1 in Study 2
(2) CSFT: 462 vs. 387 in Study 1 and 509 vs. 432 in Study 2
(3) Area of CNV: 5.4 vs. 3.7 in Study 1 and 3.0 vs. 2.2 in Study 2

Table 11: Baseline ocular characteristics in brolucizumab 6mg arm by q12w status

	Study 1 brolucizumab 6mg		**Study 2 brolucizumab 6mg**	
	switch to q8w [1]	**q12w [2]**	**switch to q8w**	**q12w**
Full Analysis Set	N = 184	N = 176	N = 200	N = 170
Baseline BCVA				
Mean (SD)	59.4 (14.7)	62.3 (12.3)	60.2 (13.6)	63.1 (11.1)
Median	62.5	65.0	63.0	65.0
Min, Max	23, 85	23, 78	22, 78	31, 78
Baseline BCVA Category				
<=55 letters	58 (31.5)	43 (24.4)	64 (32.0)	38 (22.4)
>=71 letters	50 (27.2)	52 (29.5)	53 (26.5)	44 (25.9)
56-70 letters	76 (41.3)	81 (46.0)	83 (41.5)	88 (51.8)
CSFT (µm) †				
Mean (SD)	507.6 (191.3)	416.6 (120.1)	509.2 (175.0)	431.7 (157.5)
Median	462.0	386.5	478.5	392.0
Min, Max	221, 1204	217, 1043	200, 1192	221, 1182
CSFT Category				
<400 µm	59 (32.1)	98 (55.7)	61 (30.5)	87 (51.2)
>=400 µm	125 (67.9)	78 (44.3)	139 (69.5)	83 (48.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Area of CNV † within a Lesion (mm^2)				
Mean (SD)	5.4 (4.4)	3.7 (3.5)	3.0 (2.9)	2.2 (2.5)
Median	4.4	2.7	2.1	1.2
Min, Max	0, 20	0, 19	0, 14	0, 14

	Study 1 brolucizumab 6mg		Study 2 brolucizumab 6mg	
	switch to q8w [1]	q12w [2]	switch to q8w	q12w

† CSFT: Central Sub-Field Thickness; CNV: Choroidal Neo-Vascularization.
[1] switch to q8w: subgroup of subjects in the brolucizumab 6mg arm who switched to q8w treatment within Week 48
[2] q12w: subgroup of subjects in the brolucizumab 6mg arm who remained on q12w treatment up to Week 48
Source: This table was produced by the reviewer.

It is unclear whether more frequent injections (q8w) than the originally scheduled injections (q12w) were beneficial for the subjects in Group B. The reviewer does not think that one can reliably answer this question using the current data. This is mainly because we have not observed potential outcomes if they would have received injections every 12 weeks as originally scheduled.

Recall that the first key secondary endpoint is the average change in BCVA from baseline over the period of Week 36 through Week 48. The two studies demonstrated statistical noninferiority of brolucizumab 6mg to aflibercept 2mg with the NI margin of 4 letters in terms of the first key secondary endpoint (Table 12). The treatment difference (brolucizumab 6mg - aflibercept 2mg) is -0.03 [95% CI: (**-1.96**, 1.86)] in Study 1 and -1.16 [95% CI: (**-2.78**, 0.45)] in Study 2.

Table 12: Average change in BCVA from baseline over Week 36 through Week 48 (FAS with LAO[3])

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg	Brolucizumab 6mg	Aflibercept 2mg	Brolucizumab 6mg	Aflibercept 2mg
Descriptive Statistics					
N	358	360	360	370	369
Mean (SD)	5.99 (13.37)	6.51 (13.85)	6.93 (12.61)	6.56 (11.10)	7.70 (11.81)
Median	7	7	8	8	8
Min, Max	-64, 54	-67, 50	-52, 52	-58, 37	-38, 47
Pairwise ANOVA [1]					
LS Mean (SE) [2]					
BRO 3 mg vs. AFL 2mg	6.20 (0.67)		6.72 (0.67)		
BRO 6 mg vs. AFL 2mg		6.71 (0.68)	6.73 (0.68)	6.54 (0.58)	7.71 (0.58)
LS Mean Difference	**-0.52**	**-0.03**		**-1.16**	
95% CI	**(-2.38, 1.34)**	**(-1.91, 1.86)**		**(-2.78, 0.45)**	
NI p-value	0.0001	<.0001		0.0003	

[1] ANOVA model with treatment, baseline BCVA categories, and age categories
[2] BRO: Brolucizumab; AFL: Aflibercept
[3] LAO: the last available observation (LAO) prior to start of alternative anti-VEGF treatments was used if a subject received alternative anti-VEGF treatments. Missing values were also imputed by the LAO prior to missed assessments.
Source: Table 14.2-2.1 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

In this review, a subject with BCVA gain of ≥ 15 letters from baseline is referred to as a 'responder'. Table 13 presents proportions of responders at Week 48 and Week 96. Note that subjects with BCVA of ≥ 84 letters are also considered as responders as planned in the SAPs. In this table, the first two columns under 'Observed' present the results using observed data where subjects with unavailable BCVA assessments are excluded. The next two columns under 'LAO' show the results using the last available observation (LAO): BCVA values after starting alternative anti-VEGF therapies or missing BCVA values were imputed by the last available

BCVA values prior to occurrence of those events. The last three columns under 'Logistic Regression' present the responder rates adjusted by baseline factors using the logistic regression with the LAO.

In Study 1, the adjusted proportion of responders by the logistic regression is slightly higher in the brolucizumab 6mg arm compared to that in the aflibercept 2mg arm: 33.6% vs. 25.4% at Week 48 and 34.2% vs. 27.0% at Week 96. However, in Study 2, the adjusted responder rates are similar between the two groups: 29.3% vs. 29.9% at Week 48 and 29.1% vs. 31.4% at Week 96. See Table 34 and Table 35 of Appendix F for the rates of responders at each post-baseline visit.

Table 13: Proportion of subjects either with BCVA gain of ≥ 15 letters or with BCVA of ≥ 84 letters (FAS)

	Observed [1], n/N (%)		LAO[3], n/N (%)		Logistic Regression [4], %		
	AFL2 [2]	BRO6 [2]	AFL2	BRO6	AFL2	BRO6	Difference (95% CI)
Study 1							
Week 48	90/320 (28.1)	116/326 (35.6)	93/360 (25.8)	119/360 (33.1)	25.4	33.6	8.2 (2.2, 15.0)
Week 96	94/297 (31.6)	112/304 (36.8)	99/360 (27.5)	121/360 (33.6)	27.0	34.2	7.2 (1.4, 13.8)
Study 2							
Week 48	107/349 (30.7)	104/352 (29.5)	110/369 (29.8)	109/370 (29.5)	29.9	29.3	-0.6 (-7.1, 5.8)
Week 96	112/329 (34.0)	103/342 (30.1)	116/369 (31.4)	108/370 (29.2)	31.5	29.1	-2.4 (-8.8, 4.1)

[1] Subjects with BCVA assessments. [2] AFL2: Aflibercept 2mg; BRO6: Brolucizumab 6mg.
[3] LAO: the last available observation (LAO) prior to start of alternative anti-VEGF treatments was used if a subject received alternative anti-VEGF treatments. Missing values were also imputed by the LAO prior to missed assessments.
[4] Logistic regression model included baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment. The model was fitted separately at each week using the FAS with LOCF. The 95% CI (confidence interval) for the difference was estimated by a bootstrap method based on 1000 bootstrap samples.
Source: Table 14.2-25.1 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

Table 14 presents proportion of subjects with BCVA loss of ≥ 15 letters at Week 48 and Week 96. In this review, a subject with BCVA loss of ≥ 15 letters from baseline is referred to as a 'non-responder'. The adjusted proportions of non-responders at Week 48 by the logistic model are comparable between the brolucizumab 6mg arm and the aflibercept 2mg arm: 6.4% vs. 5.5% in Study 1 and 3.8% vs. 4.8% in Study 2. Proportions of non-responders at Week 96 are slightly higher (ranging from 7% to 8%) than those at Week 48. See Table 36 and Table 37 of Appendix F for the proportion of non-responders at each post-baseline visit.

Table 14: Proportion of subjects with BCVA loss of ≥ 15 letters (FAS)

	Observed [1], n/N (%)		LAO[3], n/N (%)		Logistic Regression [4], %		
	AFL2 [2]	BRO6 [2]	AFL2	BRO6	AFL2	BRO6	Difference (95% CI)
Study 1							
Week 48	19/320 (5.9)	19/326 (5.8)	20/360 (5.6)	23/360 (6.4)	5.5	6.4	0.9 (-2.7, 4.3)
Week 96	23/297 (7.7)	17/304 (5.6)	27/360 (7.5)	29/360 (8.1)	7.4	8.1	0.7 (-3.6, 4.6)
Study 2							
Week 48	18/349 (5.2)	8/352 (2.3)	18/369 (4.9)	14/370 (3.8)	4.8	3.8	-1.0 (-3.9, 2.2)
Week 96	26/329 (7.9)	19/342 (5.6)	28/369 (7.6)	26/370 (7.0)	7.5	7.1	-0.4 (-3.8, 3.3)

[1] Subjects with BCVA assessments. [2] AFL2: Aflibercept 2mg; BRO6: Brolucizumab 6mg.

[3] LAO: the last available observation (LAO) prior to start of alternative anti-VEGF treatments was used if a subject received alternative anti-VEGF treatments. Missing values were also imputed by the LAO prior to missed assessments.
[4] Logistic regression model included baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment. The model was fitted separately at each week using the FAS with LOCF. The 95% CI (confidence interval) for the difference was estimated by a bootstrap method based on 1000 bootstrap samples.
Source: Table 14.2-27.1 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

3.2.4.2 Q12w Treatment Status

Recall that the second and third secondary endpoints are as follows:

- q12w treatment status at Week 48 for subjects randomized to brolucizumab
- q12w treatment status at Week 48 for subjects who are randomized to brolucizumab and have no q8-need during the first q12 cycle (Week 16, Week 20)

The primary analyses of these endpoints are performed using the Kaplan-Meier method for time to the first 'q8w-need' event as planned in the SAPs. Table 15 presents the results of the Kaplan-Meier analysis with the 'efficacy/safety' approach for intercurrent events (see Section 3.2.2). Within the brolucizumab 6mg arm, the estimated probability that a subject remained on q12w treatment schedule at Week 48 is 0.56 [95% CI: (0.50, 0.61)] for Study 1 and 0.51 [95% CI: (0.46, 0.56)] for Study 2. At Week 96, this probability is 0.45 [95% CI: (0.40, 0.51)] for Study 1 and 0.39 [95% CI: (0.33, 0.44)] for Study 2.

Table 15: Time to first q8w need (brolucizumab 6mg)

	Study 1			Study 2		
Week	**N.risk[1]**	**N.event[2]**	**Probability of remaining on q12w (95% CI)[3]**	**N risk[1]**	**N.event[2]**	**Probability of remaining on q12w (95% CI)[3]**
16	346	83	0.76 (0.71, 0.80)	364	83	0.77 (0.73, 0.81)
20	259	37	0.65 (0.60, 0.70)	273	52	0.62 (0.57, 0.67)
28				220	13	0.59 (0.54, 0.64)
32	217	19	0.59 (0.54, 0.64)	201	11	0.56 (0.50, 0.61)
40				189	6	0.54 (0.48, 0.59)
44	**188**	**12**	**0.56 (0.50, 0.61)**	**179**	**9**	**0.51 (0.46, 0.56)**
52				169	5	0.50 (0.44, 0.55)
56	168	18	0.50 (0.44, 0.55)	162	10	0.47 (0.41, 0.52)
64				150	6	0.45 (0.39, 0.50)
68	142	4	0.48 (0.43, 0.54)	143	4	0.43 (0.38, 0.49)
76				138	4	0.42 (0.37, 0.47)
80	133	6	0.46 (0.41, 0.51)	132	6	0.40 (0.35, 0.45)
88				119	5	0.39 (0.33, 0.44)
92	**124**	**2**	**0.45 (0.40, 0.51)**	**119**	**5**	**0.39 (0.33, 0.44)**

[1] N.risk: Number of subjects at risk; [2] N.event: Number of subjects with q8 need among the subjects at risk.
[3] Probability of remaining on q12 treatment estimated by Kaplan-Meier analysis (95% confidence interval).
Source: Table 14.2-6.1 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

The results of the supportive analyses can be found in Appendix G. One of the supportive analyses is the 'conservative approach' where all missing DAAs and active treatments other than the scheduled ones are considered as negative q12 status. In this approach, the proportion of subjects who remained on q12 treatment at Week 48 is 48.9% [95% CI: (43.6%, 54.2%)] for

Study 1 and 45.9% [95% CI: (40.8%, 51.2%)] for Study 2. Even for the conservative approach, the proportion of subjects who remained on the q12w dosing schedule is approximately 50%. See Appendix G for further details of supportive analyses.

The Kaplan-Meier analysis is also performed for the subgroup of subjects who had no q8w-need during the first 12 cycle (Week16 and Week 20). Table 16 presents the results of this analysis. Within this subgroup, the estimated probability that a subject remains on q12w treatment at Week 48 is 0.85 [95% CI: (0.80, 0.90)] for Study 1 and 0.82 [95% CI: (0.76, 0.86)] for Study 2. These results may indicate that subjects with no q8w-need during the first q12 cycle are likely to remain on q12w dosing schedule up to Week 48 with high chance (0.85 in Study 1 and 0.82 in Study 2). At Week 96, this probability is 0.70 [95% CI: (0.63, 0.76)] for Study 1 and 0.62 [95% CI: (0.55, 0.62)] for Study 2. The supportive analysis results for this endpoint can be found in Appendix G.

Table 16: Time to first q8w need in subjects with no q8w need during the 1st q12w cycle (brolucizumab 6mg)

	Study 1			Study 2		
Week	**N.risk[1]**	**N.event[2]**	**Probability of remaining on q12w (95% CI) [3]**	**N risk[1]**	**N.event[2]**	**Probability of remaining on q12w (95% CI) [3]**
28				220	13	0.94 (0.90, 0.97)
32	217	19	0.91 (0.87, 0.94)	201	11	0.89 (0.84, 0.92)
40				189	6	0.86 (0.81, 0.90)
44	**188**	**12**	**0.85 (0.80, 0.90)**	**179**	**9**	**0.82 (0.76, 0.86)**
52				169	5	0.79 (0.73, 0.84)
56	168	18	0.76 (0.70, 0.82)	162	10	0.74 (0.68, 0.80)
64				150	6	0.71 (0.65, 0.77)
68	142	4	0.74 (0.68, 0.80)	143	4	0.69 (0.63, 0.75)
76				138	4	0.67 (0.61, 0.73)
80	133	6	0.71 (0.64, 0.77)	132	6	0.64 (0.57, 0.71)
88				119	5	0.62 (0.55, 0.68)
92	**124**	**2**	**0.70 (0.63, 0.76)**	**119**	**5**	**0.62 (0.55, 0.68)**

[1] N.risk: Number of subjects at risk; [2] N.event: Number of subjects with q8 need among the subjects at risk.
[3] Probability of remaining on q12 treatment estimated by Kaplan-Meier analysis (95% confidence interval).
Source: Table 14.2-6.3 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

The Kaplan-Meier analysis is also performed for the subgroup of subjects who had no q8w-need through Week 48. Within this subgroup, the estimated probability that a subject remains on q12w treatment at Week 96 is 0.82 [95% CI: (0.75, 0.87)] for Study 1 and 0.75 [95% CI: (0.78, 0.81)] for Study 2. Thus, it appears that a subject tends to remain on the q12w treatment until Week 96 once he/she had no q8w-need within Week 48.

3.2.4.3 Exploratory Efficacy Endpoints

This section presents the analysis results for the following secondary endpoints:

- Change in central subfield thickness (CSFT) from baseline to Weeks 16, 48, and 96

- Proportion of subjects with intra-retinal fluid (IRF) and/or sub-retinal fluid (SRF) at Weeks 16, 48, and 96
- Proportion of subjects with sub-RPE (subretinal pigment epithelium) fluid at Weeks 16, 48, and 96

Change in CSFT from baseline to Weeks 16, 48, and 96

Table 17 presents the analysis results for CSFT change from baseline. The CSFT reduction at Week 16 estimated by the ANOVA is larger for the brolucizumab 6mg arm compared to that for the aflibercept 2mg arm: -161.4 vs. -133.4 in Study 1 and -174.4 vs. -134.2 in Study 2. This reduction is maintained or slightly improved through Week 96 in all arms. Note that Study 1 had a proper multiplicity adjustment for testing the CSFT change from baseline at Weeks 16 and 48 while Study 2 had no multiplicity adjustment for these endpoints. See Appendix C for further details regarding the multiplicity adjustment performed in Study 1.

Table 17: Mean change from baseline in CSFT (FAS)

	Study 1			Study 2	
	BRO3 [2]	**BRO6** [2]	**AFL2** [2]	**BRO6** [2]	**AFL2** [2]
Baseline CSFT					
N	358	360	360	370	369
Mean (SD)	466.6 (167.4)	463.1 (166.6)	457.9 (146.4)	473.6 (171.4)	465.3 (151.2)
Mean change from Baseline					
Week 16					
N	358 (11)	360 (15)	360 (19)	370 (13)	369 (15)
Mean (SD)	-151.70 (145.40)	-159.62 (133.91)	-135.11 (132.61)	-170.92 (152.48)	-137.68 (136.76)
LS Mean (SE) [1]					
BRO3 vs. AFL2	-153.30 (6.54)		-133.41 (6.52)		
BRO6 vs. AFL2		**-161.37 (6.22)**	**-133.55 (6.22)**	**-174.42 (6.71)**	**-134.17 (6.72)**
LS Mean Difference	-19.88	**-27.81**		**-40.25**	
95% CI	(-38.02, -1.75)	**(-45.08, -10.55)**		**(-58.90, -21.59)**	
p-value	0.0316	**0.0016**		**<.0001**	
Week 48					
N	358 (35)	360 (41)	360 (50)	370 (22)	369 (24)
Mean (SD)	-165.65 (152.60)	-170.76 (142.58)	-145.42 (145.57)	-189.83 (158.35)	-147.84 (144.97)
LS Mean (SE) [1]					
BRO3 vs. AFL2	-167.42 (6.93)		-143.55 (6.91)		
BRO6 vs. AFL2		**-172.77 (6.70)**	**-143.72 (6.70)**	**-193.79 (6.84)**	**-143.87 (6.84)**
LS Mean Difference	-23.86	**-29.04**		**-49.92**	
95% CI	(-43.07, -4.66)	**(-47.63, -10.45)**		**(-68.91, -30.93)**	
p-value	0.0149	**0.0022**		**<.0001**	
Week 96					
N	358 (60)	360 (69)	360 (78)	370 (38)	369 (49)
Mean (SD)	-177.77 (155.03)	-172.85 (156.38)	-150.66 (154.86)	-193.62 (163.97)	-159.25 (146.26)
LS Mean (SE) [1]					
BRO3 vs. AFL2	-179.68 (7.08)		-148.75 (7.06)		
BRO6 vs. AFL2		**-174.77 (7.27)**	**-148.74 (7.27)**	**-197.75 (6.97)**	**-155.12 (6.98)**
LS Mean Difference	-30.93	**-26.03**		**-42.63**	
95% CI	(-50.55, -11.31)	**(-46.21, -5.86)**		**(-61.98, -23.27)**	

	Study 1			Study 2	
	BRO3 [2]	**BRO6** [2]	**AFL2** [2]	**BRO6** [2]	**AFL2** [2]
p-value	0.0020	**0.0115**		**<.0001**	

[1] ANOVA model with treatment, baseline CST total categories, and age categories
[2] BRO3: Brolucizumab 3mg; BRO6: Brolucizumab 6mg; AFL: Aflibercept 2mg.
Source: Table 14.2-15.1 and Table 14.2-15.1_y2 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

Proportion of subjects with IRF and/or SRF at Weeks 16, 48, and 96

Table 18 presents proportion of subjects with IRF and/or SRF. In both pivotal studies, the brolucizumab 6mg arm shows lower proportion of subjects with IRF and/or SRF compared to that in the aflibercept 2mg arm: (1) 33.9% vs. 52.2% in Study 1 and 29.4% vs. 45.1% in Study 2 at Week 16, (2) 31.2% vs. 44.6% in Study 1 and 25.8% vs. 43.9% in Study 2 at Week 48, and (3) 24.0% vs. 36.9% in Study 1 and 24.4% vs. 38.5% in Study 2 at Week 96.

Table 18: Proportion of subjects with IRF and/or SRF (FAS), %

	Study 1			Study 2		
	Aflibercept 2mg	**Brolucizumab 6mg**	**Difference (95% CI)**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Difference (95% CI)**
Week 16	52.2	33.9	-18.2 (-25.3, -10.9)	45.1	29.4	-15.7 (-22.9, -9.0)
Week 48	44.6	31.2	-13.5 (-20.7, -6.1)	43.9	25.8	-18.1 (-24.9, -11.8)
Week 96	36.9	24.0	-12.9 (-19.7, -6.6)	38.5	24.4	-14.1 (-21.3, -7.2)

The proportions were estimated by ANOVA models including treatment, baseline fluid status, and age categories.
Source: Table 14.2-34.1 and Table 14.2-34.1_y2 of the clinical study reports for Study1 and Study 2. This table was produced by the reviewer.

Proportion of subjects with sub-RPE-fluid at Weeks 16, 48, and 96

Table 19 presents proportion of subjects with sub-RPE-fluid. In both pivotal studies, the brolucizumab 6mg arm shows lower proportion of subjects with sub-RPE-fluid compared to that in the aflibercept 2mg arm: (1) 18.7% vs. 27.3% in Study 1 and 16.0% vs. 23.8% in Study 2 at Week 16, (2) 13.5% vs. 21.6% in Study 1 and 12.9% vs. 22.0% in Study 2 at Week 48, and (3) 10.9% vs. 14.7% in Study 1 and 16.5% vs. 22.4% in Study 2 at Week 96.

Table 19: Proportion of subjects with sub-RPE-fluid (FAS), %

	Study 1			Study 2		
	Aflibercept 2mg	**Brolucizumab 6mg**	**Difference (95% CI)**	**Aflibercept 2mg**	**Brolucizumab 6mg**	**Difference (95% CI)**
Week 16	27.3	18.7	-8.6 (-14.4, -2.9)	23.8	16.0	-7.8 (-13.0, -2.7)
Week 48	21.6	13.5	-8.1 (-13.6, -2.7)	22.0	12.9	-9.2 (-13.8, -3.9)
Week 96	14.7	10.9	-3.8 (-8.5, 0.8)	22.4	16.5	-5.9 (-11.5, -0.3)

The proportions were estimated by ANOVA models including treatment, baseline fluid status, and age categories.
Source: Table 14.2-32.1 and Table 14.2-32.1_y2 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

3.2.4.4 Efficacy Conclusion

The two pivotal studies provide adequate statistical evidence demonstrating that brolucizumab 6mg is effective for improving visual acuity in subjects with nAMD. In terms of the BCVA

change from baseline to Week 48, brolucizumab 6mg is statistically noninferior to aflibercept 2mg with an NI margin of ≥ 3 letters. Most of the BCVA improvement observed at Week 48 was maintained through Week 96. The proportions of subjects with BCVA gain of ≥ 15 letters at Weeks 48 and 96 are also comparable between the brolucizumab 6mg arm and the aflibercept 2mg arm. In addition, the two pivotal studies provide supportive evidence showing that anatomical outcomes in the brolucizumab 6mg arm are comparable to or slightly better than those in the aflibercept 2mg arm: the brolucizumab 6mg arm shows larger reduction in central subfield thickness and lower proportion of subjects with intra-retinal fluid and/or sub-retinal fluid at Week 48.

3.3 Evaluation of Safety

In this section, high-level summaries of adverse events are provided; see the FDA medical reviews for a comprehensive safety evaluation.

3.3.1 Extent of Exposure

Table 20 presents a summary of the number of active injections prior to Week 48. Most subjects in the brolucizumab 6mg arm received 6 active injections (59.7% in Study 1 and 54.9% in Study 2) as a result of the q12w dosing schedule. However, the majority of subjects in the aflibercept 2mg arm received 7 active injections (81.4% in Study 1 and 90.2% in Study 2) as a result of the q8w dosing schedule.

Table 20: Number of active injections prior to Week 48

	Study 1			Study 2	
	AFL2[1]	**BRO3**[1]	**BRO6**[1]	**AFL2**	**BRO6**
Safety Analysis Set	N = 360	N = 358	N = 360	N = 369	N = 370
Number of injections					
1	8 (2.2)	0 (0.0)	3 (0.8)	2 (0.5)	1 (0.3)
2	3 (0.8)	3 (0.8)	4 (1.1)	3 (0.8)	2 (0.5)
3	6 (1.7)	8 (2.2)	9 (2.5)	6 (1.6)	11 (3.0)
4	14 (3.9)	7 (2.0)	8 (2.2)	2 (0.5)	2 (0.5)
5	7 (1.9)	21 (5.9)	12 (3.3)	5 (1.4)	6 (1.6)
6	29 (8.1)	195 (54.5)	215 (59.7)	17 (4.6)	203 (54.9)
7	293 (81.4)	124 (34.6)	109 (30.3)	333 (90.2)	145 (39.2)
8	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

[1] AFL2: Aflibercept 2mg; BRO3: Brolucizumab 3mg; BRO6: Brolucizumab 6mg
Source: Table 14.1-1.1.1 of the CSRs for Study 1 and Study 2.

See Table 44 in Appendix H for a summary of the number of active injections throughout the study. The majority of aflibercept 2mg subjects received 13 active injections during the study: 67.5% in Study 1 and 78.6% in Study 2. On the other hand, only 24.4% of brolucizumab 6mg subjects in Study 1 and 34.1% of brolucizumab 6mg subjects in Study 2 received 13 active injections during the study. The proportion of brolucizumab 6mg subjects who received 10 active injections as planned in the q12w dosing schedule was 39.2% in Study 1 and 34.3% in Study 2.

3.3.2 Summary of Adverse Events

Table 21 presents a summary of ocular adverse events (AE). For both studies, the proportions of subjects with ocular AEs up to Week 48 are comparable between the aflibercept 2mg arm and the brolucizumab 6mg arm: 47.2% vs. 49.7% in Study 1 and 32.2% vs. 33% in Study 2. The proportions of subjects with AEs up to Week 96 are also comparable between the two arms. No notable imbalance between the treatment groups is observed. No ocular AEs resulted in death.

Table 21: Summary of ocular adverse events (AEs)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1]	**BRO3**[1]	**BRO6**[1]	**AFL2**	**BRO6**
Safety Analysis Set	360	358	360	369	370
Up to Week 48					
Subjects with AE	170 (47.2%)	175 (48.9%)	179 (49.7%)	119 (32.2%)	122 (33%)
Subjects with Serious AE	3 (0.8%)	5 (1.4%)	11 (3.1%)	4 (1.1%)	9 (2.4%)
Subjects withdrawn due to AE	3 (0.8%)	6 (1.7%)	4 (1.1%)	0 (0%)	2 (0.5%)
Death due to AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Up to Week 96					
Subjects with AE	201 (55.8%)	218 (60.9%)	220 (61.1%)	176 (47.7%)	174 (47%)
Subjects with Serious AE (SAE)	5 (1.4%)	7 (2%)	12 (3.3%)	6 (1.6%)	13 (3.5%)
Subjects withdrawn due to AE	3 (0.8%)	8 (2.2%)	4 (1.1%)	0 (0%)	3 (0.8%)
Death due to AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[1] AFL2: Aflibercept 2mg; BRO3: Brolucizumab 3mg; BRO6: Brolucizumab 6mg
Source: Reviewer's analysis

See Table 22 for the list of frequent ocular AEs reported up to Week 48. The most frequent AEs reported in both studies are 'visual acuity reduced', 'conjunctival haemorrhage', 'eye pain', and 'vitreous floaters'. See Appendix H for a table of list of frequent ocular AEs up to Week 96.

Table 22: Frequent ocular adverse events up to Week 48

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1] **(N=360)**	**BRO3**[1] **(N=358)**	**BRO6**[1] **(N=360)**	**AFL2 (N=369)**	**BRO6 (N=370)**
Subjects with AEs	170 (47.2%)	175 (48.9%)	179 (49.7%)	119 (32.2%)	122 (33.0%)
Preferred Term, n(%)					
Visual acuity reduced	**24 (6.7%)**	**23 (6.4%)**	**19 (5.3%)**	**20 (5.4%)**	**20 (5.4%)**
Conjunctival haemorrhage	**20 (5.6%)**	**30 (8.4%)**	**23 (6.4%)**	**12 (3.3%)**	**7 (1.9%)**
Eye pain	**15 (4.2%)**	**21 (5.9%)**	**16 (4.4%)**	**12 (3.3%)**	**10 (2.7%)**
Vitreous floaters	**11 (3.1%)**	**24 (6.7%)**	**18 (5.0%)**	**3 (0.8%)**	**11 (3.0%)**
Intraocular pressure increased	8 (2.2%)	11 (3.1%)	9 (2.5%)	9 (2.4%)	12 (3.2%)
Dry eye	15 (4.2%)	11 (3.1%)	14 (3.9%)	6 (1.6%)	8 (2.2%)
Vitreous detachment	13 (3.6%)	16 (4.5%)	10 (2.8%)	5 (1.4%)	7 (1.9%)
Cataract	8 (2.2%)	10 (2.8%)	7 (1.9%)	12 (3.3%)	4 (1.1%)
Retinal haemorrhage	16 (4.4%)	10 (2.8%)	13 (3.6%)	2 (0.5%)	5 (1.4%)
Retinal pigment epithelial tear	4 (1.1%)	5 (1.4%)	12 (3.3%)	4 (1.1%)	6 (1.6%)
Blepharitis	7 (1.9%)	4 (1.1%)	8 (2.2%)	3 (0.8%)	8 (2.2%)
Eye irritation	8 (2.2%)	8 (2.2%)	10 (2.8%)	1 (0.3%)	3 (0.8%)
Conjunctivitis	3 (0.8%)	2 (0.6%)	7 (1.9%)	3 (0.8%)	10 (2.7%)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1] (N=360)	BRO3[1] (N=358)	BRO6[1] (N=360)	AFL2 (N=369)	BRO6 (N=370)
Lenticular opacities	3 (0.8%)	6 (1.7%)	0 (0.0%)	7 (1.9%)	8 (2.2%)
Posterior capsule opacification	7 (1.9%)	5 (1.4%)	9 (2.5%)	1 (0.3%)	5 (1.4%)
Vision blurred	5 (1.4%)	11 (3.1%)	6 (1.7%)	2 (0.5%)	1 (0.3%)
Visual impairment	10 (2.8%)	10 (2.8%)	6 (1.7%)	2 (0.5%)	0 (0.0%)
Uveitis	1 (0.3%)	5 (1.4%)	8 (2.2%)	0 (0.0%)	3 (0.8%)
Punctate keratitis	8 (2.2%)	5 (1.4%)	6 (1.7%)	3 (0.8%)	1 (0.3%)
Visual field defect	3 (0.8%)	7 (2.0%)	7 (1.9%)	0 (0.0%)	1 (0.3%)
Conjunctivitis allergic	3 (0.8%)	4 (1.1%)	2 (0.6%)	3 (0.8%)	4 (1.1%)
Foreign body sensation in eyes	6 (1.7%)	5 (1.4%)	4 (1.1%)	4 (1.1%)	0 (0.0%)
Lacrimation increased	4 (1.1%)	6 (1.7%)	3 (0.8%)	2 (0.5%)	1 (0.3%)
Ocular discomfort	3 (0.8%)	5 (1.4%)	4 (1.1%)	2 (0.5%)	1 (0.3%)
Subretinal fluid	2 (0.6%)	2 (0.6%)	3 (0.8%)	3 (0.8%)	4 (1.1%)
Macular fibrosis	4 (1.1%)	6 (1.7%)	3 (0.8%)	1 (0.3%)	1 (0.3%)
Vitreous opacities	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.8%)	5 (1.4%)
Corneal abrasion	8 (2.2%)	5 (1.4%)	5 (1.4%)	1 (0.3%)	0 (0.0%)

[1] AFL2: Aflibercept 2mg; BRO3: Brolucizumab 3mg; BRO6: Brolucizumab 6mg
Source: Table 12-7 of the clinical study reports for Study 1 and Study 2. This table was produced by the reviewer.

Table 23 presents a summary of non-ocular adverse events (AE). For both studies, the proportions of subjects with non-ocular AEs are comparable between the aflibercept 2mg arm and the brolucizumab 6mg arm. No notable imbalance between the two arms is observed.

Up to Week 96, a total of 29 subjects died in Study 1. Among them, one subject in the brolucizumab 3mg arm experienced a serious AE (cerebrovascular accident) which was considered to be related to study treatment by the investigator. Except this case, none of the deaths were considered to be related to study treatment. In Study 2, 11 subjects died up to Week 96. Per the clinical study report, none of the deaths were suspected to be related to study drug by the investigator. See Appendix H for lists of frequent non-ocular AEs.

Table 23: Summary of non-ocular adverse events (AEs)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1]	BRO3[1]	BRO6[1]	AFL2	BRO6
Safety Population	360	358	360	369	370
Up to Week 48					
Subjects with AE	258 (71.7%)	242 (67.6%)	232 (64.4%)	211 (57.2%)	219 (59.2%)
Subjects with Serious AE	68 (18.9%)	47 (13.1%)	47 (13.1%)	43 (11.7%)	35 (9.5%)
Subjects withdrawn due to AE	12 (3.3%)	5 (1.4%)	6 (1.7%)	4 (1.1%)	6 (1.6%)
Death due to AE	6 (1.7%)	4 (1.1%)	4 (1.1%)	4 (1.1%)	3 (0.8%)
Up to Week 96					
Subjects with AE	303 (84.2%)	301 (84.1%)	289 (80.3%)	272 (73.7%)	282 (76.2%)
Subjects with Serious AE (SAE)	110 (30.6%)	88 (24.6%)	85 (23.6%)	85 (23%)	69 (18.6%)
Subjects withdrawn due to AE	21 (5.8%)	11 (3.1%)	11 (3.1%)	10 (2.7%)	10 (2.7%)
Death due to AE	12 (3.3%)	9 (2.5%)	8 (2.2%)	7 (1.9%)	4 (1.1%)

[1] AFL2: Aflibercept 2mg; BRO3: Brolucizumab 3mg; BRO6: Brolucizumab 6mg; Source: Reviewer's analysis.

3.3.3 Safety Conclusion

For both studies, overall AE rates are comparable between the brolucizumab 6mg arm and aflibercept 2mg arm. No notable imbalance between the treatment groups is observed; however, deference is made to the FDA medical reviews for a comprehensive safety evaluation and conclusion.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the primary efficacy endpoint (change in BCVA from baseline to Week 48) is analyzed across the subgroups defined by the following factors: age (<75, or ≥75 years), gender, race, and baseline BCVA (≤55, 56-70, or ≥71 letters). For each subgroup, analysis is performed using the same ANOVA model used in the primary efficacy analysis. For the subgroups defined by baseline BCVA and age categories, the corresponding fixed factors are removed from the model.

Figure 4 shows the results of the subgroup analyses. The plots in the right side of the figure present 95% CIs for the differences in the mean BCVA change from baseline to Week 48 (brolucizumab 6mg – aflibercept 2mg).

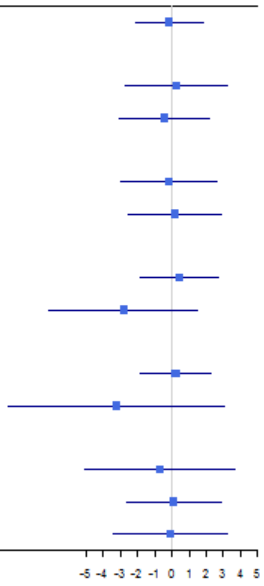
In Study 1, the estimated treatment difference ranges from -3.2 to 0.4. It ranges from -3.5 to 1.0 in Study 2. The mean BCVA change from baseline to Week 48 is comparable between the two treatment arms for most of the subgroups except the following subgroups: “Asian” group, “Hispanic or Latino” group, and subgroup of subjects with baseline BCVA of ≤ 55 letters.

In “Asian” group and “Hispanic or Latino” group, BCVA improvement in the brolucizumab 6mg arm appears to be smaller than that in the aflibercept 2mg arm. However, these results need to be interpreted with caution given larger variability in these subgroups due to relatively smaller sample sizes.

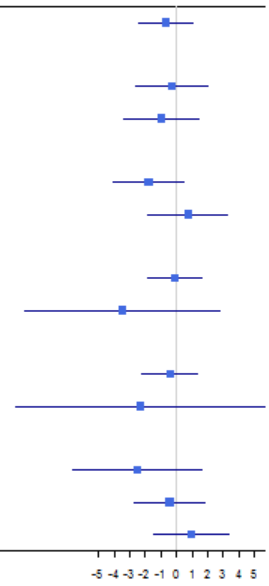
In the subgroup of subjects with baseline BCVA of ≤ 55 letters in Study 2, BCVA improvement in the brolucizumab 6mg arm appears to be smaller than that in the aflibercept 2mg arm. However, difference between the two arms for this subgroup is not apparent in Study 1.

Figure 4: Mean BCVA change from baseline to Week 48 by subgroups (FAS)

Study 201	BRO 6mg	AFL 2mg	Difference
Subgroup	N/ Mean	N/ Mean	(95% CI)
Overall	360/ 6.6	360/ 6.8	-0.2 (-2.13, 1.80)
Age			
<75	138/ 8.4	149/ 8.2	0.3 (-2.72, 3.22)
>=75	222/ 5.4	211/ 5.9	-0.5 (-3.09, 2.16)
Sex			
Female	205/ 5.9	194/ 6.0	-0.2 (-3.01, 2.64)
Male	155/ 7.7	166/ 7.5	0.2 (-2.53, 2.87)
Race			
White	285/ 6.3	287/ 5.9	0.4 (-1.87, 2.69)
Asian	61/ 7.6	53/ 10.5	-2.8 (-7.17, 1.52)
Ethnicity			
Not Hispanic or Latino	329/ 6.3	319/ 6.1	0.2 (-1.88, 2.29)
Hispanic or Latino	29/ 8.9	40/ 12.1	-3.2 (-9.50, 3.09)
Baseline BCVA			
<=55 letters	101/ 9.6	116/ 10.3	-0.7 (-5.03, 3.67)
56-70 letters	157/ 7.1	153/ 7.0	0.1 (-2.65, 2.86)
>=71 letters	102/ 2.4	91/ 2.4	-0.1 (-3.41, 3.26)



Study 202	BRO 6mg	AFL 2mg	Difference
Subgroup	N/ Mean	N/ Mean	(95% CI)
Overall	370/ 6.9	369/ 7.6	-0.7 (-2.39, 1.00)
Age			
<75	168/ 8.4	154/ 8.7	-0.3 (-2.66, 2.03)
>=75	202/ 5.8	215/ 6.7	-1.0 (-3.38, 1.44)
Sex			
Female	210/ 5.5	212/ 7.3	-1.8 (-4.05, 0.44)
Male	160/ 8.7	157/ 8.0	0.7 (-1.83, 3.31)
Race			
White	340/ 6.9	341/ 7.1	-0.1 (-1.85, 1.58)
Asian	22/ 11.4	23/ 14.8	-3.5 (-9.76, 2.82)
Ethnicity			
Not Hispanic or Latino	321/ 6.9	322/ 7.3	-0.4 (-2.19, 1.34)
Hispanic or Latino	23/ 8.7	25/ 11.1	-2.4 (-10.39, 5.65)
Baseline BCVA			
<=55 letters	102/ 8.5	107/ 11.0	-2.6 (-6.71, 1.59)
56-70 letters	171/ 7.2	170/ 7.7	-0.5 (-2.76, 1.85)
>=71 letters	97/ 4.6	92/ 3.6	1.0 (-1.45, 3.40)



1. BRO 6mg: brolucizumab 6mg; AFL 2mg: aflibercept 2mg
2. Note: the mean changes and differences between the two groups were obtained by fitting ANOVA model separately by subgroups. The ANOVA model included treatment, baseline BCVA categories, and age categories. For the subgroups by BCVA and age categories, the corresponding fixed factors were removed from the model.
3. Source: this figure was produced by the reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The reviewer did not identify any major statistical issues that can impact the overall conclusions. One minor statistical issue identified during the review is as follows. The method used for computing 95% CIs for the treatment differences in the binary additional secondary endpoints was a bootstrap method while the SAP-defined method was a delta method. In the reviewer's analyses, the 95% CIs by the delta method were similar to those by the bootstrap method (see Appendix I). Given relatively sufficient sample sizes of the pivotal studies, it appears that the two different methods provide similar CIs.

5.2 Collective Evidence

The Applicant seeks approval of brolucizumab intravitreal injection for the treatment of neovascular (wet) age-related macular degeneration. Efficacy and safety were evaluated in the two pivotal studies, Study 1 and Study 2.

In terms of BCVA improvement from baseline to Week 48, the two pivotal studies demonstrated that brolucizumab 6mg is noninferior to aflibercept 2mg: 6.61 letters vs. 6.78 letters in Study 1 and 6.91 letters vs. 7.61 letters in Study 2. The treatment difference (brolucizumab 6mg - aflibercept 2mg) is -0.16 [95% CI: (**-2.13**, 1.80)] in Study 1 and -0.70 [95% CI: (**-2.39**, 1.00)] in Study 2. The lower bounds of the 95% CIs for the treatment differences are larger than the pre-specified noninferiority margin of -4 letters, which demonstrates statistical non-inferiority. Most of the BCVA improvement observed at Week 48 was maintained through Week 96. In Study 1, the mean BCVA change from baseline to Week 96 is 5.87 letters for the brolucizumab 6mg arm and 5.34 letters for the aflibercept 2mg arm. In Study 2, it is 6.13 letters and 6.57 letters for the brolucizumab 6mg arm and aflibercept 2mg arm, respectively.

In Study 1, proportion of subjects with BCVA gain of ≥ 15 letters is slightly higher in the brolucizumab 6mg arm compared to that in the aflibercept 2mg arm: 33.6% vs. 25.4% at Week 48 and 34.2% vs. 27.0% at Week 96. However, in Study 2, this proportion is similar between the two arms: 29.3% vs. 29.9% at Week 48 and 29.1% vs. 31.4% at Week 96.

Proportion of subjects with BCVA loss of ≥ 15 letters at Week 48 is similar between the brolucizumab 6mg arm and aflibercept 2mg arm: 6.4% vs. 5.5% in Study 1 and 3.8% vs. 4.8% in Study 2. At Week 96, this proportion is slightly higher ranging from 7% to 8%.

In terms of safety, the rate of ocular AEs up to Week 48 is similar between the brolucizumab 6mg arm and aflibercept 2mg arm: 49.7% vs. 47.2% in Study 1 and 33% vs. 32.2% in Study 2. The rate of non-ocular AEs up to Week 48 is also similar between the two arms: 64.4% vs. 71.1% in Study 1 and 59.2% vs. 57.2% in Study 2. No notable imbalance between the treatment groups in the AE profile is observed.

5.3 Conclusions and Recommendations

Study 1 and Study 2 demonstrated that brolucizumab 6mg is noninferior to aflibercept 2mg with respect to visual acuity improvement and provided adequate evidence of efficacy to support an approval of the brolucizumab 6mg for the proposed indication.

5.4 Labeling Recommendations

(b) (4)

APPENDICES

Appendix A. Schedule of Procedures and Assessments

Table 24: Schedule of procedures in RTH258-C001 (HAWK)

Table 9-3 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

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

†Source: Table 9-3 of the CSR for Study RTH258-C001.

Table 25: Schedule of procedures in RTH258-C002 (HARRIER)

Table 9-3 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]

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 Brolucizumab[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 Autoflouorescence[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	

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

†Source: Table 9-3 of the CSR for Study RTH258-C002.

Appendix B. Additional Secondary and Exploratory Efficacy Endpoints in Studies 1 and 2

The SAP-defined additional secondary efficacy endpoints are as follows:

- Change in BCVA from Baseline to each postbaseline visit
- Average change in BCVA from Baseline over the period Week 84 through Week 96
- Average change in BCVA from Baseline over the period Week 4 to Week 48/96
- Average change in BCVA from Baseline over the period Week 12 to Week 48/96
- Number and percentage of subjects with BCVA gain of 15/10/5 letters or more from Baseline to each postbaseline visit (Note: Subjects with BCVA value of 84 letters or more at a postbaseline visit are considered as responders for the corresponding endpoint.)
- Number and percentage of subjects with BCVA of 73 letters or more at each visit
- Number and percentage of subjects with BCVA loss of 15/10/5 letters or more from Baseline to each postbaseline visit
- q12 treatment status at Week 96
- q12 treatment status at Week 96 within the subjects with no q8 need during the first q12 cycle
- Number and percentage of subjects with q8 treatment need at Week 16
- Change in Central Subfield Thickness (CSFT) from Baseline to each postbaseline visit
- Average change in CSFT from Baseline over the period Week 36 through Week 48/ over the period Week 84 through Week 96
- Average change in CSFT from Baseline over the period Week 4 to Week 48/96
- Change in Central Subfield Thickness-neurosensory retina (CSFTns) from Baseline to each postbaseline visit
- Average change in CSFTns from Baseline over the period Week 36 through Week 48/ Week 84 through Week 96 (Study 1 only; not in Study 2)
- Average change in CSFTns from Baseline over the period Week 12 through Week 48/96
- Change in area of Choroidal Neovascularization (CNV) within the lesion from Baseline to Weeks 12, 48 and 96
- Number and percentage of subjects with presence of subretinal fluid (central subfield) at each postbaseline visit
- Number and percentage of subjects with presence of intraretinal fluid (central subfield) at each postbaseline visit
- Number and percentage of subjects with presence of sub RPE fluid (central subfield) at each postbaseline visit
- Number and percentage of subjects with simultaneous absence of subretinal and intraretinal fluid (central subfield) at each postbaseline visit
- Number of visits with simultaneous absence of subretinal and intraretinal fluid (central subfield) during Week 36 to Week 48 (Study 1 only; not in Study 2)
- Number and percentage of subjects with presence of subretinal hemorrhage (central subfield) at each assessment visit
- Number and percentage of subjects with presence of intraretinal hemorrhage (central subfield) at each assessment visit
- Number and percentage of subjects with simultaneous absence of subretinal and intraretinal hemorrhage (central subfield) at each assessment visit
- Number of visits with simultaneous absence of subretinal and intraretinal fluid (central subfield) during Week 36 to Week 48 (Study 1 only; not in Study 2)

- Change in patient- reported outcomes (VFQ-25) total and subscale scores from Baseline to Weeks 24, 48, 72 and 96

The SAP-defined exploratory efficacy endpoints are as follows:

- Change in BCVA from Week 12 to Week 16
- Number and percent of subjects with q8 treatment need at Weeks 20, 32, 44, 56, 68, 80, and 92 (Study 1 only; not in Study 2)
- Number and percent of subjects withq8 treatment need at Weeks 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88 and 92 (Study 2 only; not in Study 1)
- q12 treatment status at Week 48 within the subjects with no q8 need during the 1st and 2nd q12 cycles (positive q12 at Week 32)
- q12 treatment status at Week 96 within the subjects with no q8 need during the 1st and 2nd q12 cycles (positive q12 at Week 32)
- Change in CSFT and categorical change (≥ 50 µm, ≥75µm, ≥100µm increase) from Week 12 to Week 16
- Change in CSFT from Week 12 to Week 16
- Change in CSFTns from Week 12 to Week 16
- Change in SRF / IRF from Week 12 to Week 16
- Change in status regarding simultaneous absence of subretinal and intraretinal fluid (central subfield) from Week 12 to Week 16 (Study 1 only; not in Study 2)
- Number and percent of subjects by time of first q8-need identification for Eylea treatment arm using KM analysis
- Presence of fibrosis from color fundus photography by assessment visit (Study 1 only; not in Study 2)
- BCVA change from Baseline by visit for subjects with retinal angiomatous proliferation (RAP) lesions at baseline (Study 2 only; not in Study 1)

Appendix C. Hypothesis Tests of Additional Secondary Endpoints in Study 1

In Study 1, formal hypothesis tests are performed for some additional secondary efficacy variables if the non-inferiority related to BCVA is successfully demonstrated for all 4 comparisons in the primary and first key secondary endpoints. All tests are one-sided for superiority of brolucizumab to aflibercept. The global one-sided alpha level of 0.025 is split as follows:

A. Change from baseline in CSFT: 0.005
B. Fluid-status ‘yes/no’ (no = absence of SRF and IRF): 0.01
C. Disease activity ‘yes/no’ (yes = q8-need): 0.01

For each efficacy variable of A, B, or C, multiple tests are performed as follows:

A. Change from baseline in CSFT is compared using ANOVA models with treatment, baseline CSFT categories (<400, or ≥400 µm), and age categories (<75 or ≥75 years). Multiple tests arising from multiple doses and times points are sequentially tested in the following order:
    1. brolucizumab 6 mg vs. aflibercept at Week 16
    2. brolucizumab 6 mg vs. aflibercept at Week 48
    3. brolucizumab 6 mg vs. aflibercept for average over Weeks 36, 40, 44, and 48
    4. brolucizumab 3 mg vs. aflibercept at Week 16
    5. brolucizumab 3 mg vs. aflibercept at Week 48

6. brolucizumab 3 mg vs. aflibercept for average over Weeks 36, 40, 44, and 48

B. Fluid-status is compared in the following order:

1. brolucizumab 6 mg vs. aflibercept at Week 16
2. brolucizumab 6 mg vs. aflibercept at Week 48
3. brolucizumab 6 mg vs. aflibercept for number of visits without fluid during Week 36 to Week 48
4. brolucizumab 3 mg vs. aflibercept at Week 16
5. brolucizumab 3 mg vs. aflibercept at Week 48
6. brolucizumab 3 mg vs. aflibercept for number of visits without fluid during Week 36 to Week 48

For 1, 2, 4, and 5, the proportion of subjects with absence of fluid is compared using logistic regression with treatment, baseline fluid status, and age categories (<75 or ≥75 years). For 3 and 6, the number of visits without fluid is compared using CMH-test stratified by baseline fluid status and age categories (<75 or ≥75 years).

C. Disease activity is compared using logistic regression with treatment and age categories (<75 or ≥75 years) in the following order:

1. brolucizumab 6 mg vs. aflibercept at Week 16
2. brolucizumab 3 mg vs. aflibercept at Week 16

The graphical approach for multiple tests (Bretz et al., Statistics in Medicine, 2009; 28:586–604) is applied to the three sets of tests (A, B, and C). Specifically, once all null-hypotheses related to one set could be rejected, the corresponding alpha assigned to this set is passed with a 50:50 split to the two other sets. In case that all null-hypotheses of a second set can also be rejected, the hierarchical testing related to the remaining set can be performed at the one-sided alpha of 0.025.

Table 26 summarizes the results of these multiple tests. The p-values in Table 26 are one-sided p-values computed by the methods specified above. The p-values in red color are the ones satisfying the pre-specified win criteria. The brolucizumab 6 mg arm met the statistical significance criteria for all endpoints except one endpoint: average BCVA change over Week 36 to 48.

Table 26: Hypothesis tests of additional secondary endpoints in Study 1[1]

	BRO3 vs. AFL2				BRO6 vs. AFL2			
	BRO3	**AFL2**	**Diff**	**p-value**	**BRO6**	**AFL2**	**Diff**	**p-value**
A. Mean change from baseline in CSFT								
Week 16	-153.30	-133.41	-19.88	0.0158	-161.37	-133.55	-27.81	0.0008
Week 48	-167.42	-143.55	-23.86	0.0075	-172.77	-143.72	-29.04	0.0011
Average over Week 36 to 48	-169.10	-149.64	-19.47	0.0182	-172.17	-149.76	-22.40	0.0075
B. Fluid Status								
% of subjects with SRF or IRF at Week 16	41.8	52.0	-10.2	0.0030	33.9	52.2	-18.2	<.0001
% of subjects with SRF or IRF at Week 48	34.1	44.7	-10.5	0.0020	31.2	44.6	-13.5	0.0001
Mean number of visits without fluid (Week 36 to 48)	2.6	2.4		0.0574	2.8			0.0012
C. Disease Activity								
% of subjects with disease activity at Week 16	28.3	34.6	-6.2	0.0389	24.2	34.5	-10.4	0.0015

[1] BRO3: brolucizumab 3mg; BRO6: brolucizumab 6mg; AFL2: aflibercept 2mg; Diff: Difference (brolucizumab -aflibercept) p-value: one-sided p-value using the methods specified in Appendix C. This table was produced by the reviewer.

Appendix D. Supportive Efficacy Analyses of Primary Efficacy Endpoint

Table 27: Baseline BCVA and change from baseline in BCVA to Week 48 (FAS without censoring [1])

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg (N=358)	**Brolucizumab 6mg (N=360)**	**Aflibercept 2mg (N=360)**	**Brolucizumab 6mg (N=370)**	**Aflibercept 2mg (N=369)**
Baseline BCVA					
Mean (SD)	61.0 (13.6)	60.8 (13.7)	60.0 (13.9)	61.5 (12.6)	60.8 (12.9)
Median	64.5	64.0	63.0	64.0	64.0
Min, Max	23, 85	23, 85	16, 83	22, 78	23, 79
BCVA Change from baseline					
A. Descriptive Statistics					
Number of LAO [2]	31	34	40	18	20
Mean (SD)	6.0 (13.5)	6.5 (14.3)	7.0 (13.4)	7.0 (11.3)	7.6 (12.5)
Median	7.0	8.0	8.0	8.0	8.0
Min, Max	-57, 51	-69, 52	-57, 54	-57, 38	-37, 50
B. Pairwise ANOVA [3]					
LS Mean (SE)					
BRO 3 mg vs. AFL 2mg	6.18 (0.70)		6.75 (0.69)		
BRO 6 mg vs. AFL 2mg		6.74 (0.71)	6.76 (0.71)	6.99 (0.61)	7.63 (0.61)
LS Mean Difference	-0.57	**-0.02**		**-0.63**	
95% CI	(-2.50, 1.36)	**(-2.00, 1.96)**		**(-2.32, 1.05)**	
NI p-value	0.0003	<.0001		<.0001	

[1] For subjects who received alternative anti-VEGF treatments prior to Week 48, their observed BCVA values at Week 48 were used in the analysis if they were collected. Missing values were imputed by the LAO prior to missed assessments.
[2] Number of subjects who's the LAO other than Week 48 values were used in the analysis.
[3] LS Mean: Least squares mean; SE: Standard error; BRO: Brolucizumab; AFL: Aflibercept; CI: confidence interval.
Source: this table was produced by the reviewer.

Table 28: Baseline BCVA and change from baseline in BCVA to Week 48 (PPS with LAO [1])

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg (N=325)	**Brolucizumab 6mg (N=328)**	**Aflibercept 2mg (N=312)**	**Brolucizumab 6mg (N=351)**	**Aflibercept 2mg (N=341)**
Baseline BCVA					
Mean (SD)	60.8 (13.5)	60.6 (13.7)	60.1 (13.3)	61.9 (12.5)	61.0 (12.8)
Median	64.0	64.0	63.0	65.0	64.0
Min, Max	23, 78	23, 79	23, 81	22, 78	23, 79
BCVA Change from baseline					
A. Descriptive Statistics					
Number of LAO [2]	23	23	26	12	14
Mean (SD)	6.3 (13.4)	6.6 (14.7)	7.4 (12.7)	7.0 (11.2)	7.8 (12.5)
Median	7.0	8.0	8.0	8.0	8.0
Min, Max	-56, 51	-69, 52	-57, 51	-57, 38	-35, 50
B. Pairwise ANOVA [3]					
LS Mean (SE)					
BRO 3 mg vs. AFL 2mg	6.54 (0.71)		7.17 (0.73)		
BRO 6 mg vs. AFL 2mg		6.86 (0.74)	7.15 (0.76)	7.02 (0.62)	7.80 (0.63)
LS Mean Difference	-0.63	**-0.29**		**-0.78**	

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg (N=325)	**Brolucizumab 6mg (N=328)**	**Aflibercept 2mg (N=312)**	**Brolucizumab 6mg (N=351)**	**Aflibercept 2mg (N=341)**
95% CI	(-2.63, 1.37)	**(-2.38, 1.79)**		**(-2.51, 0.95)**	
NI p-value	0.0005	0.0003		0.0001	

[1] LAO: the last available observation (LAO) prior to start of alternative anti-VEGF treatments was used in the primary analysis if a subject received alternative anti-VEGF treatments. Missing values were also imputed by the LAO prior to missed assessments.
[2] Number of subjects who's the LAO other than Week 48 values were used in the analysis.
[3] LS Mean: Least squares mean; SE: Standard error; BRO: Brolucizumab; AFL: Aflibercept; CI: confidence interval.
Source: Table 11-5 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

Table 29: Baseline BCVA and change from baseline in BCVA to Week 48 (FAS - Observed)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg (N=358)	**Brolucizumab 6mg (N=360)**	**Aflibercept 2mg (N=360)**	**Brolucizumab 6mg (N=370)**	**Aflibercept 2mg (N=369)**
Baseline BCVA					
Mean (SD)	61.0 (13.6)	60.8 (13.7)	60.0 (13.9)	61.5 (12.6)	60.8 (12.9)
Median	64.5	64.0	63.0	64.0	64.0
Min, Max	23, 85	23, 85	16, 83	22, 78	23, 79
BCVA Change from baseline					
A. Descriptive Statistics					
N observed [1]	324	322	310	349	345
Mean (SD)	6.7 (12.4)	7.2 (14.2)	7.7 (12.9)	7.5 (10.7)	7.9 (12.5)
Median	7.5	8.0	8.0	8.0	9.0
Min, Max	-55, 51	-69, 52	-57, 54	-57, 38	-37, 50
B. Pairwise MMRM [2]					
LS Mean (SE) [3]					
BRO 3 mg vs. AFL 2mg	6.40 (0.68)		7.32 (0.69)		
BRO 6 mg vs. AFL 2mg		6.59 (0.72)	7.31 (0.73)	7.23 (0.61)	7.68 (0.61)
LS Mean Difference	-0.92	**-0.72**		**-0.45**	
95% CI	(-2.83, 0.98)	**(-2.74, 1.30)**		**(-2.14, 1.25)**	
NI p-value	0.0008	0.0008		<.0001	

[1] N observed: Number of subjects with observed BCVA values at Week 48
[2] MMRM model with treatment, visit, baseline BCVA categories, and age categories, and treatment by visit interaction.
[3] BRO: Brolucizumab; AFL: Aflibercept
Source: Table 14.2-1.3 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

Table 30: Baseline BCVA and change from baseline in BCVA to Week 48 (PPS - Observed)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg (N=325)	**Brolucizumab 6mg (N=328)**	**Aflibercept 2mg (N=312)**	**Brolucizumab 6mg (N=351)**	**Aflibercept 2mg (N=341)**
Baseline BCVA					
Mean (SD)	60.8 (13.5)	60.6 (13.7)	60.1 (13.3)	61.9 (12.5)	61.0 (12.8)
Median	64.0	64.0	63.0	65.0	64.0
Min, Max	23, 78	23, 79	23, 81	22, 78	23, 79
BCVA Change from baseline					
A. Descriptive Statistics					

	Study 1 (HAWK)			Study 2 (HARRIER)	
	Brolucizumab 3mg (N=325)	**Brolucizumab 6mg (N=328)**	**Aflibercept 2mg (N=312)**	**Brolucizumab 6mg (N=351)**	**Aflibercept 2mg (N=341)**
N observed [1]	302	305	286	339	327
Mean (SD)	6.9 (12.4)	7.0 (14.4)	7.8 (12.8)	7.4 (10.6)	8.2 (12.4)
Median	8.0	8.0	8.0	8.0	9.0
Min, Max	-55, 51	-69, 52	-57, 51	-57, 38	-35, 50
B. Pairwise MMRM [2]					
LS Mean (SE) [3]					
BRO 3 mg vs. AFL 2mg	6.77 (0.69)		7.39 (0.71)		
BRO 6 mg vs. AFL 2mg		6.76 (0.75)	7.38 (0.78)	7.24 (0.61)	7.80 (0.62)
LS Mean Difference	-0.62	**-0.62**		**-0.56**	
95% CI	(-2.57, 1.34)	**(-2.74, 1.51)**		**(-2.27, 1.15)**	
NI p-value	0.0004	0.0009		<.0001	

[1] N observed: Number of subjects with observed BCVA values at Week 48
[2] MMRM model with treatment, visit, baseline BCVA categories, and age categories, and treatment by visit interaction.
[3] BRO: Brolucizumab; AFL: Aflibercept
Source: Table 14.2-1.4 of the CSRs for Study1 and Study. This table was produced by the reviewer.

Appendix E. Mean Baseline and Change in BCVA from Baseline to each Visit

Table 31: Change from baseline in BCVA in Study 1 (FAS; brolucizumab 3mg vs. aflibercept 2mg)

	Mean (SD) – Observed [1]		Mean (SD) – LOCF [3]		LS Mean (SE) in ANOVA [4]		
Week	**AFL2 [2]**	**BRO3 [2]**	**AFL2**	**BRO3**	**AFL2**	**BRO3**	**Difference (95% CI)**
Baseline BCVA							
0	60.0 (13.9)	61.0 (13.6)					
Change from baseline							
4	4.23 (7.98)	3.69 (8.38)	4.16 (7.93)	3.66 (8.36)	4.03 (0.42)	3.80 (0.42)	-0.22 (-1.38, 0.93)
8	6.26 (9.65)	5.68 (8.85)	6.09 (9.48)	5.71 (8.83)	5.94 (0.47)	5.86 (0.47)	-0.08 (-1.38, 1.22)
12	6.39 (10.50)	5.85 (9.70)	6.29 (10.41)	5.70 (10.19)	6.14 (0.53)	5.85 (0.53)	-0.29 (-1.77, 1.19)
16	6.32 (10.96)	5.82 (11.04)	6.13 (10.89)	5.66 (11.44)	5.97 (0.58)	5.82 (0.58)	-0.15 (-1.76, 1.46)
20	7.40 (11.18)	6.56 (10.99)	7.10 (11.25)	6.18 (11.40)	6.93 (0.58)	6.35 (0.59)	-0.59 (-2.21, 1.04)
24	7.10 (11.74)	6.41 (11.58)	6.85 (11.72)	6.11 (11.95)	6.68 (0.61)	6.28 (0.61)	-0.40 (-2.11, 1.30)
28	6.91 (12.62)	6.79 (11.79)	6.67 (12.30)	6.23 (12.67)	6.50 (0.65)	6.41 (0.65)	-0.08 (-1.88, 1.72)
32	6.81 (12.83)	5.96 (13.13)	6.58 (12.43)	5.63 (13.42)	6.37 (0.67)	5.84 (0.67)	-0.53 (-2.38, 1.32)
36	7.58 (12.73)	6.39 (12.27)	7.09 (12.46)	5.60 (13.45)	6.86 (0.67)	5.83 (0.67)	-1.03 (-2.88, 0.82)
40	7.41 (13.52)	7.00 (13.30)	6.92 (12.96)	6.20 (13.96)	6.72 (0.69)	6.41 (0.70)	-0.31 (-2.24, 1.62)
44	7.10 (13.98)	6.77 (13.35)	6.74 (13.37)	6.20 (14.05)	6.52 (0.71)	6.41 (0.71)	-0.11 (-2.08, 1.85)
48	**7.31 (13.65)**	**6.73 (12.34)**	**6.97 (13.16)**	**5.94 (13.49)**	**6.77 (0.69)**	**6.14 (0.69)**	**-0.62 (-2.54, 1.29)**
52	7.24 (14.82)	6.92 (12.89)	6.82 (14.10)	6.18 (14.00)	6.59 (0.72)	6.41 (0.73)	-0.18 (-2.19, 1.83)
56	7.61 (13.99)	7.06 (12.73)	7.09 (13.31)	6.18 (14.08)	6.88 (0.71)	6.39 (0.71)	-0.49 (-2.45, 1.48)
60	7.17 (14.95)	7.35 (12.98)	6.73 (13.96)	6.20 (14.26)	6.53 (0.73)	6.40 (0.73)	-0.12 (-2.14, 1.90)
64	7.28 (14.49)	7.03 (13.46)	6.61 (13.75)	5.89 (14.67)	6.40 (0.73)	6.10 (0.74)	-0.30 (-2.35, 1.74)
68	7.55 (13.97)	6.84 (13.09)	6.53 (13.95)	6.04 (14.60)	6.32 (0.74)	6.26 (0.74)	-0.06 (-2.11, 1.99)
72	7.01 (15.13)	6.62 (13.61)	6.25 (14.50)	5.97 (14.95)	6.03 (0.76)	6.19 (0.76)	0.15 (-1.96, 2.27)
76	7.18 (14.79)	6.78 (13.40)	6.29 (14.21)	6.17 (14.91)	6.08 (0.75)	6.39 (0.75)	0.31 (-1.78, 2.40)
80	6.39 (15.19)	6.88 (13.42)	5.84 (14.42)	6.05 (14.83)	5.63 (0.76)	6.26 (0.76)	0.64 (-1.46, 2.74)

	Mean (SD) – Observed [1]		Mean (SD) – LOCF [3]		LS Mean (SE) in ANOVA [4]		
Week	**AFL2 [2]**	**BRO3 [2]**	**AFL2**	**BRO3**	**AFL2**	**BRO3**	**Difference (95% CI)**
84	6.11 (15.08)	6.53 (13.83)	5.64 (14.36)	5.80 (15.01)	5.44 (0.76)	6.00 (0.76)	0.57 (-1.54, 2.68)
88	6.45 (15.59)	6.57 (14.15)	5.83 (14.67)	5.78 (15.43)	5.62 (0.78)	6.00 (0.78)	0.38 (-1.78, 2.54)
92	6.72 (15.60)	6.41 (14.54)	5.88 (14.64)	5.76 (15.48)	5.67 (0.78)	5.97 (0.78)	0.30 (-1.86, 2.47)
96	**6.34 (15.56)**	**6.09 (14.94)**	**5.57 (14.78)**	**5.39 (15.86)**	**5.34 (0.79)**	**5.62 (0.79)**	**0.27 (-1.92, 2.47)**

[1] Subjects with BCVA assessments. [2] AFL2: Aflibercept 2mg; BRO3: Brolucizumab 3mg.
[3] Missing BCVA values were imputed by LOCF.
[4] ANOVA model included baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment.
Source: Table 14.2-9.1 and Table 14.2-9.1_y2 of the CSR for Study 1. This table was produced by the reviewer.

Table 32: Change from baseline in BCVA in Study 1 (FAS; brolucizumab 6mg vs. aflibercept 2mg)

	Mean (SD) – Observed [1]		Mean (SD) – LOCF [3]		LS Mean (SE) in ANOVA [4]		
Week	**AFL2 [2]**	**BRO6 [2]**	**AFL2**	**BRO6**	**AFL2**	**BRO6**	**Difference (95% CI)**
Baseline BCVA							
0	60.0 (13.9)	60.8 (13.7)					
Change from baseline							
4	4.23 (7.98)	3.79 (9.79)	4.16 (7.93)	3.78 (9.77)	4.04 (0.45)	3.91 (0.45)	-0.13 (-1.40, 1.13)
8	6.26 (9.65)	5.59 (10.78)	6.09 (9.48)	5.53 (10.71)	5.94 (0.52)	5.68 (0.52)	-0.26 (-1.70, 1.17)
12	6.39 (10.50)	6.35 (11.19)	6.29 (10.41)	5.99 (11.71)	6.13 (0.57)	6.16 (0.57)	0.03 (-1.54, 1.60)
16	6.32 (10.96)	6.71 (11.13)	6.13 (10.89)	6.34 (11.65)	5.97 (0.58)	6.50 (0.58)	0.53 (-1.07, 2.13)
20	7.40 (11.18)	6.55 (11.83)	7.10 (11.25)	6.25 (12.30)	6.93 (0.60)	6.42 (0.60)	-0.51 (-2.19, 1.17)
24	7.10 (11.74)	6.85 (12.00)	6.85 (11.72)	6.37 (12.50)	6.67 (0.62)	6.54 (0.62)	-0.14 (-1.86, 1.59)
28	6.91 (12.62)	7.39 (12.53)	6.67 (12.30)	6.67 (13.23)	6.49 (0.65)	6.86 (0.65)	0.38 (-1.44, 2.19)
32	6.81 (12.83)	7.44 (12.88)	6.58 (12.43)	6.82 (13.41)	6.39 (0.66)	7.01 (0.66)	0.63 (-1.21, 2.46)
36	7.58 (12.73)	7.07 (13.20)	7.09 (12.46)	6.45 (13.74)	6.88 (0.67)	6.65 (0.67)	-0.23 (-2.09, 1.63)
40	7.41 (13.52)	7.29 (14.13)	6.92 (12.96)	6.62 (14.55)	6.72 (0.71)	6.82 (0.71)	0.09 (-1.86, 2.05)
44	7.10 (13.98)	7.14 (13.49)	6.74 (13.37)	6.57 (14.01)	6.55 (0.70)	6.75 (0.70)	0.20 (-1.75, 2.16)
48	**7.31 (13.65)**	**7.25 (14.14)**	**6.97 (13.16)**	**6.42 (14.40)**	**6.78 (0.71)**	**6.61 (0.71)**	**-0.16 (-2.13, 1.80)**
52	7.24 (14.82)	7.20 (13.97)	6.82 (14.10)	6.24 (14.58)	6.62 (0.74)	6.43 (0.74)	-0.19 (-2.24, 1.85)
56	7.61 (13.99)	6.92 (14.43)	7.09 (13.31)	6.07 (14.88)	6.90 (0.73)	6.26 (0.73)	-0.64 (-2.65, 1.38)
60	7.17 (14.95)	7.39 (13.97)	6.73 (13.96)	6.17 (14.72)	6.52 (0.74)	6.38 (0.74)	-0.15 (-2.19, 1.90)
64	7.28 (14.49)	7.04 (14.57)	6.61 (13.75)	6.04 (15.16)	6.40 (0.74)	6.25 (0.74)	-0.15 (-2.21, 1.91)
68	7.55 (13.97)	7.21 (14.31)	6.53 (13.95)	5.94 (15.10)	6.30 (0.74)	6.17 (0.74)	-0.13 (-2.19, 1.93)
72	7.01 (15.13)	6.66 (13.84)	6.25 (14.50)	5.58 (14.80)	6.05 (0.75)	5.78 (0.75)	-0.27 (-2.36, 1.82)
76	7.18 (14.79)	7.35 (14.04)	6.29 (14.21)	5.88 (15.09)	6.08 (0.75)	6.09 (0.75)	0.01 (-2.07, 2.10)
80	6.39 (15.19)	7.57 (14.31)	5.84 (14.42)	6.14 (15.33)	5.63 (0.76)	6.35 (0.76)	0.72 (-1.40, 2.84)
84	6.11 (15.08)	6.91 (13.76)	5.64 (14.36)	5.52 (14.94)	5.43 (0.75)	5.73 (0.75)	0.30 (-1.79, 2.39)
88	6.45 (15.59)	7.11 (14.42)	5.83 (14.67)	5.69 (15.45)	5.62 (0.77)	5.90 (0.77)	0.29 (-1.86, 2.43)
92	6.72 (15.60)	7.29 (14.16)	5.88 (14.64)	5.83 (15.21)	5.67 (0.77)	6.04 (0.77)	0.37 (-1.77, 2.50)
96	**6.34 (15.56)**	**7.13 (14.54)**	**5.57 (14.78)**	**5.64 (15.62)**	**5.34 (0.78)**	**5.87 (0.78)**	**0.53 (-1.63, 2.69)**

[1] Subjects with BCVA assessments. [2] AFL2: Aflibercept 2mg; BRO6: Brolucizumab 3mg.
[3] Missing BCVA values were imputed by LOCF.
[4] ANOVA model included baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment.
Source: Table 14.2-9.1 and Table 14.2-9.1_y2 of the CSR for Study 1. This table was produced by the reviewer.

Table 33: Change from baseline in BCVA in Study 2 (FAS)

	Mean (SD) – Observed [1]	Mean (SD) – LOCF [3]	LS Mean (SE) in ANOVA [4]

Week	AFL2 [2]	BRO6 [2]	AFL2	BRO6	AFL2	BRO6	Difference (95% CI)
Baseline BCVA							
0	60.8 (12.9)	61.5 (12.6)					
Change from baseline							
4	4.74 (7.63)	3.69 (7.04)	4.72 (7.62)	3.67 (7.03)	4.70 (0.37)	3.69 (0.37)	-1.02 (-2.05, 0.01)
8	6.10 (9.33)	5.06 (8.13)	6.03 (9.32)	5.00 (8.16)	6.01 (0.44)	5.02 (0.44)	-1.00 (-2.23, 0.24)
12	6.52 (10.19)	5.37 (9.31)	6.43 (10.14)	5.44 (9.35)	6.43 (0.50)	5.44 (0.50)	-0.99 (-2.37, 0.39)
16	6.35 (10.51)	5.35 (9.59)	6.27 (10.46)	5.41 (9.65)	6.26 (0.51)	5.41 (0.51)	-0.85 (-2.28, 0.57)
20	7.08 (10.72)	5.58 (9.79)	6.92 (10.66)	5.44 (10.42)	6.92 (0.54)	5.45 (0.54)	-1.47 (-2.96, 0.02)
24	6.81 (11.23)	5.91 (10.02)	6.69 (11.17)	5.77 (10.76)	6.69 (0.56)	5.77 (0.56)	-0.92 (-2.46, 0.63)
28	7.64 (11.92)	6.36 (10.81)	7.39 (11.86)	6.28 (10.97)	7.39 (0.58)	6.28 (0.58)	-1.11 (-2.72, 0.49)
32	7.63 (11.49)	6.47 (10.66)	7.33 (11.44)	6.45 (10.92)	7.34 (0.57)	6.45 (0.57)	-0.90 (-2.48, 0.69)
36	7.87 (12.10)	6.89 (10.28)	7.62 (11.99)	6.44 (11.32)	7.63 (0.59)	6.43 (0.59)	-1.20 (-2.85, 0.44)
40	7.83 (11.95)	6.80 (10.79)	7.57 (11.85)	6.40 (11.66)	7.59 (0.60)	6.38 (0.60)	-1.20 (-2.86, 0.46)
44	8.24 (12.39)	7.04 (10.76)	8.00 (12.28)	6.46 (11.51)	8.01 (0.61)	6.46 (0.61)	-1.55 (-3.23, 0.13)
48	**7.87 (12.59)**	**7.41 (10.68)**	**7.60 (12.47)**	**6.93 (11.47)**	**7.61 (0.61)**	**6.91 (0.61)**	**-0.70 (-2.39, 1.00)**
52	7.76 (12.98)	7.27 (11.37)	7.41 (12.91)	6.76 (12.03)	7.43 (0.64)	6.75 (0.64)	-0.68 (-2.45, 1.08)
56	7.58 (13.08)	7.21 (11.10)	7.20 (13.04)	6.56 (12.43)	7.21 (0.65)	6.55 (0.65)	-0.66 (-2.47, 1.14)
60	7.99 (13.19)	7.16 (11.51)	7.36 (13.49)	6.54 (12.23)	7.38 (0.66)	6.53 (0.66)	-0.85 (-2.67, 0.97)
64	7.48 (14.08)	6.82 (11.72)	7.18 (13.79)	6.55 (12.51)	7.19 (0.67)	6.53 (0.67)	-0.66 (-2.53, 1.20)
68	7.58 (14.72)	7.13 (11.12)	7.14 (14.29)	6.52 (12.22)	7.16 (0.68)	6.50 (0.68)	-0.65 (-2.54, 1.23)
72	7.26 (14.28)	6.43 (12.72)	6.90 (13.74)	6.06 (13.32)	6.91 (0.69)	6.05 (0.69)	-0.86 (-2.77, 1.06)
76	7.19 (14.13)	6.93 (12.05)	6.77 (13.80)	6.26 (13.44)	6.78 (0.70)	6.25 (0.70)	-0.52 (-2.46, 1.41)
80	6.94 (14.43)	7.25 (11.40)	6.55 (13.97)	6.41 (13.43)	6.56 (0.70)	6.40 (0.70)	-0.16 (-2.11, 1.79)
84	7.12 (14.40)	6.61 (12.25)	6.68 (14.04)	5.81 (13.76)	6.69 (0.71)	5.80 (0.71)	-0.89 (-2.86, 1.08)
88	7.35 (14.37)	6.99 (11.66)	6.88 (14.02)	6.27 (13.40)	6.89 (0.70)	6.26 (0.70)	-0.62 (-2.57, 1.32)
92	7.01 (14.82)	6.93 (12.55)	6.53 (14.29)	6.14 (13.85)	6.54 (0.72)	6.13 (0.72)	-0.40 (-2.41, 1.60)
96	**6.92 (14.93)**	**6.92 (12.76)**	**6.57 (14.55)**	**6.14 (14.06)**	**6.57 (0.73)**	**6.13 (0.73)**	**-0.44 (-2.48, 1.59)**

[1] Subjects with BCVA assessments. [2] AFL2: Aflibercept 2mg; BRO6: Brolucizumab 3mg.
[3] Missing BCVA values were imputed by LOCF
[4] ANOVA model included baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment.
Source: Table 14.2-9.1 and Table 14.2-9.1_y2 of the CSR for Study 2. This table was produced by the reviewer.

Appendix F. Responder Analysis of BCVA by Visit

Table 34: Proportion of subjects either with BCVA gain of ≥ 15 letters or with BCVA of ≥ 84 letters in Study 1

	Observed [1]		LOCF [3]		Logistic Regression [4]		
Week	AFL2 [2]	BRO6 [2]	AFL2	BRO6	AFL2	BRO6	Difference (95% CI)
4	35/354 (9.9)	38/359 (10.6)	35/360 (9.7)	39/360 (10.8)	9.5	11.1	1.6 (-2.8, 5.8)
8	56/350 (16.0)	68/355 (19.2)	56/360 (15.6)	69/360 (19.2)	15.3	19.5	4.2 (-1.2, 10.0)
12	73/352 (20.7)	87/348 (25.0)	73/360 (20.3)	88/360 (24.4)	20.0	24.8	4.9 (-0.5, 11.0)
16	75/347 (21.6)	80/348 (23.0)	75/360 (20.8)	81/360 (22.5)	20.5	22.8	2.3 (-3.8, 7.5)
20	82/340 (24.1)	90/344 (26.2)	82/360 (22.8)	93/360 (25.8)	22.4	26.2	3.8 (-2.4, 10.1)
24	76/335 (22.7)	101/345 (29.3)	79/360 (21.9)	102/360 (28.3)	21.6	28.8	7.2 (0.8, 13.4)
28	93/332 (28.0)	100/338 (29.6)	93/360 (25.8)	101/360 (28.1)	25.4	28.5	3.2 (-3.4, 9.4)
32	88/330 (26.7)	112/338 (33.1)	90/360 (25.0)	115/360 (31.9)	24.6	32.5	7.9 (1.5, 14.4)
36	88/327 (26.9)	112/336 (33.3)	89/360 (24.7)	114/360 (31.7)	24.2	32.3	8.1 (2.1, 14.5)

	Observed [1]		LOCF [3]		Logistic Regression [4]		
Week	AFL2 [2]	BRO6 [2]	AFL2	BRO6	AFL2	BRO6	Difference (95% CI)
40	94/320 (29.4)	116/329 (35.3)	95/360 (26.4)	121/360 (33.6)	25.9	34.2	8.3 (2.0, 15.1)
44	98/324 (30.2)	116/327 (35.5)	99/360 (27.5)	123/360 (34.2)	27.1	34.7	7.6 (0.7, 13.8)
48	**90/320 (28.1)**	**116/326 (35.6)**	**93/360 (25.8)**	**119/360 (33.1)**	**25.4**	**33.6**	**8.2 (2.2, 15.0)**
52	99/311 (31.8)	106/321 (33.0)	101/360 (28.1)	114/360 (31.7)	27.5	32.3	4.8 (-1.5, 11.4)
56	105/313 (33.5)	106/318 (33.3)	107/360 (29.7)	114/360 (31.7)	29.2	32.2	3.0 (-3.1, 9.7)
60	98/304 (32.2)	109/311 (35.0)	103/360 (28.6)	117/360 (32.5)	28.1	33.0	4.9 (-1.3, 11.4)
64	98/308 (31.8)	106/308 (34.4)	100/360 (27.8)	117/360 (32.5)	27.3	33.0	5.8 (-0.4, 12.3)
68	98/308 (31.8)	108/302 (35.8)	101/360 (28.1)	117/360 (32.5)	27.5	33.1	5.6 (0.0, 9.3)
72	93/299 (31.1)	102/306 (33.3)	99/360 (27.5)	113/360 (31.4)	27.0	32.0	5.1 (-1.1, 11.4)
76	97/298 (32.6)	109/301 (36.2)	103/360 (28.6)	117/360 (32.5)	28.1	33.1	5.0 (-1.2, 11.6)
80	92/297 (31.0)	117/301 (38.9)	100/360 (27.8)	128/360 (35.6)	27.3	36.1	8.8 (2.7, 15.4)
84	86/293 (29.4)	100/306 (32.7)	96/360 (26.7)	108/360 (30.0)	26.2	30.5	4.2 (-2.2, 10.3)
88	91/294 (31.0)	113/300 (37.7)	100/360 (27.8)	125/360 (34.7)	27.3	35.3	8.0 (1.9, 14.6)
92	96/295 (32.5)	107/300 (35.7)	101/360 (28.1)	118/360 (32.8)	27.5	33.4	5.9 (-0.0, 12.5)
96	**94/297 (31.6)**	**112/304 (36.8)**	**99/360 (27.5)**	**121/360 (33.6)**	**27.0**	**34.2**	**7.2 (1.4, 13.8)**

[1] Subjects with BCVA assessments. [2] AFL2: Aflibercept 2mg; BRO6: Brolucizumab 6mg.
[3] Missing BCVA values were imputed by LOCF; BCVA assessments after start of alternative anti-VEGF treatment are censored and imputed by the last value prior to start of the alternative treatment.
[4] Logistic regression model included baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment. The model was fitted separately at each week using the FAS with LOCF. The 95% CI (confidence interval) for the difference was estimated by a bootstrap method based on 1000 bootstrap samples.
Source: Table 14.2-25.1 of the CSR of Study 1. This table was produced by the reviewer.

Table 35: Proportion of subjects either with BCVA gain of ≥ 15 letters or with BCVA of ≥ 84 letters in Study 2

	Observed [1]		LOCF [3]		Logistic Regression [4]		
Week	AFL2 [2]	BRO6 [2]	AFL2	BRO6	AFL2	BRO6	Difference (95% CI)
4	33/367 (9.0)	28/368 (7.6)	33/369 (8.9)	28/370 (7.6)	8.9	7.6	-1.3 (-5.1, 2.9)
8	67/365 (18.4)	52/368 (14.1)	67/369 (18.2)	52/370 (14.1)	18.1	14.1	-4.0 (-9.2, 1.3)
12	79/362 (21.8)	60/365 (16.4)	79/369 (21.4)	61/370 (16.5)	21.5	16.4	-5.0 (-10.5, 0.3)
16	80/357 (22.4)	72/361 (19.9)	82/369 (22.2)	74/370 (20.0)	22.3	20.0	-2.3 (-8.4, 3.7)
20	86/356 (24.2)	74/359 (20.6)	87/369 (23.6)	76/370 (20.5)	23.6	20.5	-3.1 (-8.8, 2.8)
24	82/357 (23.0)	85/359 (23.7)	84/369 (22.8)	88/370 (23.8)	22.8	23.7	0.9 (-5.2, 6.7)
28	97/353 (27.5)	86/360 (23.9)	100/369 (27.1)	88/370 (23.8)	27.2	23.7	-3.4 (-9.7, 2.7)
32	105/353 (29.7)	93/359 (25.9)	106/369 (28.7)	95/370 (25.7)	28.8	25.6	-3.3 (-10.3, 2.8)
36	112/353 (31.7)	95/355 (26.8)	114/369 (30.9)	97/370 (26.2)	31.0	26.1	-4.9 (-11.6, 1.3)
40	114/351 (32.5)	98/355 (27.6)	116/369 (31.4)	101/370 (27.3)	31.6	27.2	-4.4 (-11.2, 2.1)
44	112/352 (31.8)	98/354 (27.7)	115/369 (31.2)	99/370 (26.8)	31.3	26.6	-4.6 (-11.3, 1.8)
48	**107/349 (30.7)**	**104/352 (29.5)**	**110/369 (29.8)**	**109/370 (29.5)**	**29.9**	**29.3**	**-0.6 (-7.1, 5.8)**
52	109/344 (31.7)	109/349 (31.2)	113/369 (30.6)	112/370 (30.3)	30.8	30.1	-0.6 (-7.0, 5.5)
56	109/346 (31.5)	105/345 (30.4)	113/369 (30.6)	110/370 (29.7)	30.7	29.7	-1.1 (-7.7, 5.4)
60	109/340 (32.1)	103/351 (29.3)	113/369 (30.6)	106/370 (28.6)	30.7	28.5	-2.2 (-8.3, 4.2)
64	110/341 (32.3)	102/344 (29.7)	114/369 (30.9)	110/370 (29.7)	31.0	29.6	-1.4 (-7.9, 5.4)
68	113/335 (33.7)	100/344 (29.1)	119/369 (32.2)	107/370 (28.9)	32.3	28.9	-3.5 (-9.9, 3.1)
72	114/337 (33.8)	95/345 (27.5)	116/369 (31.4)	102/370 (27.6)	31.5	27.5	-4.1 (-10.2, 2.3)
76	109/337 (32.3)	99/341 (29.0)	113/369 (30.6)	105/370 (28.4)	30.7	28.3	-2.4 (-8.8, 4.0)
80	106/332 (31.9)	98/341 (28.7)	112/369 (30.4)	104/370 (28.1)	30.5	28.0	-2.6 (-9.4, 3.3)
84	111/333 (33.3)	95/340 (27.9)	115/369 (31.2)	102/370 (27.6)	31.3	27.5	-3.8 (-9.9, 2.8)
88	117/330 (35.5)	94/337 (27.9)	122/369 (33.1)	102/370 (27.6)	33.2	27.4	-5.8 (-11.8, 0.3)

	Observed [1]		LOCF [3]		Logistic Regression [4]		
Week	AFL2 [2]	BRO6 [2]	AFL2	BRO6	AFL2	BRO6	Difference (95% CI)
92	108/322 (33.5)	103/337 (30.6)	114/369 (30.9)	109/370 (29.5)	31.0	29.3	-1.7 (-7.9, 4.5)
96	**112/329 (34.0)**	**103/342 (30.1)**	**116/369 (31.4)**	**108/370 (29.2)**	**31.5**	**29.1**	**-2.4 (-8.8, 4.1)**

[1] Subjects with BCVA assessments. [2] AFL2: Aflibercept 2mg; BRO6: Brolucizumab 6mg.
[3] Missing BCVA values were imputed by LOCF; BCVA assessments after start of alternative anti-VEGF treatment are censored and imputed by the last value prior to start of the alternative treatment.
[4] Logistic regression model included baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment. The model was fitted separately at each week using the FAS with LOCF. The 95% CI (confidence interval) for the difference was estimated by a bootstrap method based on 1000 bootstrap samples.
Source: Table 14.2-25.1 of the CSR of Study 2. This table was produced by the reviewer.

Table 36: Proportion of subjects with BCVA loss of ≥ 15 letters in Study 1 (FAS)

	Observed [1]		LOCF [3]		Logistic Regression [4]		
Week	AFL2 [2]	BRO6 [2]	AFL2	BRO6	AFL2	BRO6	Difference (95% CI)
4	5/354 (1.4)	11/359 (3.1)	5/360 (1.4)	11/360 (3.1)	1.4	3.1	1.7 (-0.5, 4.0)
8	8/350 (2.3)	10/355 (2.8)	8/360 (2.2)	10/360 (2.8)	2.2	2.8	0.7 (-1.7, 2.9)
12	14/352 (4.0)	11/348 (3.2)	14/360 (3.9)	13/360 (3.6)	3.9	3.6	-0.3 (-3.2, 2.7)
16	11/347 (3.2)	11/348 (3.2)	12/360 (3.3)	13/360 (3.6)	3.3	3.6	0.3 (-2.4, 3.1)
20	8/340 (2.4)	15/344 (4.4)	9/360 (2.5)	17/360 (4.7)	2.5	4.8	2.3 (-0.3, 5.3)
24	13/335 (3.9)	16/345 (4.6)	14/360 (3.9)	19/360 (5.3)	3.9	5.3	1.5 (-1.8, 4.6)
28	15/332 (4.5)	15/338 (4.4)	16/360 (4.4)	20/360 (5.6)	4.4	5.6	1.1 (-2.3, 4.6)
32	14/330 (4.2)	18/338 (5.3)	15/360 (4.2)	23/360 (6.4)	4.2	6.4	2.2 (-1.3, 5.8)
36	11/327 (3.4)	19/336 (5.7)	12/360 (3.3)	23/360 (6.4)	3.3	6.4	3.1 (0.0, 6.5)
40	13/320 (4.1)	21/329 (6.4)	15/360 (4.2)	25/360 (6.9)	4.1	7.0	2.8 (-0.7, 6.3)
44	15/324 (4.6)	19/327 (5.8)	16/360 (4.4)	23/360 (6.4)	4.4	6.4	2.0 (-1.4, 5.2)
48	**19/320 (5.9)**	**19/326 (5.8)**	**20/360 (5.6)**	**23/360 (6.4)**	**5.5**	**6.4**	**0.9 (-2.7, 4.3)**
52	18/311 (5.8)	19/321 (5.9)	21/360 (5.8)	25/360 (6.9)	5.8	7.0	1.3 (-1.3, 4.0)
56	17/313 (5.4)	21/318 (6.6)	19/360 (5.3)	28/360 (7.8)	5.3	7.8	2.6 (-1.5, 6.3)
60	19/304 (6.2)	15/311 (4.8)	21/360 (5.8)	25/360 (6.9)	5.8	7.0	1.2 (-2.9, 4.9)
64	20/308 (6.5)	22/308 (7.1)	21/360 (5.8)	31/360 (8.6)	5.8	8.7	2.8 (-1.2, 6.7)
68	19/308 (6.2)	18/302 (6.0)	23/360 (6.4)	27/360 (7.5)	6.4	7.5	1.1 (-2.9, 4.9)
72	20/299 (6.7)	18/306 (5.9)	22/360 (6.1)	27/360 (7.5)	6.1	7.6	1.5 (-2.7, 5.3)
76	20/298 (6.7)	18/301 (6.0)	22/360 (6.1)	29/360 (8.1)	6.1	8.1	2.0 (-2.1, 6.0)
80	27/297 (9.1)	17/301 (5.6)	29/360 (8.1)	28/360 (7.8)	8.0	7.8	-0.2 (-4.6, 3.9)
84	24/293 (8.2)	17/306 (5.6)	26/360 (7.2)	28/360 (7.8)	7.2	7.8	0.6 (-3.2, 4.5)
88	26/294 (8.8)	17/300 (5.7)	29/360 (8.1)	29/360 (8.1)	8.0	8.1	0.1 (-3.7, 4.1)
92	21/295 (7.1)	18/300 (6.0)	25/360 (6.9)	29/360 (8.1)	6.9	8.1	1.2 (-3.0, 5.1)
96	**23/297 (7.7)**	**17/304 (5.6)**	**27/360 (7.5)**	**29/360 (8.1)**	**7.4**	**8.1**	**0.7 (-3.6, 4.6)**

[1] Subjects with BCVA assessments. [2] AFL2: Aflibercept 2mg; BRO6: Brolucizumab 6mg.
[3] Missing BCVA values were imputed by LOCF; BCVA assessments after start of alternative anti-VEGF treatment are censored and imputed by the last value prior to start of the alternative treatment.
[4] Logistic regression model included baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment. The model was fitted separately at each week using the FAS with LOCF. The 95% CI (confidence interval) for the difference was estimated by a bootstrap method based on 1000 bootstrap samples.
Source: Table 14.2-27 .1 of the CSR of Study 1. This table was produced by the reviewer

Table 37: Proportion of subjects with BCVA loss of ≥ 15 letters in Study 2 (FAS)

	Observed [1]		LOCF [3]		Logistic Regression [4]		
Week	AFL2 [2]	BRO6 [2]	AFL2	BRO6	AFL2	BRO6	Difference (95% CI)
4	4/367 (1.1)	4/368 (1.1)	4/369 (1.1)	4/370 (1.1)	1.1	1.1	-0.0 (-1.6, 1.4)
8	6/365 (1.6)	4/368 (1.1)	6/369 (1.6)	4/370 (1.1)	1.6	1.1	-0.6 (-2.3, 1.1)

	Observed [1]		LOCF [3]		Logistic Regression [4]		
Week	**AFL2 [2]**	**BRO6 [2]**	**AFL2**	**BRO6**	**AFL2**	**BRO6**	**Difference (95% CI)**
12	7/362 (1.9)	7/365 (1.9)	7/369 (1.9)	7/370 (1.9)	1.9	1.9	0.0 (-1.9, 2.2)
16	8/357 (2.2)	8/361 (2.2)	8/369 (2.2)	8/370 (2.2)	2.2	2.2	0.0 (-2.1, 2.3)
20	11/356 (3.1)	12/359 (3.3)	11/369 (3.0)	13/370 (3.5)	3.0	3.5	0.6 (-2.0, 3.3)
24	12/357 (3.4)	8/359 (2.2)	12/369 (3.3)	10/370 (2.7)	3.2	2.7	-0.5 (-3.0, 2.2)
28	12/353 (3.4)	9/360 (2.5)	13/369 (3.5)	11/370 (3.0)	3.5	3.0	-0.5 (-3.0, 2.3)
32	13/353 (3.7)	10/359 (2.8)	14/369 (3.8)	12/370 (3.2)	3.8	3.3	-0.5 (-3.5, 2.6)
36	13/353 (3.7)	9/355 (2.5)	13/369 (3.5)	14/370 (3.8)	3.5	3.8	0.4 (-2.3, 3.3)
40	16/351 (4.6)	14/355 (3.9)	16/369 (4.3)	20/370 (5.4)	4.3	5.5	1.2 (-1.7, 4.6)
44	17/352 (4.8)	12/354 (3.4)	17/369 (4.6)	17/370 (4.6)	4.5	4.7	0.1 (-2.7, 3.4)
48	**18/349 (5.2)**	**8/352 (2.3)**	**18/369 (4.9)**	**14/370 (3.8)**	**4.8**	**3.8**	**-1.0 (-3.9, 2.2)**
52	19/344 (5.5)	11/349 (3.2)	21/369 (5.7)	17/370 (4.6)	5.6	4.7	-1.0 (-4.3, 2.3)
56	18/346 (5.2)	14/345 (4.1)	20/369 (5.4)	22/370 (5.9)	5.4	6.0	0.6 (-2.8, 3.9)
60	18/340 (5.3)	17/351 (4.8)	21/369 (5.7)	23/370 (6.2)	5.6	6.3	0.6 (-2.7, 4.1)
64	22/341 (6.5)	19/344 (5.5)	23/369 (6.2)	25/370 (6.8)	6.2	6.8	0.7 (-2.7, 4.5)
68	23/335 (6.9)	13/344 (3.8)	24/369 (6.5)	20/370 (5.4)	6.4	5.5	-0.9 (-4.2, 2.6)
72	23/337 (6.8)	21/345 (6.1)	24/369 (6.5)	27/370 (7.3)	6.4	7.4	0.9 (-2.5, 4.5)
76	21/337 (6.2)	18/341 (5.3)	23/369 (6.2)	25/370 (6.8)	6.2	6.8	0.7 (-2.5, 4.4)
80	21/332 (6.3)	18/341 (5.3)	23/369 (6.2)	26/370 (7.0)	6.2	7.1	0.9 (-2.4, 4.6)
84	25/333 (7.5)	19/340 (5.6)	27/369 (7.3)	27/370 (7.3)	7.2	7.4	0.2 (-3.3, 4.2)
88	23/330 (7.0)	17/337 (5.0)	26/369 (7.0)	25/370 (6.8)	7.0	6.8	-0.2 (-3.5, 3.6)
92	25/322 (7.8)	18/337 (5.3)	28/369 (7.6)	26/370 (7.0)	7.5	7.1	-0.4 (-3.8, 3.3)
96	**26/329 (7.9)**	**19/342 (5.6)**	**28/369 (7.6)**	**26/370 (7.0)**	**7.5**	**7.1**	**-0.4 (-3.8, 3.3)**

[1] Subjects with BCVA assessments. [2] AFL2: Aflibercept 2mg; BRO6: Brolucizumab 6mg.
[3] Missing BCVA values were imputed by LOCF; BCVA assessments after start of alternative anti-VEGF treatment are censored and imputed by the last value prior to start of the alternative treatment.
[4] Logistic regression model included baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment. The model was fitted separately at each week using the FAS with LOCF. The 95% CI (confidence interval) for the difference was estimated by a bootstrap method based on 1000 bootstrap samples.
Source: Table 14.2-27.1 of the CSR of Study 2. This table was produced by the reviewer.

Appendix G. Supportive Analyses of Q12w Status

This section presents the supportive analyses of q12w status endpoints. The SAP-defined supportive analyses are as follows:

- 'Efficacy only' approach (also referred to as 'efficacy' approach in the CRS): This approach follows the concept of time-to-event analysis as described for the primary approach ('efficacy/safety' approach). Only difference with the primary approach is that Rule 1 is limited to the intercurrent events attributable to the lack of efficacy only. In case of the intercurrent events due to safety reasons, the q12w status is censored at the last valid DAA.
- 'Conservative' approach: This is not a time-to-event analysis. Proportion of subjects with positive q12w status at Week 48 is computed using the denominator as the number of FAS subjects and the numerator as the number of subjects with no identified q8-need at the scheduled DAA visits. Missing DAA at Week 16 is considered as no q8-need. However, missing DAA at other scheduled DAA visits are analyzed as negative q12w status. In addition, active treatments after Week 12 other than the scheduled q12-cycles (Weeks 20, 32, and 44) are also analyzed as negative q12w status.

- 'LOCF' approach: This approach follows the concepts in the conservative approach. The only difference is that only available DAAs are considered (i.e., a missing DAA is not translated into a q8-need).

The subsections G-1, G-2, and G-3 show the results of these three supportive analyses.

G-1. 'Efficacy only' approach

Table 38: Time to first q8w need (Brolucizumab 6mg)

	Study 1				Study 2			
Week	N risk [1]	N.event [2]	N.censor [3]	Survival Prob [4] (95% CI)	N risk [1]	N.event [2]	N.censor [3]	Survival Prob [4] (95% CI)
16	343	81	22	0.76 (0.72, 0.81)	361	80	18	0.78 (0.73, 0.82)
20	257	35	7	0.66 (0.61, 0.71)	272	51	3	0.63 (0.58, 0.68)
28					218	12	6	0.60 (0.54, 0.65)
32	215	16	12	0.61 (0.56, 0.66)	200	11	2	0.56 (0.51, 0.61)
40					187	5	4	0.55 (0.50, 0.60)
44	187	11	8	0.57 (0.52, 0.63)	178	9	1	0.52 (0.47, 0.57)
52					168	5	2	0.51 (0.45, 0.56)
56	168	18	8	0.51 (0.46, 0.57)	161	9	3	0.48 (0.42, 0.53)
64					149	5	1	0.46 (0.41, 0.51)
68	142	4	5	0.50 (0.44, 0.55)	143	4	1	0.45 (0.40, 0.50)
76					138	4	2	0.44 (0.38, 0.49)
80	133	6	3	0.48 (0.42, 0.53)	132	6	7	0.42 (0.36, 0.47)
88					119	5	0	0.40 (0.35, 0.45)
92	124	2	122	0.47 (0.41, 0.52)	114	0	114	0.40 (0.35, 0.45)

[1] N risk: Number of subjects at risk. [2] N.event: Number of subjects with q8 need among the subjects at risk.
[3] N.censor: Number of censored subjects among the subjects at risk.
[4] Probability of remaining on q12 treatment estimated by Kaplan-Meier analysis (95% confidence interval).
Source: Table 14.2-6.10_y2 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

Table 39: Time to first q8w need in subjects with no q8w need during the 1st q12w cycle (brolucizumab 6mg)

	Study 1				Study 2			
Week	N risk [1]	N.event [2]	N.censor [3]	Survival Prob [4] (95% CI)	N risk [1]	N.event [2]	N.censor [3]	Survival Prob [4] (95% CI)
28					218	12	9	0.94 (0.91, 0.97)
32	215	16	19	0.93 (0.88, 0.95)	200	11	2	0.89 (0.84, 0.93)
40					187	5	4	0.87 (0.82, 0.91)
44	187	11	8	0.87 (0.82, 0.91)	178	9	1	0.83 (0.77, 0.87)
52					168	5	2	0.80 (0.74, 0.85)
56	168	18	8	0.78 (0.71, 0.83)	161	9	3	0.76 (0.69, 0.81)
64					149	5	1	0.73 (0.66, 0.79)
68	142	4	5	0.76 (0.69, 0.81)	143	4	1	0.71 (0.64, 0.77)
76					138	4	2	0.69 (0.62, 0.75)
80	133	6	3	0.72 (0.65, 0.78)	132	6	7	0.66 (0.59, 0.72)
88					119	5	0	0.63 (0.56, 0.69)
92	124	2	122	0.71 (0.64, 0.77)	114	0	114	0.63 (0.56, 0.69)

[1] N risk: Number of subjects at risk. [2] N.event: Number of subjects with q8 need among the subjects at risk.
[3] N.censor: Number of censored subjects among the subjects at risk.
[4] Probability of remaining on q12 treatment estimated by Kaplan-Meier analysis (95% confidence interval).
Source: Table 14.2-6.14_2 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

G-2. 'Conservative' approach for q12 status at Week 48s

Table 40: Proportion of subjects with positive q12 status at Week 48 (FAS)

	Study 1		Study 2	
	n/N (%)	95% CI [1]	n/N (%)	95% CI [1]
Week 48	176/360 (48.9%)	(43.6%, 54.2%)	170/370 (45.9%)	(40.8%, 51.2%)

[1] CI: Confidence interval; CI was computed by Clopper-Pearson exact method.
Source: Table 14.2-5.1.1 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

Table 41: Proportion of subjects with positive q12 status at Week 48 (FAS) within subject having no q8w need during the 1st q12w cycle (FAS)

	Study 1		Study 2	
	n/N (%)	95% CI [1]	n/N (%)	95% CI [1]
Week 48	176/222 (79.3%)	(73.3%, 84.4%)	170/221 (76.9%)	(70.8%, 82.3%)

[1] CI: Confidence interval; CI was computed by Clopper-Pearson exact method.
Source: Table 14.2-5.1.2 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

G-3. 'LOCF' approach

Table 42: Proportion of subjects with positive q12 status at Week 48 (FAS)

	Study 1		Study 2	
	n/N (%)	95% CI [1]	n/N (%)	95% CI [1]
Week 48	199/360 (55.3%)	(50.0%, 60.5%)	193/370 (52.2%)	(46.9%, 57.4%)

[1] CI: Confidence interval; CI was computed by Clopper-Pearson exact method.
Source: Table 14.2-5.2.1 of the clinical study report for Study1 and Study 2. This table was produced by the reviewer.
Note: the denominator in this table by the reviewer is the number of subjects in the FAS. However, the denominator in Table 14.2-5.2.1 of the CSR was 352 for Study 1 and 361 for Study 2.

Table 43: Proportion of subjects with positive q12 status at Week 48 (FAS) within subject having no q8w need during the 1st q12w cycle (FAS)

	Study 1		Study 2	
	n/N (%)	95% CI [1]	n/N (%)	95% CI [1]
Week 48	199/228 (87.3%)	(82.2%, 91.3%)	193/231 (83.5%)	(78.1%, 88.1%)

[1] CI: Confidence interval; CI was computed by Clopper-Pearson exact method.
Source: Table 14.2-5.2.2 of the CSRs for Study1 and Study 2. This table was produced by the reviewer.

Appendix H. Tables for drug exposure and frequent AEs

Table 44: Number of active injections prior to Week 96

	Study 1			Study 2	
	AFL2[1]	BRO3[1]	BRO6[1]	AFL2	BRO6
Safety Analysis Set	N = 360	N = 358	N = 360	N = 369	N = 370
Number of injections					
1	8 (2.2)	0 (0.0)	3 (0.8)	2 (0.5)	1 (0.3)
2	3 (0.8)	3 (0.8)	4 (1.1)	3 (0.8)	2 (0.5)
3	6 (1.7)	8 (2.2)	9 (2.5)	6 (1.6)	11 (3.0)
4	14 (3.9)	6 (1.7)	8 (2.2)	1 (0.3)	2 (0.5)

	Study 1			Study 2	
	AFL2[1]	BRO3[1]	BRO6[1]	AFL2	BRO6
5	6 (1.7)	11 (3.1)	10 (2.8)	4 (1.1)	3 (0.8)
6	9 (2.5)	6 (1.7)	9 (2.5)	4 (1.1)	4 (1.1)
7	8 (2.2)	5 (1.4)	8 (2.2)	3 (0.8)	4 (1.1)
8	4 (1.1)	9 (2.5)	8 (2.2)	5 (1.4)	4 (1.1)
9	5 (1.4)	12 (3.4)	12 (3.3)	8 (2.2)	12 (3.2)
10	9 (2.5)	122 (34.1)	141 (39.2)	4 (1.1)	127 (34.3)
11	13 (3.6)	27 (7.5)	20 (5.6)	11 (3.0)	34 (9.2)
12	32 (8.9)	42 (11.7)	40 (11.1)	27 (7.3)	40 (10.8)
13	243 (67.5)	107 (29.9)	88 (24.4)	290 (78.6)	126 (34.1)
14	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

[1] AFL2: Aflibercept 2mg; BRO3: Brolucizumab 3mg; BRO6: Brolucizumab 6mg
Source: Table 14.1-1.1.1_y2 of the CSRs for Study 1 and Study 2.

Table 45: Frequent ocular adverse events up to Week 96

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1] (N=360)	BRO3[1] (N=358)	BRO6[1] (N=360)	AFL2 (N=369)	BRO6 (N=370)
Subjects with AEs	201 (55.8%)	218 (60.9%)	220 (61.1%)	176 (47.7%)	174 (47.0%)
Preferred Term, n(%)					
Visual acuity reduced	29 (8.1%)	34 (9.5%)	22 (6.1%)	26 (7.0%)	32 (8.6%)
Conjunctival haemorrhage	32 (8.9%)	39 (10.9%)	29 (8.1%)	19 (5.1%)	17 (4.6%)
Cataract	13 (3.6%)	18 (5.0%)	20 (5.6%)	43 (11.7%)	11 (3.0%)
Eye pain	21 (5.8%)	28 (7.8%)	18 (5.0%)	19 (5.1%)	13 (3.5%)
Vitreous floaters	16 (4.4%)	26 (7.3%)	22 (6.1%)	5 (1.4%)	15 (4.1%)
Vitreous detachment	19 (5.3%)	24 (6.7%)	19 (5.3%)	8 (2.2%)	10 (2.7%)
Dry eye	26 (7.2%)	20 (5.6%)	19 (5.3%)	11 (3.0%)	10 (2.7%)
Intraocular pressure increased	15 (4.2%)	16 (4.5%)	13 (3.6%)	15 (4.1%)	14 (3.8%)
Retinal haemorrhage	20 (5.6%)	14 (3.9%)	21 (5.8%)	4 (1.1%)	12 (3.2%)
Posterior capsule opacification	11 (3.1%)	16 (4.5%)	14 (3.9%)	5 (1.4%)	7 (1.9%)
Blepharitis	12 (3.3%)	8 (2.2%)	13 (3.6%)	5 (1.4%)	13 (3.5%)
Conjunctivitis	3 (0.8%)	3 (0.8%)	9 (2.5%)	8 (2.2%)	15 (4.1%)
Lenticular opacities	4 (1.1%)	7 (2.0%)	1 (0.3%)	12 (3.3%)	13 (3.5%)
Vision blurred	10 (2.8%)	16 (4.5%)	11 (3.1%)	3 (0.8%)	3 (0.8%)
Retinal pigment epithelial tear	4 (1.1%)	5 (1.4%)	12 (3.3%)	5 (1.4%)	8 (2.2%)
Visual impairment	14 (3.9%)	15 (4.2%)	10 (2.8%)	3 (0.8%)	1 (0.3%)
Punctate keratitis	10 (2.8%)	11 (3.1%)	9 (2.5%)	7 (1.9%)	1 (0.3%)
Eye irritation	11 (3.1%)	10 (2.8%)	10 (2.8%)	1 (0.3%)	4 (1.1%)
Dry age-related macular degeneration	3 (0.8%)	7 (2.0%)	5 (1.4%)	4 (1.1%)	7 (1.9%)
Subretinal fluid	5 (1.4%)	4 (1.1%)	4 (1.1%)	5 (1.4%)	7 (1.9%)
Macular fibrosis	4 (1.1%)	10 (2.8%)	5 (1.4%)	1 (0.3%)	3 (0.8%)
Lacrimation increased	5 (1.4%)	7 (2.0%)	4 (1.1%)	3 (0.8%)	4 (1.1%)
Foreign body sensation in eyes	9 (2.5%)	8 (2.2%)	4 (1.1%)	4 (1.1%)	1 (0.3%)
Uveitis	1 (0.3%)	6 (1.7%)	8 (2.2%)	0 (0.0%)	3 (0.8%)
Visual field defect	5 (1.4%)	9 (2.5%)	7 (1.9%)	0 (0.0%)	1 (0.3%)
Ocular discomfort	4 (1.1%)	6 (1.7%)	6 (1.7%)	2 (0.5%)	1 (0.3%)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1] (N=360)	BRO3[1] (N=358)	BRO6[1] (N=360)	AFL2 (N=369)	BRO6 (N=370)
Corneal abrasion	10 (2.8%)	6 (1.7%)	7 (1.9%)	1 (0.3%)	1 (0.3%)
Conjunctivitis allergic	6 (1.7%)	4 (1.1%)	2 (0.6%)	4 (1.1%)	4 (1.1%)
Vitreous opacities	2 (0.6%)	1 (0.3%)	3 (0.8%)	4 (1.1%)	6 (1.6%)
Iritis	1 (0.3%)	3 (0.8%)	9 (2.5%)	1 (0.3%)	0 (0.0%)
Photopsia	1 (0.3%)	5 (1.4%)	4 (1.1%)	2 (0.5%)	2 (0.5%)
Eye pruritus	5 (1.4%)	4 (1.1%)	3 (0.8%)	4 (1.1%)	1 (0.3%)
Neovascular age-related macular degeneration	2 (0.6%)	2 (0.6%)	1 (0.3%)	4 (1.1%)	5 (1.4%)
Retinal tear	3 (0.8%)	1 (0.3%)	6 (1.7%)	2 (0.5%)	3 (0.8%)

[1] AFL2: Aflibercept 2mg; BRO3: Brolucizumab 3mg; BRO6: Brolucizumab 6mg
Source: Table 12-8 of the CSRs for Study 1 and Study 2. This table was produced by the reviewer.

Table 46: Frequent non-ocular adverse events up to Week 48

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1] (N=360)	BRO3[1] (N=358)	BRO6[1] (N=360)	AFL2 (N=369)	BRO6 (N=370)
Subjects with AEs	258 (71.7%)	242 (67.6%)	232 (64.4%)	211 (57.2%)	219 (59.2%)
Preferred Term, n(%)					
Nasopharyngitis	33 (9.2%)	30 (8.4%)	25 (6.9%)	16 (4.3%)	25 (6.8%)
Hypertension	14 (3.9%)	24 (6.7%)	12 (3.3%)	13 (3.5%)	17 (4.6%)
Urinary tract infection	25 (6.9%)	26 (7.3%)	19 (5.3%)	9 (2.4%)	10 (2.7%)
Bronchitis	8 (2.2%)	9 (2.5%)	9 (2.5%)	15 (4.1%)	19 (5.1%)
Influenza	8 (2.2%)	8 (2.2%)	13 (3.6%)	15 (4.1%)	10 (2.7%)
Back pain	10 (2.8%)	14 (3.9%)	7 (1.9%)	13 (3.5%)	8 (2.2%)
Arthralgia	10 (2.8%)	7 (2.0%)	9 (2.5%)	8 (2.2%)	10 (2.7%)
Upper respiratory tract infection	7 (1.9%)	8 (2.2%)	9 (2.5%)	11 (3.0%)	3 (0.8%)
Cough	6 (1.7%)	10 (2.8%)	9 (2.5%)	3 (0.8%)	6 (1.6%)
Diarrhoea	8 (2.2%)	5 (1.4%)	9 (2.5%)	3 (0.8%)	8 (2.2%)
Pneumonia	13 (3.6%)	5 (1.4%)	14 (3.9%)	5 (1.4%)	1 (0.3%)
Pain in extremity	6 (1.7%)	7 (2.0%)	8 (2.2%)	3 (0.8%)	7 (1.9%)
Headache	11 (3.1%)	7 (2.0%)	7 (1.9%)	4 (1.1%)	7 (1.9%)
Sinusitis	7 (1.9%)	10 (2.8%)	8 (2.2%)	2 (0.5%)	1 (0.3%)
Atrial fibrillation	10 (2.8%)	7 (2.0%)	6 (1.7%)	4 (1.1%)	3 (0.8%)
Cystitis	2 (0.6%)	3 (0.8%)	1 (0.3%)	4 (1.1%)	12 (3.2%)
Anaemia	8 (2.2%)	7 (2.0%)	5 (1.4%)	3 (0.8%)	4 (1.1%)
Nausea	9 (2.5%)	7 (2.0%)	9 (2.5%)	2 (0.5%)	1 (0.3%)
Osteoarthritis	5 (1.4%)	7 (2.0%)	4 (1.1%)	1 (0.3%)	7 (1.9%)
Syncope	2 (0.6%)	4 (1.1%)	6 (1.7%)	5 (1.4%)	3 (0.8%)
Blood pressure increased	5 (1.4%)	2 (0.6%)	7 (1.9%)	6 (1.6%)	2 (0.5%)
Gamma-glutamyltransferase increased	4 (1.1%)	6 (1.7%)	6 (1.7%)	1 (0.3%)	4 (1.1%)
Hypercholesterolaemia	2 (0.6%)	3 (0.8%)	3 (0.8%)	3 (0.8%)	8 (2.2%)
Constipation	8 (2.2%)	4 (1.1%)	7 (1.9%)	2 (0.5%)	3 (0.8%)
Dizziness	2 (0.6%)	2 (0.6%)	3 (0.8%)	6 (1.6%)	5 (1.4%)
Anxiety	6 (1.7%)	9 (2.5%)	4 (1.1%)	2 (0.5%)	1 (0.3%)
Vertigo	3 (0.8%)	4 (1.1%)	2 (0.6%)	5 (1.4%)	4 (1.1%)
Gastrooesophageal reflux disease	1 (0.3%)	7 (2.0%)	4 (1.1%)	3 (0.8%)	1 (0.3%)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1] (N=360)	BRO3[1] (N=358)	BRO6[1] (N=360)	AFL2 (N=369)	BRO6 (N=370)
Arthritis	10 (2.8%)	2 (0.6%)	8 (2.2%)	3 (0.8%)	2 (0.5%)
Blood urea increased	4 (1.1%)	7 (2.0%)	1 (0.3%)	5 (1.4%)	1 (0.3%)
Contusion	7 (1.9%)	6 (1.7%)	5 (1.4%)	1 (0.3%)	1 (0.3%)
Insomnia	7 (1.9%)	6 (1.7%)	4 (1.1%)	1 (0.3%)	2 (0.5%)
Chronic obstructive pulmonary disease	8 (2.2%)	2 (0.6%)	8 (2.2%)	1 (0.3%)	2 (0.5%)
Fall	4 (1.1%)	8 (2.2%)	3 (0.8%)	1 (0.3%)	0 (0.0%)
Neck pain	2 (0.6%)	2 (0.6%)	6 (1.7%)	3 (0.8%)	1 (0.3%)
Depression	6 (1.7%)	3 (0.8%)	4 (1.1%)	4 (1.1%)	1 (0.3%)
Abdominal pain	5 (1.4%)	2 (0.6%)	4 (1.1%)	3 (0.8%)	2 (0.5%)
Vomiting	4 (1.1%)	4 (1.1%)	1 (0.3%)	3 (0.8%)	3 (0.8%)
Gastroenteritis	4 (1.1%)	1 (0.3%)	2 (0.6%)	5 (1.4%)	3 (0.8%)
Blood cholesterol increased	5 (1.4%)	2 (0.6%)	3 (0.8%)	1 (0.3%)	5 (1.4%)
Musculoskeletal pain	2 (0.6%)	3 (0.8%)	6 (1.7%)	1 (0.3%)	1 (0.3%)
Basal cell carcinoma	2 (0.6%)	3 (0.8%)	6 (1.7%)	0 (0.0%)	2 (0.5%)
Sciatica	2 (0.6%)	0 (0.0%)	1 (0.3%)	6 (1.6%)	4 (1.1%)

[1] AFL2: Aflibercept 2mg; BRO3: Brolucizumab 3mg; BRO6: Brolucizumab 6mg
Source: Table 12-9 of the CSRs for Study 1 and Study 2. This table was produced by the reviewer.

Table 47: Frequent non-ocular adverse events up to Week 96

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1] (N=360)	BRO3[1] (N=358)	BRO6[1] (N=360)	AFL2 (N=369)	BRO6 (N=370)
Subjects with AEs	303 (84.2%)	301 (84.1%)	289 (80.3%)	272 (73.7%)	282 (76.2%)
Preferred Term, n(%)					
Nasopharyngitis	44 (12.2%)	44 (12.3%)	38 (10.6%)	31 (8.4%)	43 (11.6%)
Hypertension	24 (6.7%)	33 (9.2%)	25 (6.9%)	25 (6.8%)	28 (7.6%)
Urinary.tract.infection	41 (11.4%)	41 (11.5%)	27 (7.5%)	19 (5.1%)	16 (4.3%)
Influenza	20 (5.6%)	17 (4.7%)	17 (4.7%)	27 (7.3%)	24 (6.5%)
Back.pain	17 (4.7%)	26 (7.3%)	14 (3.9%)	28 (7.6%)	16 (4.3%)
Bronchitis	22 (6.1%)	13 (3.6%)	13 (3.6%)	21 (5.7%)	23 (6.2%)
Pneumonia	20 (5.6%)	17 (4.7%)	32 (8.9%)	13 (3.5%)	7 (1.9%)
Arthralgia	21 (5.8%)	19 (5.3%)	15 (4.2%)	13 (3.5%)	14 (3.8%)
Upper.respiratory.tract.infection	16 (4.4%)	17 (4.7%)	18 (5.0%)	14 (3.8%)	6 (1.6%)
Cough	17 (4.7%)	20 (5.6%)	13 (3.6%)	8 (2.2%)	12 (3.2%)
Osteoarthritis	11 (3.1%)	14 (3.9%)	9 (2.5%)	7 (1.9%)	19 (5.1%)
Pain.in.extremity	10 (2.8%)	14 (3.9%)	15 (4.2%)	4 (1.1%)	9 (2.4%)
Headache	13 (3.6%)	10 (2.8%)	12 (3.3%)	8 (2.2%)	12 (3.2%)
Diarrhoea	13 (3.6%)	11 (3.1%)	14 (3.9%)	6 (1.6%)	10 (2.7%)
Fall	7 (1.9%)	18 (5.0%)	10 (2.8%)	7 (1.9%)	3 (0.8%)
Atrial.fibrillation	15 (4.2%)	13 (3.6%)	8 (2.2%)	10 (2.7%)	5 (1.4%)
Cystitis	4 (1.1%)	9 (2.5%)	5 (1.4%)	5 (1.4%)	17 (4.6%)
Nausea	12 (3.3%)	17 (4.7%)	12 (3.3%)	3 (0.8%)	1 (0.3%)
Anaemia	15 (4.2%)	12 (3.4%)	7 (1.9%)	8 (2.2%)	5 (1.4%)
Sinusitis	14 (3.9%)	17 (4.7%)	11 (3.1%)	3 (0.8%)	1 (0.3%)
Constipation	13 (3.6%)	11 (3.1%)	13 (3.6%)	2 (0.5%)	5 (1.4%)
Blood.pressure.increased	9 (2.5%)	9 (2.5%)	9 (2.5%)	11 (3.0%)	2 (0.5%)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1] **(N=360)**	**BRO3**[1] **(N=358)**	**BRO6**[1] **(N=360)**	**AFL2 (N=369)**	**BRO6 (N=370)**
Hypercholesterolaemia	4 (1.1%)	5 (1.4%)	5 (1.4%)	8 (2.2%)	13 (3.5%)
Dizziness	6 (1.7%)	9 (2.5%)	8 (2.2%)	9 (2.4%)	5 (1.4%)
Contusion	12 (3.3%)	7 (2.0%)	12 (3.3%)	7 (1.9%)	4 (1.1%)
Syncope	6 (1.7%)	6 (1.7%)	7 (1.9%)	8 (2.2%)	8 (2.2%)
Chronic.obstructive.pulmonary.disease	12 (3.3%)	6 (1.7%)	12 (3.3%)	4 (1.1%)	6 (1.6%)
Sciatica	5 (1.4%)	5 (1.4%)	4 (1.1%)	8 (2.2%)	9 (2.4%)
Gastrooesophageal.reflux.disease	3 (0.8%)	11 (3.1%)	7 (1.9%)	5 (1.4%)	2 (0.5%)
Gamma.glutamyltransferase.increased	7 (1.9%)	8 (2.2%)	8 (2.2%)	5 (1.4%)	4 (1.1%)
Anxiety	10 (2.8%)	13 (3.6%)	5 (1.4%)	3 (0.8%)	3 (0.8%)
Arthritis	13 (3.6%)	4 (1.1%)	12 (3.3%)	3 (0.8%)	4 (1.1%)
Benign.prostatic hyperplasia	5 (1.4%)	8 (2.2%)	5 (1.4%)	4 (1.1%)	6 (1.6%)
Vomiting	5 (1.4%)	7 (2.0%)	6 (1.7%)	5 (1.4%)	3 (0.8%)
Insomnia	10 (2.8%)	11 (3.1%)	5 (1.4%)	3 (0.8%)	2 (0.5%)
Blood.urea.increased	5 (1.4%)	10 (2.8%)	2 (0.6%)	6 (1.6%)	2 (0.5%)
Cardiac.failure.congestive	6 (1.7%)	6 (1.7%)	9 (2.5%)	3 (0.8%)	1 (0.3%)
Herpes.zoster	8 (2.2%)	6 (1.7%)	8 (2.2%)	2 (0.5%)	3 (0.8%)
Basal.cell.carcinoma	6 (1.7%)	5 (1.4%)	8 (2.2%)	1 (0.3%)	5 (1.4%)
Vertigo	5 (1.4%)	5 (1.4%)	2 (0.6%)	5 (1.4%)	6 (1.6%)
Abdominal.pain	7 (1.9%)	5 (1.4%)	5 (1.4%)	6 (1.6%)	2 (0.5%)
Depression	7 (1.9%)	7 (2.0%)	5 (1.4%)	4 (1.1%)	2 (0.5%)
Oedema.peripheral	8 (2.2%)	4 (1.1%)	7 (1.9%)	3 (0.8%)	3 (0.8%)
Pharyngitis	2 (0.6%)	2 (0.6%)	1 (0.3%)	12 (3.3%)	2 (0.5%)
Blood.cholesterol.increased	5 (1.4%)	4 (1.1%)	4 (1.1%)	3 (0.8%)	6 (1.6%)
Musculoskeletal.pain	4 (1.1%)	4 (1.1%)	10 (2.8%)	2 (0.5%)	1 (0.3%)
Neck.pain	3 (0.8%)	2 (0.6%)	8 (2.2%)	4 (1.1%)	3 (0.8%)
Dental.caries	7 (1.9%)	6 (1.7%)	8 (2.2%)	1 (0.3%)	1 (0.3%)
Dyspnoea	8 (2.2%)	9 (2.5%)	6 (1.7%)	1 (0.3%)	0 (0.0%)
Pyrexia	2 (0.6%)	4 (1.1%)	2 (0.6%)	5 (1.4%)	4 (1.1%)
Gastroenteritis	5 (1.4%)	3 (0.8%)	2 (0.6%)	6 (1.6%)	4 (1.1%)
Tooth.infection	5 (1.4%)	6 (1.7%)	2 (0.6%)	4 (1.1%)	3 (0.8%)
Laceration	6 (1.7%)	9 (2.5%)	5 (1.4%)	0 (0.0%)	1 (0.3%)
Spinal.osteoarthritis	3 (0.8%)	3 (0.8%)	3 (0.8%)	7 (1.9%)	2 (0.5%)
Hypotension	5 (1.4%)	5 (1.4%)	6 (1.7%)	1 (0.3%)	3 (0.8%)
Coronary.artery.disease	3 (0.8%)	9 (2.5%)	3 (0.8%)	1 (0.3%)	1 (0.3%)
Toothache	4 (1.1%)	4 (1.1%)	2 (0.6%)	5 (1.4%)	3 (0.8%)
Fatigue	4 (1.1%)	5 (1.4%)	5 (1.4%)	3 (0.8%)	1 (0.3%)
Blood.uric.acid.increased	4 (1.1%)	7 (2.0%)	4 (1.1%)	2 (0.5%)	1 (0.3%)
Asthenia	2 (0.6%)	7 (2.0%)	3 (0.8%)	3 (0.8%)	0 (0.0%)
Cholelithiasis	5 (1.4%)	5 (1.4%)	2 (0.6%)	1 (0.3%)	5 (1.4%)
Seasonal.allergy	9 (2.5%)	3 (0.8%)	10 (2.8%)	0 (0.0%)	0 (0.0%)
Lower.respiratory.tract.infection	2 (0.6%)	4 (1.1%)	1 (0.3%)	4 (1.1%)	4 (1.1%)
Diabetes.mellitus	3 (0.8%)	2 (0.6%)	6 (1.7%)	3 (0.8%)	2 (0.5%)
Hyperlipidaemia	2 (0.6%)	3 (0.8%)	4 (1.1%)	2 (0.5%)	4 (1.1%)
Oropharyngeal.pain	6 (1.7%)	4 (1.1%)	3 (0.8%)	5 (1.4%)	1 (0.3%)
Gastroenteritis.viral	2 (0.6%)	5 (1.4%)	4 (1.1%)	1 (0.3%)	2 (0.5%)

	Study 1 (HAWK)			Study 2 (HARRIER)	
	AFL2[1] (N=360)	BRO3[1] (N=358)	BRO6[1] (N=360)	AFL2 (N=369)	BRO6 (N=370)
Rib.fracture	5 (1.4%)	1 (0.3%)	6 (1.7%)	1 (0.3%)	4 (1.1%)
Hyponatraemia	3 (0.8%)	6 (1.7%)	5 (1.4%)	0 (0.0%)	1 (0.3%)
Cerebrovascular.accident	3 (0.8%)	3 (0.8%)	4 (1.1%)	5 (1.4%)	0 (0.0%)
Transient.ischaemic.attack	2 (0.6%)	4 (1.1%)	1 (0.3%)	3 (0.8%)	4 (1.1%)
Asthma	2 (0.6%)	5 (1.4%)	2 (0.6%)	1 (0.3%)	4 (1.1%)
Varicose.vein	0 (0.0%)	0 (0.0%)	3 (0.8%)	5 (1.4%)	4 (1.1%)
Hypoacusis	1 (0.3%)	5 (1.4%)	1 (0.3%)	3 (0.8%)	2 (0.5%)
Dyspepsia	2 (0.6%)	4 (1.1%)	1 (0.3%)	3 (0.8%)	3 (0.8%)
Haemorrhoids	3 (0.8%)	3 (0.8%)	2 (0.6%)	4 (1.1%)	2 (0.5%)
Large.intestine.polyp	1 (0.3%)	2 (0.6%)	6 (1.7%)	0 (0.0%)	3 (0.8%)
Cellulitis	3 (0.8%)	4 (1.1%)	5 (1.4%)	1 (0.3%)	1 (0.3%)
Diverticulitis	4 (1.1%)	3 (0.8%)	4 (1.1%)	2 (0.5%)	2 (0.5%)
Respiratory.tract.infection	4 (1.1%)	0 (0.0%)	1 (0.3%)	6 (1.6%)	4 (1.1%)
Sepsis	1 (0.3%)	3 (0.8%)	5 (1.4%)	2 (0.5%)	1 (0.3%)
Limb.injury	1 (0.3%)	3 (0.8%)	2 (0.6%)	5 (1.4%)	1 (0.3%)
Blood.creatinine.increased	1 (0.3%)	4 (1.1%)	2 (0.6%)	4 (1.1%)	1 (0.3%)
Vitamin.D.deficiency	4 (1.1%)	3 (0.8%)	6 (1.7%)	1 (0.3%)	1 (0.3%)
Muscle.spasms	7 (1.9%)	1 (0.3%)	4 (1.1%)	2 (0.5%)	4 (1.1%)
Nephrolithiasis	4 (1.1%)	1 (0.3%)	7 (1.9%)	1 (0.3%)	2 (0.5%)
Rhinitis.allergic	3 (0.8%)	2 (0.6%)	2 (0.6%)	4 (1.1%)	3 (0.8%)
Eczema	2 (0.6%)	4 (1.1%)	3 (0.8%)	3 (0.8%)	1 (0.3%)

[1] AFL2: Aflibercept 2mg; BRO3: Brolucizumab 3mg; BRO6: Brolucizumab 6mg
Source: Table 12-10 of the CSRs for Study 1 and Study 2. This table was produced by the reviewer.

Appendix I. Comparison between Delta Method and Bootstrap Method.

Recall that the additional secondary endpoints include the followings:

- Proportion of subjects with BCVA gain of ≥ 15 letters from baseline to each visit; and
- Proportion of subjects with BCVA loss of ≥ 15 letters from baseline to each visit.

For these endpoints, the difference in proportions between the treatment groups was computed by the logistic regression model including baseline BCVA category (≤55, 56-70, ≥71), age category (<75, ≥75), and treatment. The SAP-defined method to compute a 95% confidence interval (CI) for difference in proportions is a delta method. However, as stated in the CSRs, there was a change in the final method for the calculation of the confidence intervals. The 95% confidence intervals reported in the CSRs were computed by using a bootstrap method. This section compares the two 95% CIs (one by the bootstrap method and the other by the delta method) for the difference in proportions. In this comparison, the delta method was implemented by the reviewer's own R codes.

Table 48 and Table 49 present the results for the rate of responders and for the rate of non-responders, respectively. In general, the delta method and bootstrap method produce very similar 95% CIs. The reviewer does not find any significant discrepancies between them. In addition, it does not appear that one method provides consistently narrower 95% CIs than the other.

The column "Unadjusted" in Table 48 and Table 49 presents unadjusted difference and its 95% CI using the normal approximation of binomial distribution without any covariate adjustment. In terms of width of

the 95% CI, the unadjusted method and the adjusted methods by the logistic regression perform similarly: the widths of the 95% CIs are almost the same across three different methods.

Table 48: Difference (95% CI) [1] in proportion (%) of subjects with BCVA gain of ≥ 15 letters

Week	Study 1			Study 2		
	Unadjusted[2]	Logistic Regression		Unadjusted	Logistic Regression	
		Delta	Bootstrap[3]		Delta Method	Bootstrap
4	1.1 (-3.3 ,5.5)	1.6 (-2.8, 6.0)	1.6 (-2.8, 5.8)	-1.4 (-5.3 ,2.6)	-1.3 (-5.2, 2.6)	-1.3 (-5.1, 2.9)
8	3.6 (-1.9 ,9.1)	4.2 (-1.3, 9.7)	4.2 (-1.2, 10.0)	-4.1 (-9.4 ,1.2)	-4.0 (-9.2, 1.2)	-4.0 (-9.2, 1.3)
12	4.2 (-1.9 ,10.2)	4.9 (-1.1, 10.9)	4.9 (-0.5, 11.0)	-4.9 (-10.6 ,0.7)	-5.0 (-10.6, 0.6)	-5.0 (-10.5, 0.3)
16	1.7 (-4.4 ,7.7)	2.3 (-3.6, 8.3)	2.3 (-3.8, 7.5)	-2.2 (-8.1 ,3.7)	-2.3 (-8.1, 3.5)	-2.3 (-8.4, 3.7)
20	3.1 (-3.2 ,9.3)	3.8 (-2.4, 10.0)	3.8 (-2.4, 10.1)	-3.0 (-9.0 ,2.9)	-3.1 (-9.0, 2.8)	-3.1 (-8.8, 2.8)
24	6.4 (0.1 ,12.7)	7.2 (1.0, 13.4)	7.2 (0.8, 13.4)	1.0 (-5.1 ,7.1)	0.9 (-5.0, 6.9)	0.9 (-5.2, 6.7)
28	2.2 (-4.3 ,8.7)	3.2 (-3.2, 9.5)	3.2 (-3.4, 9.4)	-3.3 (-9.6 ,3.0)	-3.4 (-9.5, 2.7)	-3.4 (-9.7, 2.7)
32	6.9 (0.4 ,13.5)	7.9 (1.4, 14.4)	7.9 (1.5, 14.4)	-3.1 (-9.5 ,3.4)	-3.3 (-9.6, 3.1)	-3.3 (-10.3, 2.8)
36	6.9 (0.4 ,13.5)	8.1 (1.7, 14.4)	8.1 (2.1, 14.5)	-4.7 (-11.2 ,1.8)	-4.9 (-11.3, 1.5)	-4.9 (-11.6, 1.3)
40	7.2 (0.5 ,13.9)	8.3 (1.8, 14.8)	8.3 (2.0, 15.1)	-4.1 (-10.7 ,2.4)	-4.4 (-10.8, 2.1)	-4.4 (-11.2, 2.1)
44	6.7 (-0.1 ,13.4)	7.6 (1.0, 14.2)	7.6 (0.7, 13.8)	-4.4 (-10.9 ,2.1)	-4.6 (-11.1, 1.8)	-4.6 (-11.3, 1.8)
48	7.2 (0.6 ,13.9)	8.2 (1.7, 14.7)	8.2 (2.2, 15.0)	-0.4 (-6.9 ,6.2)	-0.6 (-7.1, 5.9)	-0.6 (-7.1, 5.8)
52	3.6 (-3.1 ,10.3)	4.8 (-1.6, 11.3)	4.8 (-1.5, 11.4)	-0.4 (-7.0 ,6.3)	-0.6 (-7.2, 5.9)	-0.6 (-7.0, 5.5)
56	1.9 (-4.8 ,8.7)	3.0 (-3.6, 9.6)	3.0 (-3.1, 9.7)	-0.9 (-7.5 ,5.7)	-1.1 (-7.6, 5.5)	-1.1 (-7.7, 5.4)
60	3.9 (-2.8 ,10.6)	4.9 (-1.7, 11.5)	4.9 (-1.3, 11.4)	-2.0 (-8.6 ,4.6)	-2.2 (-8.7, 4.3)	-2.2 (-8.3, 4.2)
64	4.7 (-2.0 ,11.4)	5.8 (-0.8, 12.3)	5.8 (-0.4, 12.3)	-1.2 (-7.8 ,5.5)	-1.4 (-8.0, 5.1)	-1.4 (-7.9, 5.4)
68	4.4 (-2.3 ,11.1)	5.6 (-0.9, 12.1)	5.6 (0.0, 9.3)	-3.3 (-10.0 ,3.3)	-3.5 (-10.0, 3.1)	-3.5 (-9.9, 3.1)
72	3.9 (-2.8 ,10.5)	5.1 (-1.4, 11.5)	5.1 (-1.1, 11.4)	-3.9 (-10.4 ,2.7)	-4.1 (-10.5, 2.3)	-4.1 (-10.2, 2.3)
76	3.9 (-2.8 ,10.6)	5.0 (-1.5, 11.6)	5.0 (-1.2, 11.6)	-2.2 (-8.8 ,4.3)	-2.4 (-8.9, 4.0)	-2.4 (-8.8, 4.0)
80	7.8 (1.0 ,14.5)	8.8 (2.2, 15.5)	8.8 (2.7, 15.4)	-2.2 (-8.8 ,4.3)	-2.6 (-9.0, 3.8)	-2.6 (-9.4, 3.3)
84	3.3 (-3.2 ,9.9)	4.2 (-2.2, 10.7)	4.2 (-2.2, 10.3)	-3.6 (-10.2 ,3.0)	-3.8 (-10.2, 2.6)	-3.8 (-9.9, 2.8)
88	6.9 (0.2 ,13.7)	8.0 (1.5, 14.6)	8.0 (1.9, 14.6)	-5.5 (-12.1 ,1.1)	-5.8 (-12.3, 0.6)	-5.8 (-11.8, 0.3)
92	4.7 (-2.0 ,11.4)	5.9 (-0.6, 12.4)	5.9 (-0.0, 12.5)	-1.4 (-8.1 ,5.2)	-1.7 (-8.2, 4.8)	-1.7 (-7.9, 4.5)
96	6.1 (-0.6 ,12.8)	7.2 (0.7, 13.8)	7.2 (1.4, 13.8)	-2.2 (-8.9 ,4.4)	-2.4 (-8.9, 4.2)	-2.4 (-8.8, 4.1)

[1] Difference: difference in proportions (brolucizumab 6mg – aflibercept 2mg); CI: confidence interval
[2] Unadjusted: difference and 95% CI was obtained using normal approximation of binomial distribution.
[3] Bootstrap method based on 1000 bootstrap samples. This table was produced by the reviewer.

Table 49: Difference (95% CI) [1] in proportion (%) of subjects with BCVA loss of ≥ 15 letters

Week	Study 1			Study 2		
	Unadjusted[2]	Logistic Regression		Unadjusted	Logistic Regression	
		Delta	Bootstrap[3]		Delta Method	Bootstrap
4	1.7 (-0.5 ,3.8)	1.7 (-0.5, 3.9)	1.7 (-0.5, 4.0)	-0.0 (-1.5 ,1.5)	-0.0 (-1.5, 1.5)	-0.0 (-1.6, 1.4)
8	0.6 (-1.7 ,2.8)	0.7 (-1.6, 2.9)	0.7 (-1.7, 2.9)	-0.5 (-2.2 ,1.1)	-0.6 (-2.2, 1.1)	-0.6 (-2.3, 1.1)
12	-0.3 (-3.1 ,2.5)	-0.3 (-3.0, 2.5)	-0.3 (-3.2, 2.7)	-0.0 (-2.0 ,2.0)	0.0 (-1.9, 2.0)	0.0 (-1.9, 2.2)
16	0.3 (-2.4 ,3.0)	0.3 (-2.4, 3.0)	0.3 (-2.4, 3.1)	-0.0 (-2.1 ,2.1)	0.0 (-2.1, 2.1)	0.0 (-2.1, 2.3)
20	2.2 (-0.5 ,4.9)	2.3 (-0.4, 5.1)	2.3 (-0.3, 5.3)	0.5 (-2.0 ,3.1)	0.6 (-2.0, 3.1)	0.6 (-2.0, 3.3)
24	1.4 (-1.7 ,4.4)	1.5 (-1.6, 4.5)	1.5 (-1.8, 4.6)	-0.5 (-3.0 ,1.9)	-0.5 (-3.0, 1.9)	-0.5 (-3.0, 2.2)
28	1.1 (-2.1 ,4.3)	1.1 (-2.1, 4.3)	1.1 (-2.3, 4.6)	-0.6 (-3.1 ,2.0)	-0.5 (-3.0, 2.1)	-0.5 (-3.0, 2.3)
32	2.2 (-1.0 ,5.5)	2.2 (-1.0, 5.5)	2.2 (-1.3, 5.8)	-0.6 (-3.2 ,2.1)	-0.5 (-3.1, 2.2)	-0.5 (-3.5, 2.6)
36	3.1 (-0.1 ,6.2)	3.1 (-0.0, 6.3)	3.1 (0.0, 6.5)	0.3 (-2.4 ,3.0)	0.4 (-2.3, 3.1)	0.4 (-2.3, 3.3)
40	2.8 (-0.6 ,6.1)	2.8 (-0.5, 6.2)	2.8 (-0.7, 6.3)	1.1 (-2.0 ,4.2)	1.2 (-1.9, 4.3)	1.2 (-1.7, 4.6)

Week	Study 1			Study 2		
	Unadjusted[2]	Logistic Regression		Unadjusted	Logistic Regression	
		Delta	Bootstrap[3]		Delta Method	Bootstrap
44	1.9 (-1.4 ,5.2)	2.0 (-1.3, 5.3)	2.0 (-1.4, 5.2)	-0.0 (-3.0 ,3.0)	0.1 (-2.9, 3.1)	0.1 (-2.7, 3.4)
48	0.8 (-2.6 ,4.3)	0.9 (-2.6, 4.3)	0.9 (-2.7, 4.3)	-1.1 (-4.0 ,1.8)	-1.0 (-3.9, 1.9)	-1.0 (-3.9, 2.2)
52	1.1 (-2.5 ,4.7)	1.3 (-2.3, 4.8)	1.3 (-1.3, 4.0)	-1.1 (-4.3 ,2.1)	-1.0 (-4.1, 2.2)	-1.0 (-4.3, 2.3)
56	2.5 (-1.1 ,6.1)	2.6 (-1.0, 6.2)	2.6 (-1.5, 6.3)	0.5 (-2.8 ,3.9)	0.6 (-2.7, 4.0)	0.6 (-2.8, 3.9)
60	1.1 (-2.5 ,4.7)	1.2 (-2.4, 4.8)	1.2 (-2.9, 4.9)	0.5 (-2.9 ,3.9)	0.6 (-2.8, 4.0)	0.6 (-2.7, 4.1)
64	2.8 (-1.0 ,6.6)	2.8 (-0.9, 6.6)	2.8 (-1.2, 6.7)	0.5 (-3.0 ,4.1)	0.7 (-2.9, 4.2)	0.7 (-2.7, 4.5)
68	1.1 (-2.6 ,4.8)	1.1 (-2.6, 4.8)	1.1 (-2.9, 4.9)	-1.1 (-4.5 ,2.3)	-0.9 (-4.3, 2.5)	-0.9 (-4.2, 2.6)
72	1.4 (-2.3 ,5.1)	1.5 (-2.2, 5.2)	1.5 (-2.7, 5.3)	0.8 (-2.9 ,4.4)	0.9 (-2.7, 4.6)	0.9 (-2.5, 4.5)
76	1.9 (-1.8 ,5.7)	2.0 (-1.7, 5.8)	2.0 (-2.1, 6.0)	0.5 (-3.0 ,4.1)	0.7 (-2.9, 4.2)	0.7 (-2.5, 4.4)
80	-0.3 (-4.2 ,3.7)	-0.2 (-4.1, 3.7)	-0.2 (-4.6, 3.9)	0.8 (-2.8 ,4.4)	0.9 (-2.7, 4.5)	0.9 (-2.4, 4.6)
84	0.6 (-3.3 ,4.4)	0.6 (-3.2, 4.5)	0.6 (-3.2, 4.5)	-0.0 (-3.8 ,3.7)	0.2 (-3.6, 3.9)	0.2 (-3.3, 4.2)
88	0.0 (-4.0 ,4.0)	0.1 (-3.9, 4.1)	0.1 (-3.7, 4.1)	-0.3 (-3.9 ,3.4)	-0.2 (-3.8, 3.5)	-0.2 (-3.5, 3.6)
92	1.1 (-2.7 ,5.0)	1.2 (-2.7, 5.0)	1.2 (-3.0, 5.1)	-0.6 (-4.3 ,3.2)	-0.4 (-4.2, 3.3)	-0.4 (-3.8, 3.3)
96	0.6 (-3.4 ,4.5)	0.7 (-3.2, 4.6)	0.7 (-3.6, 4.6)	-0.6 (-4.3 ,3.2)	-0.4 (-4.1, 3.3)	-0.4 (-3.8, 3.3)

[1] Difference: difference in proportions (brolucizumab 6mg – aflibercept 2mg); CI: confidence interval
[2] Unadjusted: difference and 95% CI was obtained using normal approximation of binomial distribution.
[3] Bootstrap method based on 1000 bootstrap samples. This table was produced by the reviewer.

Appendix J. Assessment of NI Margin

This section provides the reviewer's assessment of the NI margin of 4 letters for the primary efficacy endpoint (change in BCVA from baseline to Week 48).

Recall that the active comparator in Study 1 and Study 2 is aflibercept 2mg q8w. The two pivotal studies of Eylea (aflibercept 2mg) in wet AMD patients, VIEW 1 and VIEW 2, compared aflibercept 2mg q8w to ranibizumab 0.5mg monthly injection. Note that there was no placebo or sham group in VIEW 1 and VIEW 2. Thus, an estimate of treatment effect of aflibercept 2mg against placebo (M1 margin per Non-inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry) cannot be estimated solely based on VIEW 1 and VIEW 2. Thus, the reviewer also relies on one of the pivotal studies of Lucentis (ranibizumab 0.5mg) in wet AMD patients, MARINA (Study FVF2598g), which compared ranibizumab 0.5mg monthly injection to a sham control.

In Study MARINA, the estimated treatment effect of ranibizumab 0.5mg against sham was 17.4 letters (Table 50) in terms of the mean BCVA change from baseline to Week 48. Note that the lower bound of a 95% CI for the treatment effect was 14.4 letters. Thus, an M1 margin for ranibizumab 0.5mg against sham is larger than 14 letters. In the meanwhile, in terms of the mean BCVA change from baseline to Week 48, the differences between the aflibercept 2mg arm and ranibizumab 0.5mg arm in Studies VIEW 1 and VIEW2 were less than 1 letters: -0.4 [95% CI: (**-2.8**, 2.0)] in VIEW 1 and -0.9 [95% CI: (**-3.2**, 1.3)] in VIEW 1. Given an M1 margin of ≥ 14 letters for ranibizumab 0.5mg from MARINA and the similar performance (with a difference less than 4 letters) between aflibercept 2mg and ranibizumab 0.5mg in VIEW 1 and VIEW2, the reviewer finds the NI margin of 4 letters in the primary analysis acceptable.

Table 50: Mean BCVA change from baseline to Week 48 in Studies MARINA, VIEW 1, and VIEW 2

	MARINA		VIEW 1		VIEW 2	
	Ranibizumab 0.5 mg (N = 240)	**Sham** (N = 238)	**Aflibercept 2mg** (N = 301)	**Ranibizumab 0.5 mg** (N = 304)	**Aflibercept 2mg** (N = 306)	**Ranibizumab 0.5 mg** (N = 291)
Mean (SD)	6.3 (14.1)	-11.0 (17.9)	8.1 (14.9)	8.5 (15.1)	8.1 (14.3)	9.0 (13.7)
Difference (95% CI) [1]		**17.4 (14.4, 20.3)**		**-0.4 (-2.8, 2.0)**		**-0.9 (-3.2, 1.3)**

[1] Difference: ranibizumab - sham for MARINA and aflibercept – ranibizumab for VIEW 1 and VIEW 2; 95% CIs were computed using two-sample t-tests. This table was produced by the reviewer.

While the NI margin of 4 letters is acceptable from the statistical view of the previous wet AMD studies (MARINA, VIEW 1, and VIEW 2), the reviewer noticed that Study 1 and Study 2 differ in baseline BCVA compared with the previous wet ADM studies (Table 51): 60~61 letters vs. 52~55 letters.

Table 51: Comparison of baseline disease characteristics across studies

Study	**MARINA** (N = 478)	**VIEW 1** (N = 605)	**VIEW 2** (N = 597)	**Study 1** (N = 360)	**Study 2** (N = 369)
Baseline BCVA					
Mean (SD)	53.4 (14.8)	54.8 (13.1)	52.7 (13.7)	60.0 (13.9)	60.8 (12.9)
Median	55.0	56.0	55.0	63.0	64.0
Min, Max	0, 88	10, 83	10, 83	16, 83	23, 79
Baseline Area of CNV † (mm^2)					
Mean (SD)	4.3 (2.5)	6.5 (5.2)	7.7 (5.4)	4.4 (3.7)	2.9 (3.9)
Median	3.8	5.3	6.4	3.7	1.6
Min, Max	0, 12	0, 33	0, 29	0, 19	0, 34
Baseline CNV Type					
Minimally Classic	178 (37.2)	211 (34.9)	210 (35.2)	34 (9.4)	34 (9.2)
Occult	299 (62.6)	233 (38.5)	226 (37.9)	209 (58.1)	187 (50.7)
Predominantly Classic	1 (0.2)	153 (25.3)	158 (26.5)	116 (32.2)	144 (39.0)
Missing	0 (0.0)	8 (1.3)	3 (0.5)	0 (0.0)	0 (0.0)

† CNV: Choroidal Neo-Vascularization. This table was produced by the reviewer.

As the primary efficacy endpoint is the change in BCVA from baseline to Week 48, the difference in baseline BCVA across the studies needs to be considered in the assessment of the NI margin. To address the difference in baseline BCVA, the reviewer performs the following analysis:

Step 1: For each of MARINA, VIEW 1, and VIEW2, fit a linear regression model for change from baseline in BCVA to Week 48. The model includes baseline BCVA, treatment, and baseline BCVA by treatment interaction(see Figure 5 for the graphical presentation of data and regression fits).

Step 2: Using each of the regression model fitted in Step 1, obtain a predicted BCVA change from baseline to Week 48 under each treatment arm for each subject in Study 1 and Study 2.

Step 3: Average the predicted BCVA changes in Step 2 within each treatment arm to obtain estimates of mean change in BCVA from baseline to Week 48 under each treatment. These estimates are referred to as “predicted” mean change in BCVA from baseline to Week 48 which is adjusted for baseline BCVA of the subjects in Study 1 and Study 2.

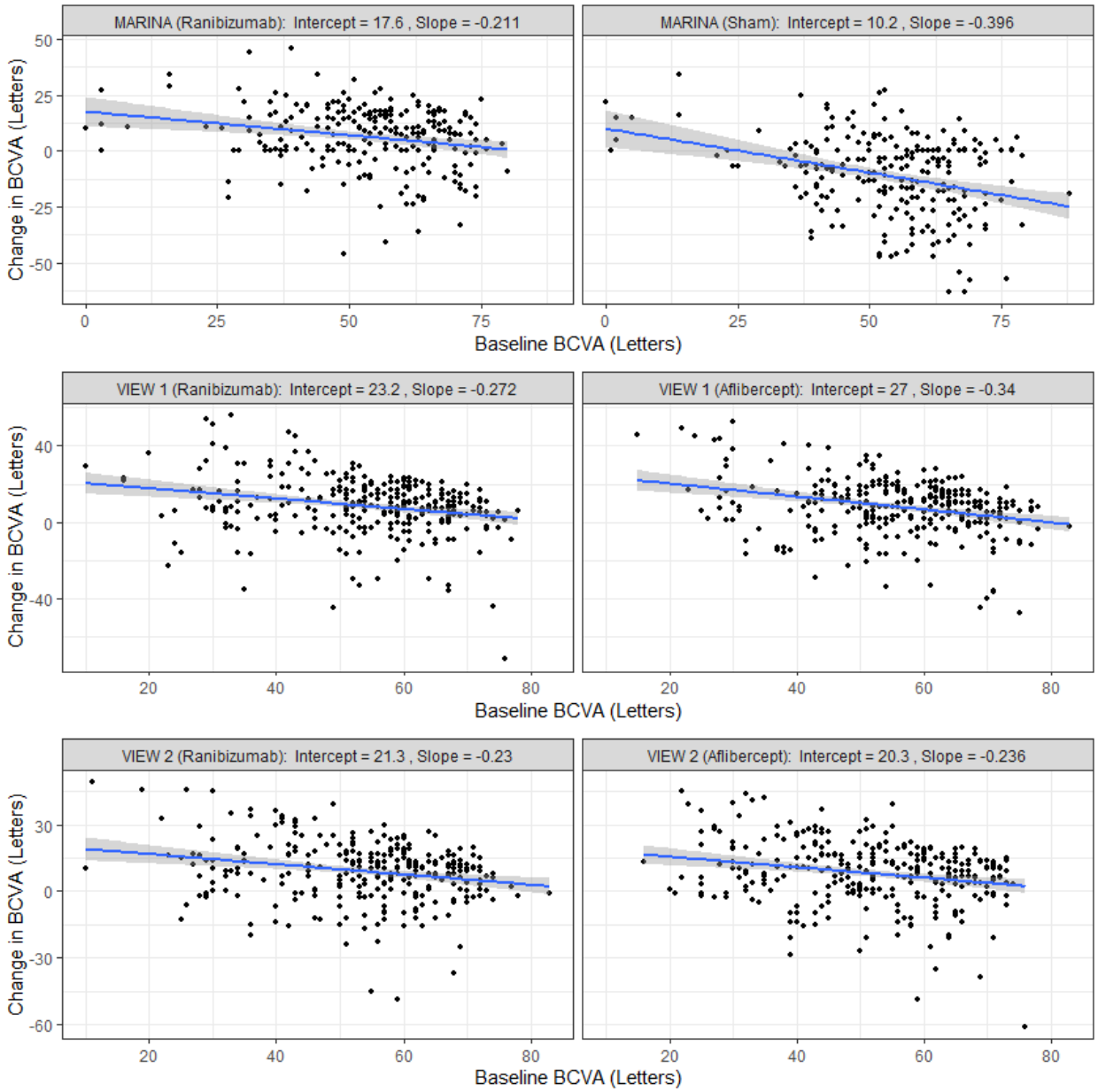
Table 52 presents the predicted mean change in BCVA from baseline to Week 48 and estimated treatment differences from them. The estimated treatment effect of ranibizumab 0.5mg against sham from MARINA is 18.5 letters [95% CI: (15.4, 21.6)] when adjusted for Study 1 and 18.7 letters [95% CI: (15.5, 21.8)] when adjusted for Study 2. Note that the lower bound of the 95% CIs are larger than 15 letters. In the meanwhile, the difference between the aflibercept 2mg arm and ranibizumab 0.5mg arm in Study VIEW 1 is -0.3 letters [95% CI: (-2.7, 2.2)] when adjusted for Study 1 and -0.3 letters [95% CI: (-2.9, 2.2)] when adjusted for Study 2. In Study VIEW 2, it is -1.5 letters [95% CI: (-4.0, 1.0)] when adjusted for Study 1 and -1.5 letters [95% CI: (-4.0, 1.1)] when adjusted for Study 2. Thus, given an M1 margin of ≥ 15 letters for ranibizumab 0.5mg from MARINA and the similar performance (with a difference less than 4 letters) between aflibercept 2mg and ranibizumab 0.5mg in VIEW 1 and VIEW2, the reviewer still finds the NI margin of 4 letters in the primary analysis acceptable.

Table 52: Predicted mean BCVA change from baseline to Week 48 adjusted for Study 1 and Study 2

	MARINA		VIEW 1		VIEW 2	
	Ranibizumab 0.5 mg	**Sham**	**Aflibercept 2mg**	**Ranibizumab 0.5 mg**	**Aflibercept 2mg**	**Ranibizumab 0.5 mg**
Adjusted for Study 1						
LS Mean (SE) [1]	4.9 (1.1)	-13.6 (1.1)	6.6 (0.9)	6.9 (0.9)	6.1 (0.9)	7.6 (0.9)
Difference (95% CI) [2]		**18.5 (15.4 ,21.6)**		**-0.3 (-2.7 ,2.2)**		**-1.5 (-4.0 ,1.0)**
Adjusted for Study 2						
LS Mean (SE) [1]	4.7 (1.1)	-13.9 (1.1)	6.3 (0.9)	6.6 (0.9)	5.9 (0.9)	7.4 (0.9)
Difference (95% CI) [2]		**18.7 (15.5 ,21.8)**		**-0.3 (-2.9 ,2.2)**		**-1.5 (-4.0 ,1.1)**

[1] LS mean and SE (standard error) were obtained from the regression fits with the values of covariates for the subjects in ether Study 1 or Study 2 being the reference grids for the LS mean computation.
[2] Difference: ranibizumab - sham for MARINA and aflibercept – ranibizumab for VIEW 1 and VIEW 2; CI: confidence interval.
This table was produced by the reviewer.

Figure 5: Linear regression of BCVA change at Week 48 on baseline BCVA

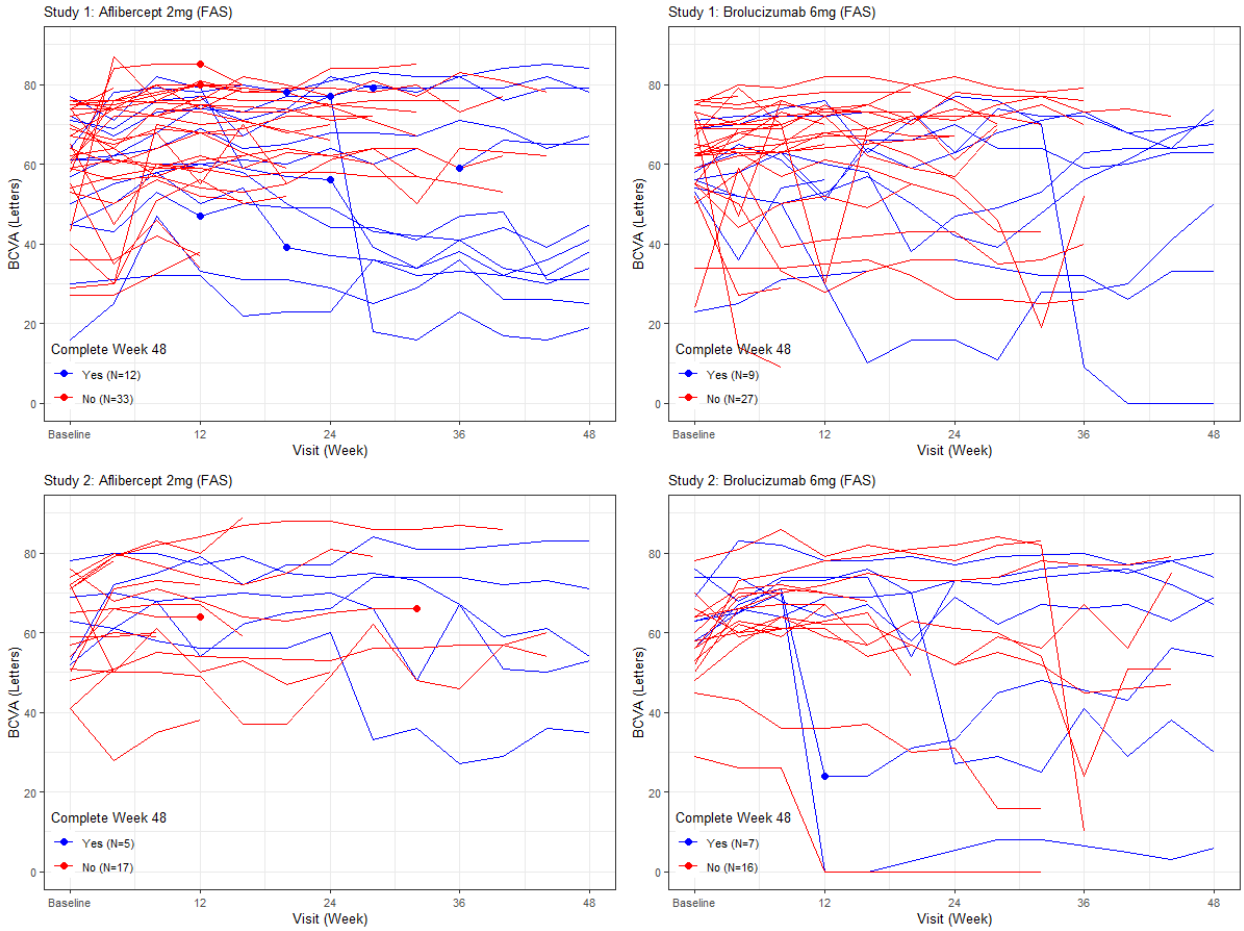


Source: this table was produced by the reviewer.

Appendix K. BCVA Profile for Subjects with Treatment Discontinuation

This section presents the time profile of BCVA for the subgroup of patients who discontinued the study treatment prematurely prior to Week 48. In Figure 6, the top panels show BCVA profile for these subjects in Study 1 and the bottom panels present BCVA profile for these subjects in Study 2. In each panel, the red curves are the BCVA profiles for the subjects who did not complete Week 48 visit and the blue curves are the BCVA profiles for the subjects who completed Week 48 visit.
The reviewer does not find any notable pattern which differentiating between the completer group (blue) and non-completer group (red). In addition, no notable difference is found between the aflibercept 2mg arm (left panels) and the brolucizumab 6mg arm (right panels).

Figure 6: BCVA for subjects who discontinued study treatment prematurely prior to Week 48



Note: For subjects who discontinued the study treatment prior to Week 48 due to either “Lack of Efficacy” or “Progressive Disease”, the last time points prior to the treatment discontinuation are marked with dots.
Source: this table was produced by the reviewer.

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/s/

WONYUL N LEE
07/22/2019 02:54:57 PM

YAN WANG
07/22/2019 04:58:36 PM
I concur.