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APPLICATION NUMBER:

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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 Serial Number:	125,387/SN-0000
Drug Name:	Aflibercept ophthalmic solution (VEGF Trap-Eye)
Indication(s):	Treatment of neovascular (wet) age-related macular degeneration (AMD)
Applicant:	Regeneron Pharmaceuticals, Inc.
Date(s):	Submitted: February 17, 2011
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Review Priority:	Priority
Biometrics Division:	IV
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Keywords: Neovascular (wet) age-related macular degeneration (AMD), best corrected visual acuity (BCVA)

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1 EXECUTIVE SUMMARY

This BLA application seeks the approval of VEGF Trap-Eye administered intravitreally for the treatment of neovascular (wet) age-related macular degeneration (AMD). The proposed dose for VEGF Trap-Eye is 2 mg administered by intravitreal injection once every 2 months, following 3 initial monthly injections of 2 mg. VEGF Trap-Eye may be dosed as frequently as 2 mg once per month.

The efficacy of VEGF Trap-Eye was supported by clinical data from two Phase-3 studies, VGFT-OD-0605 (VIEW 1) and 311523 (VIEW 2). Both studies were randomized, double masked, active comparator (0.5 mg ranibizumab) controlled study. Subjects eligible for the study were men and women $\geq$ 50 years of age with active primary subfoveal choroidal neovascularization (CNV) lesions secondary to AMD. For each subject, one eye was designated as the study eye. At screening, subjects had a best corrected visual acuity (BCVA) of 20/40 to 20/320 (letter score of 73 to 25) in the study eye; CNV in the study eye were at least 50% of total lesion size. Subjects were randomized to receive one of the four treatments: 2 mg VEGF Trap-Eye administered every 4 weeks, 0.5 mg VEGF Trap-Eye administered every 4 weeks, 2 mg VEGF Trap-Eye administered every 8 weeks, and 0.5 mg ranibizumab administered every 4 weeks. Subjects with all three subtypes of AMD (occult, minimally classic, and predominantly classic) were allowed to enroll in each VEGF Trap-Eye study. This reflected a synthesis of the selection criteria of all pivotal trials of the ranibizumab development program.

These two studies demonstrated that VEGF Trap-Eye is non-inferior to 0.5 mg ranibizumab with respect to the proportion of subjects who maintained vision at week 52, based on a pre-determined non-inferiority margin of 10%. The maintenance of vision was defined as a loss, relative to baseline, in visual acuity of less than 15 letters in the ETDRS letter score. In both studies, nearly 94% of subjects treated with VEGF Trap-Eye and 0.5 mg ranibizumab maintained vision at week 52. The findings for 0.5 mg ranibizumab were similar to those from the pivotal ranibizumab studies used to support its registration. Furthermore, the design and conduct of both non-inferiority studies for the VEGF Trap-Eye program are considered adequate.

Results from the analysis of secondary efficacy endpoints, including BCVA change from baseline at week 52 and the proportion of subjects who gained at least 15 letters in the BCVA score at week 52 compared with baseline, also supported the efficacy of VEGF Trap-Eye compared to 0.5 mg ranibizumab. Both VEGF Trap-Eye regimens and 0.5 mg ranibizumab were associated with fairly similar change in BCVA score and proportion of subjects who gained at least 15 letters in the BCVA score at week 52 compared with baseline. A summary of key efficacy results are presented in Table 1.

The analyses of the primary and secondary efficacy endpoints were conducted according to pre-specified statistical methodology. The Reviewer concurred with the pre-specified statistical methodology and confirmed the primary efficacy and key secondary efficacy results for visual acuity. Additional analyses employing different statistical approach or different method to handle

missing data were performed by the Reviewer. The results from these analyses were similar to those presented in the submission.

Table 1: Key efficacy results at week 52 - proportion of subjects who maintained vision, change in BCVA score from baseline, and proportion of subjects who gained ⩾15 letters in BCVA score from baseline (Full analysis set)

Study	Treatment	Number of subjects	Subjects who maintained vision (%)	Mean (SD): number of letters	Gain of ≥ 15 letters (%)
VGFT-OD-0605 (VIEW 1)	Ranibizumab 0.5Q4	304	93.8%	8.1 (15.2)	30.9%
	VTE 2Q4	304	95.1%	10.9 (13.8)	37.5%
	VTE 0.5Q4	301	95.0%	6.9 (13.4)	24.9%
	VTE 8Q4	301	94.4%	7.9 (15.0)	30.6%
311523 (VIEW 2)	Ranibizumab 0.5Q4	291	94.8%	9.4 (13.5)	34.0%
	VTE 2Q4	309	94.5%	7.6 (12.6)	29.4%
	VTE 0.5Q4	296	95.3%	9.7 (14.1)	34.8%
	VTE 8Q4	306	95.4%	8.9 (14.4)	31.4%

Note: Maintenance of vision was defined as a loss of <15 letters in the ETDRS letter score.
Source: VGFT-OD-0605 (VIEW 1) CSR Tables 20, 22, and 23; 311523 (VIEW 2) CSR Tables 21, 24, and 25.

Therefore, the efficacy of VEGF Trap-Eye regimens was supported by a non-inferiority comparison to 0.5 mg ranibizumab for the proportion of subjects who maintained vision at week 52. Similar efficacy results observed with VEGF Trap-Eye and 0.5 mg ranibizumab in the secondary visual acuity endpoints further substantiated the efficacy of VEGF Trap-Eye compared to 0.5 mg ranibizumab for treatment of neovascular AMD.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

VEGF Trap-Eye was developed for the treatment of neovascular (wet) age-related macular degeneration (AMD). The proposed dose for VEGF Trap-Eye is 2 mg administered by intravitreal injection once every 2 months, following 3 initial monthly injections of 2 mg. VEGF Trap-Eye may be dosed as frequently as 2 mg once per month.

AMD is the most common degenerative disease of the macula and is the most common cause of blindness in the developed world. There are two forms of AMD, the dry and the wet form. The dry form is more benign and accounts for 90% of all AMD cases, but only for 10% of cases of blindness due to AMD. There is no treatment for dry AMD. Antioxidants and vitamins have been shown in certain subgroups to reduce the risk of AMD progression. Dry AMD may develop into wet AMD, also known as neovascular or exudative AMD, which is less prevalent. Wet AMD affects 10% of the AMD patients and is the more aggressive form. If untreated, wet AMD leads to rapid severe visual impairment and legal blindness. About 80% to 90% of patients with severe vision loss due to AMD have wet AMD.

The treatment paradigms for wet AMD shifted tremendously when anti-VEGF treatment, notably Ranibizumab (Lucentis™; Genentech-Roche/Novartis), was introduced. Ranibizumab was approved for the treatment of wet AMD in U.S. in 2006 and since then, it has become the standard of care in the treatment of wet AMD.

In the pivotal ranibizumab studies, monthly intravitreal administration of ranibizumab maintained vision, defined as loss of <15 letters, at 12 months in approximately 95% of the patients. Additionally, ranibizumab resulted in gain of ≥15 letters in at least 1/3 of patients in these studies. Clinical meaningful improvement was observed in mean visual acuity.

Intravitreal injection of ranibizumab poses potential serious risk; and monthly regimen is burdensome to patients, caregivers, ophthalmologists and the healthcare system. VEGF Trap-Eye is developed as an alternative treatment of wet AMD, which is intended to offer similar efficacy as ranibizumab, but a more convenient dosing scheme. According to the BLA submission, VEGF Trap binds to VEGF, with binding affinity higher than does the native VEGF receptors. Moreover, unlike other anti-VEGF molecules, VEGF Trap also binds to PlGF, with higher binding affinity than does its native receptor. The combination of these properties was expected to potentially contribute to longer lasting action, thereby leading to a dosing interval longer than once monthly and, possibly, to improved visual acuity as compared to standard therapies without similar properties.

2.1.2 History of Drug Development

The development of VEGF Trap-Eye for the treatment of wet AMD was filed under IND 12462 on May 16, 2005 and opened on June 15, 2005.

The clinical development program for VEGF Trap-Eye in support of the proposed indication started with two Phase-1 studies (VGFT-OD-0502 and VGFT-OD-0603) to assess the safety of single or repeated intravitreal injections of VEGF Trap-Eye at doses between 0.05 and 4 mg.

Phase-2 study VGFT-OD-0508 (completed on June 26, 2008) was a double masked, prospective, randomized study for the safety, tolerability and biological effect of repeated intravitreal administration of VEGF trap in patients with neovascular age-related macular degeneration. Approximately 150 eligible patients were randomly assigned with an equal chance to receive ITV injections of VEGF Trap into the study eye at 4- or 12-week intervals over a 12-week period. Treatment groups were as follows:

Group A: 0.5 mg VEGF Trap at 12- week intervals
Group B: 0.5 mg VEGF Trap at 4-week intervals
Group C: 2.0 mg VEGF Trap at 12-week intervals
Group D: 2.0 mg VEGF Trap at 4-week intervals
Group E: 4.0 mg VEGF Trap at 12-week intervals

Beginning at Week 16, subjects in all treatment arms were evaluated every 4 weeks for subsequent PRN dosing at the randomized dose level for up to one year.

Visual acuity was assessed at Week 12. All treatment groups experienced improvements in visual acuity as early as Week 1, and these improvements were maintained through Week 12. The VA improvement was maintained during Weeks 16 through 52 (the PRN phase) with an average of only two additional doses during this time.

Subjects enrolled in Phase-1 or Phase-2 studies were allowed to continue treatment with VEGF Trap-Eye 2 mg PRN in an ongoing Phase-2 long-term safety study (VGFT-OD-0702).

Two Phase-3 studies were conducted to generate the pivotal support for the proposed indication.

The study protocol VGFT-OD-0605/14393 (VIEW 1) was first issued on January 15, 2007 and subsequently amended three times (Amendment 1 on May 24, 2007; Amendment 2 on January 16, 2008; and Amendment 3 on June 03, 2009).

The Applicant submitted a Special Protocol Assessment (SPA) request for VGFT-OD-0605 (VIEW 1) on January 18, 2007 (serial #060). The proposed design was a 2-year double-masked, parallel, non-inferiority study of intravitreal VEGF Trap-Eye against ranibizumab for maintenance of best-corrected visual acuity (BCVA) in patients with neovascular AMD. The proposed dose arms for the first year were 4 mg every 4 weeks (4mgQ4), 1 mg every 4 weeks (1mgQ4), and 4 mg every 12 weeks with sham doses at interim monthly visits when VEGF Trap-Eye was not administered (4mgQ12), or ranibizumab at 0.5 mg once every four weeks (RQ4). In the second year, subjects were to be evaluated every 4 weeks, and receive an

intravitreal injection at least every 12 weeks. Injections could be given as frequently as every 4 weeks, but no less frequently than every 12 weeks, according to specific criteria. The proposed primary endpoint was the proportion of subjects who maintained vision. The maintenance of vision was defined as loss of less than 15 letters in best-corrected visual acuity on the Early Treatment Diabetic Retinopathy Study [ETDRS] chart compared to baseline at 12 months.

The proposed analysis was non-inferiority compared to ranibizumab, which was analyzed sequentially for each of the VEGF Trap-Eye dose groups in the following order: 4mgQ4, followed by 1mgQ4, and then 4mgQ12. A confidence interval approach was planned for the non-inferiority evaluation using a non-inferiority margin of 10%. Key aspects of the study design and analysis plan were agreed upon by the Agency.

The Applicant submitted a second SPA request (serial #074) on May 31, 2007 for Protocol VGFT-OD-0605 (VIEW 1). Changes were made to the VEGF Trap-Eye dose regimens to include 2.0 mg VEGF Trap every 4 weeks (2Q4), 0.5 mg VEGF Trap every 4 weeks (0.5Q4) and 2.0 mg VEGF Trap every 8 weeks (2Q8) (with three consecutive doses at Day 1, Week 4 and Week 8), as well as ranibizumab0.5 mg every 4 weeks (RQ4). The proposed conditional sequence for primary endpoint analysis was VEGF Trap 2mgQ4, 0.5mgQ4 and then 2mgQ8. In addition, the primary endpoint would be at week 52 rather than week 48.

The choice of the final dose groups in the Phase-3 program, i.e., 0.5Q4, 2Q4, and 2Q8, was based on the results of Study VGFT-OD-0508. Over the first 12 weeks, 100% of patients in the 2Q4 treatment group and 0.5Q4 treatment group maintained vision (defined as losing less than 15 letters on the ETDRS scale). In addition, the improvements in visual acuity were similar in the two 2 mg groups at Week 8, suggesting that an 8-week dosing interval could potentially maintain the effects of VEGF Trap-Eye in Phase-3 studies. The time course of improvements also suggested that initiating treatment with three monthly injections was associated with a better outcome than a single injection of either 2 mg or 0.5 mg. In the PRN phase, a greater percentage of patients in the 2-mg group maintained vision than in the 0.5-mg group, indicating that efficacy of the 0.5-mg dose is more sensitive to dosing interval than efficacy with the 2-mg dose. Dosing with 4 mg did not result in greater efficacy than dosing with 2 mg.

In response to the Agency's comments as part of the SPA for this protocol, the Applicant amended the protocol (Amendment 2). Among the changes, the statistical section was updated to include treatment by site interaction analyses for all sites (including calculations of confidence intervals for differences for all sites regardless of size).

Study 311523 (VIEW 2; VGFT-OD-0618) followed essentially the same design as the VGFT-OD-0605 (VIEW 1) study. The difference between the two studies is that Study VGFT-OD-0605 (VIEW 1) was conducted primarily in North America, and Study 311523 (VIEW 2) was conducted primarily in Europe, Asia, Australia and Latin America. At the time of the BLA submission, the Phase-3 studies are still ongoing.

The present application is based on the data obtained through the end of the first year of treatment of these two studies. The first year of the studies includes a direct comparison of a

fixed dosing every two months versus the comparator treatment ranibizumab which is given at monthly dosing. One year of treatment was expected to provide clinically relevant information on the efficacy and safety of the respective treatment group. After completion of the primary endpoints, the studies continue for another year. Year 2 was designed to evaluate the impact of further prolonged dosing intervals and criteria-based flexible dosing on the maintenance of the visual acuity and morphological benefits achieved in the first year.

A pre-BLA meeting was held on September 8, 2010 to discuss clinical issues concerning the planned BLA submission. It was agreed that the key analyses for the summary of clinical efficacy would be derived from the 1-year analysis of each individual Phase 3 studies (VIEW 1 and VIEW 2), the pooled analysis of the 1-year data from the two Phase 3 studies and the Phase 2 study VGFT-OD-0508. It was also agreed that, for each individual phase 3 study, subgroup analysis for efficacy would be performed for the primary (loss of <15 letters) and secondary visual acuity (mean change and 3-line gainers) endpoints. Sensitivity analysis would be provided for primary and all secondary endpoints.

2.1.3 Specific Studies Reviewed

Two Phase-3 studies, Study VGFT-OD-0605 (VIEW 1) and Study 311523 (VIEW 2), are selected for full statistical review and evaluation.

Study VGFT-OD-0605 (VIEW 1) is a randomized, double masked, active controlled study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap in subjects with neovascular age-related macular degeneration. Subjects eligible for the study were men and women ≥ 50 years of age with active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea, as evidenced by fluorescein angiography (FA). For each subject, only one eye was designated as the study eye and received randomized treatment.

The planned sample size was 1200, and the subjects were to be recruited at multi-centers in USA and Canada. At the conclusion of the study enrollment, a total of 1217 subjects from 154 sites were randomized to one of 4 dosing regimens:

- 2 mg VEGF Trap-Eye administered every 4 weeks (2Q4; N=304),
- 0.5 mg VEGF Trap-Eye administered every 4 weeks (0.5Q4; N=304),
- 2 mg VEGF Trap-Eye administered every 8 weeks (2Q8; N=303), and
- 0.5 mg ranibizumab administered every 4 weeks (RQ4; N=306).

Subjects assigned to (2Q8) received the 2 mg injection every 4 weeks to week 8 (at day 1, week 4, and week 8) and then a sham injection at interim 4-week visits (when study drug is not administered) during the first 52 weeks of the study. No sham injection was given at Week 52.

The study duration for each subject was scheduled to be 96 weeks. For the first 52 weeks (Year 1), subjects received an intravitreal or sham injection in the study eye every 4 weeks. During the second year of study, subjects were evaluated every 4 weeks and received an

intravitreal injection at least every 12 weeks. During this period, injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks, according to pre-specified clinical criteria. Sham injections were not given during the second year of the study.

Subjects were evaluated every 4 weeks for safety and best corrected visual acuity (BCVA) using the 4 meter Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Quality of Life (QOL) was evaluated using the NEI VFQ-25 questionnaire. Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA) examinations were conducted periodically.

Study 311523 (VIEW 2) followed essentially the same design as the VIEW 1 study. The study was conducted primarily in Europe, Asia, Australia and Latin America, including the following countries (number of recruiting study centers in brackets): Argentina (6), Australia (7), Austria (3), Belgium (1), Brazil (4), Colombia (4), Czech Republic (5), France (10), Germany (21), Hungary (4), India (15), Israel (10), Italy (14), Japan (15), Latvia (2), Mexico (7), Netherlands (4), Poland (7), Portugal (2), Singapore (4), Slovakia (2), South Korea (6), Spain (16), Sweden (3), Switzerland (4), United Kingdom (10).

The planned sample size was 1200 for the study. At the conclusion of the study enrollment, a total of 1240 subjects from 186 study sites were randomized to one of 4 dosing regimens:

- 2 mg VEGF Trap-Eye administered every 4 weeks (2Q4; N=313),
- 0.5 mg VEGF Trap-Eye administered every 4 weeks (0.5Q4; N=311),
- 2 mg VEGF Trap-Eye administered every 8 weeks (2Q8; N=303), and
- 0.5 mg ranibizumab administered every 4 weeks (RQ4; N=313).

These two Phase studies generated the pivotal support for the proposed indication.

2.2 Data Sources

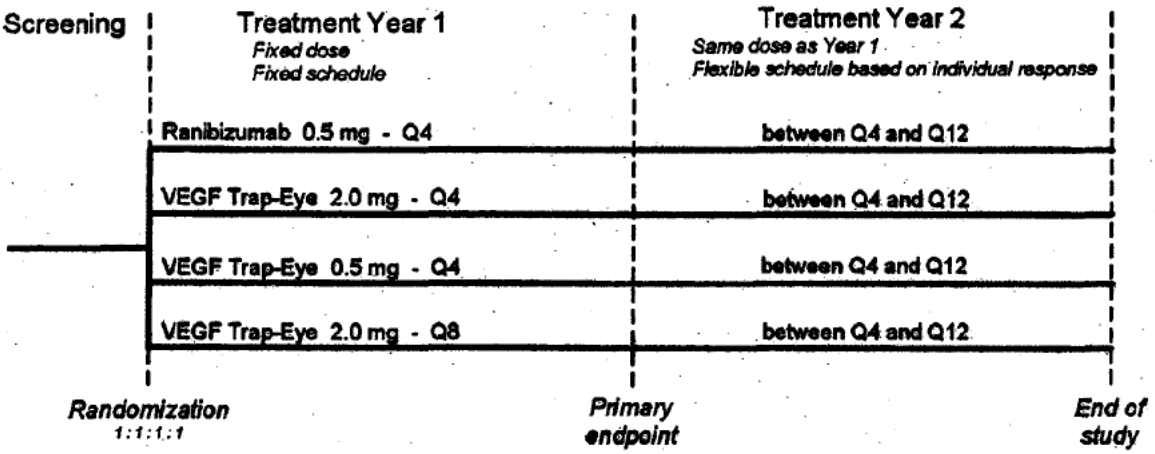
The BLA submission, including the Applicant's study reports and datasets for the clinical studies are available on EDR at \\cber-fs3\m\eCTD_Submissions\Stn125387\0000.

The study data, including the raw and analysis datasets, were provided electronically. Raw data were created following Study Data Tabulation Model (SDTM) standards. Analysis (derived) datasets were also submitted, along with the SAS programs used to generate these datasets. These datasets are available on EDR at \\Cber-fs3\m\eCTD_Submissions\STN125387\0000\m5\datasets.

3 STATISTICAL EVALUATION

For the most part, the conduct and analyses of the two pivotal Phase-3 studies, VGFT-OD-0605 (VIEW 1) and 311523 (VIEW 2), are identical. Figure 1 displays the flow chart of these two studies.

Figure 1 : General flow chart for pivotal Phase-3 studies (VIEW 1, VIEW 2)



Both studies compared three VEGF Trap-Eye regimens (0.5 mg and 2 mg dosed monthly, and 2 mg dosed every two months) to ranibizumab 0.5 mg dosed monthly. The primary efficacy endpoint is the proportion of subjects maintaining vision at Week 52. The maintenance of vision is defined as a loss, relative to baseline, in visual acuity of < 15 letters in the ETDRS letter score measured at a 4 meter distance.

The purpose of the studies is to establish non-inferiority of VEGF Trap-Eye relative to ranibizumab in preventing moderate vision loss in subjects with all angiographic subtypes of neovascular AMD. The evaluation of the non-inferiority of VEGF Trap-Eye to ranibizumab for each pivotal study was based on a non-inferiority margin of 10%.

The choice of the non-inferiority margin was based on regulatory agreement and it was supported by the observed efficacy results from ranibizumab studies.

The following sections will present detailed review of the two Phase-3 studies in VEGF Trap-Eye development program.

3.1 Data and Analysis Quality

The BLA submission included the raw and analysis datasets in electronic format. Raw data were created following Study Data Tabulation Model (SDTM) standards. Analysis (derived) datasets were also submitted, along with the SAS programs used to generate these datasets. Overall, the quality of the data is acceptable, but not without issues. Several findings are noted below.

Analysis dataset 'ADSL' includes variable 'COMPLFN' as a 1-year Completers Population flag. According to DEFINE.pdf document, COMPLFN = 1 if no discontinuation was recorded for the subject (DSREAS is missing); otherwise COMPLFN = 0. However, 28 subjects in study VIEW 1 and 23 subjects in VIEW 2 discontinued from the study during the 1st year (DSREAS is not missing), but they were indicated as 1-year completers (COMPLFN = 1). Therefore, the values of the variable COMPLFN were not derived properly according to the specification in DEFINE.pdf.

While verifying the randomized treatment assignments, it was noted that a total of 36 subjects in study VIEW 2 were classified as screening failures in analysis dataset (ADSL) and their randomization numbers were set to missing, even though they were randomized and assigned a randomization number according to raw datasets. According to the protocol, subjects were not randomized until their eligibility was confirmed, which means that they were not screening failures. The issue was raised at the BLA filing meeting and communicated thereafter with the Applicant. The Applicant confirmed that these 36 subjects were randomized, but they were not treated and were mistakenly classified as screening failures in the dataset ADSL. These 36 subjects were not included in safety, full analysis, and per-protocol populations or in any analysis results. Therefore, the analyses results and conclusions will not be affected by this issue.

Because of the designation of aforementioned 36 subjects as screening failures and the omission of their treatment assignments, dataset ADSL alone cannot be used to reproduce the subject disposition table (Table 7 in VIEW 2 CSR). The reviewer had to use the raw data to create a new dataset that corrected the mishandling of data in dataset ADSL. If the Applicant had consistently programmed to create analysis datasets for two pivotal studies, this issue could have been easily prevented.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

VGFT-OD-0605 (VIEW 1) is a multi-center, double-masked, randomized study. Subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

- 2 mg VEGF Trap-Eye administered every 4 weeks (2Q4),
- 0.5 mg VEGF Trap-Eye administered every 4 weeks (0.5Q4),
- 2 mg VEGF Trap-Eye administered every 8 weeks (2Q8),
- 0.5 mg ranibizumab administered every 4 weeks (RQ4).

Subjects assigned to the 2Q8 regimen received the 2 mg injection every 4 weeks to week 8 (at day 1, week 4, and week 8) and then a sham injection at interim 4-week visits when study drug was not administered during the first 52 weeks in the study. No sham injection was given at Week 52.

The study population consisted of men and women ≥ 50 years of age diagnosed with neovascular AMD. The planned enrollment for the study was 1200 subjects, 300 subjects per group. Assuming that 90% of subjects treated with 0.5 mg ranibizumab or VEGF Trap-Eye would maintain vision, 191 subjects per group would provide 90% power to demonstrate non-inferiority for a non-inferiority margin of 10% at a significance level of 0.049. The significance level was adjusted for Independent Data Monitoring Committee (IDMC) safety assessments (0.0001 for each of the 10 assessments) to preserve an overall alpha of 0.05 for the study. Assuming a dropout rate of approximately 30%, enrollment of 300 subjects per group was expected to provide adequate power.

Subjects were screened to determine their eligibility for the study based on the inclusion and exclusion criteria within 21 days of dosing. Once subjects' eligibility was confirmed and subjects consented to participating in the study, subjects were enrolled and randomized according to a central randomization scheme.

Subjects started receiving treatment on day 1. During the first-year treatment period, intravitreal or sham injections were given every 4 weeks. Subjects were evaluated at 4-week intervals for safety and BCVA. Quality of life was evaluated using the NEI VFQ-25 at screening, weeks 12, 24, 36 and 52. Mandatory OCT examinations were performed at screening, day 1 and at weeks 4, 12, 24, 36, and 52. In addition, optional OCT examinations could be performed at weeks 1, 8, 16, 20, 28, 32, 40, 44, and 48. Fluorescein angiography (FA) examinations were conducted at screening, and at weeks 24 and 52. Schedule of events during the first year is displayed in Table 2.

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Table 2: Schedule of events (Year one)

WEEK	Screen	Day 1	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
VISIT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	D -21 to D 0															
Sign Informed Consent	X															
Medical/Ophthalmic History	X															
Physical Exam	X															
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[2]	X[2]					X[2]			X[2]			X[2]				X[2]
ECG/NYHA	X															X
Interval History (AEs & Con Meds)[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthal/Slit Lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP[3]	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
Visual Acuity (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X[4]	X	X[5]	X	X[5]	X	X[5]	X[5]	X	X[5]	X[5]	X	X[5]	X[5]	X[5]	X
Fundus Photo/ FA	X[6]								X							X
Hematology & Chemistry Panel[7]	X					X			X			X				X
Serum Beta-HCG	X															
PT/PTT[7]	X															
Urinalysis/UPCR[7]	X					X			X			X				X[7]
Serum for antibody[7]	X					X			X			X				X
Study Drug or Sham Injection[8]		X		X	X	X[10]	X	X[10]	X	X[10]	X	X[10]	X	X[10]	X	O[11]
Telephone Safety Check[9]				X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9,10]

1. AEs should be recorded from the time the informed consent has been signed until completion. If a subject withdraws, AEs should be recorded until withdrawal or 30 days after the last dose of study drug, whichever is later.
2. NEI VFQ-25 will be administered by certified personnel at a contracted call center. Site will assist the subject at the screening visit to initiate the first call to the call center to collect all of the subject's contact information and to complete the first VFQ on the phone prior to randomization and IVT injection; the call center will initiate subsequent contact at appropriate visits to complete questionnaire.
3. Measure IOP pre-dose and 30-60 minutes post-injection
4 & 5. Both eyes at Screen visit
6. Optional at this visit.
7. Draw sample prior to administration of study drug.
8. See Appendix D of study protocol for study drug injection protocol
9. Mandatory telephone safety checks 3 days post injection or sham injection.
10. Subjects assigned to the VEGF Trap-Eye 2Q8 group will receive sham injections at these visits. A telephone safety check is mandatory after this visit.
11 Optional injection if study eye meets specific criteria Increase in central retinal thickness of ≥ 100 µm compared to the lowest previous value as measured by OCT , or A loss from the best previous letter score of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT, or new or persistent fluid as indicated by OCT, or new onset classic neovascularization, or new or persistent leak on FA, or new macular hemorrhage, or 12 weeks have elapsed since the previous injection).

Source: Protocol VGFT-OD-0605.03

During the second-year treatment period, intravitreal injections were given as needed as frequently as every 4 weeks, but no less frequently than every 12 weeks; evaluations and assessments of efficacy, safety, and tolerability were made, and blood samples were taken.

Only one eye was designated as the study eye. For subjects who met eligibility criteria in both eyes, the eye with the worse VA was selected as the study eye. If both eyes had equal VA, the eye with the clearest lens and ocular media, and least amount of subfoveal scar or geographic atrophy was selected. If there was no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology and subject preference were considered in making the selection. The non-study eye was considered the fellow eye.

The primary endpoint for the study was the proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score compared to baseline. Therefore, this study used the same primary

endpoint as the one in the pivotal ranibizumab studies to demonstrate non-inferiority of VEGF Trap-Eye to 0.5 mg ranibizumab.

To substantiate the clinical benefits of VEGF Trap-Eye, the following secondary endpoints were evaluated:

- Change from baseline in BCVA as measured by ETDRS letter score at week 52.
- Proportion of subjects who gained at least 15 letters of vision from baseline to week 52.
- Change in total NEI VFQ-25 score from baseline to week 52.
- Change in CNV area from baseline to week 52.

Multiplicity arising from the comparison of each of the three VEGF Trap-Eye regimens to ranibizumab was controlled using a conditional sequence of confidence intervals (CIs) for the statistical evaluations of non-inferiority of VEGF Trap-Eye to 0.5 mg ranibizumab. The conditional sequence was as follows:

1. 2 mg VEGF given every 4 weeks (2Q4) versus 0.5 mg ranibizumab given every 4 weeks (RQ4).
2. 0.5 mg VEGF given every 4 weeks (0.5Q4) versus 0.5 mg ranibizumab given every 4 weeks (RQ4).
3. 2 mg VEGF given every 8 weeks (2Q8) versus 0.5 mg ranibizumab given every 4 weeks (RQ4).

The non-inferiority margin was set at 10%. At each step in the conditional sequence, VEGF Trap-Eye was considered to be non-inferior to ranibizumab if the CI of the difference between ranibizumab and VEGF Trap-Eye lay entirely below 10%, where a negative difference favored VEGF Trap-Eye. VEGF Trap-Eye was considered to be superior to ranibizumab if the CI of the difference lay entirely below zero.

The statistical evaluation proposals in the protocol are acceptable. The study design, study endpoints, and duration of the evaluation (12 months for the primary endpoint and 24 months for the study) are consistent with current thinking of the reviewing medical division.

311523 (VIEW 2) had the same design and was analyzed the same way as study VGFT-OD-0605 (VIEW 1). A brief summary of key elements of these two studies are presented in Table 3.

Table 3: Brief summary of Phase 3 studies

Study	Design/Duration	Study Population	Treatment Group	Primary Efficacy Endpoint	Key Secondary Efficacy Endpoints
VGFT-OD-0605 (VIEW 1)	Multi-center, double-masked, randomized study, conducted in the United States and Canada. The study duration is 2 years with primary efficacy evaluation conducted at one year.	The study population consisted of men and women ≥ 50 years of age diagnosed with neovascular AMD.	• 2 mg VEGF Trap-Eye every 4 weeks (2Q4); n=304 • 0.5 mg VEGF Trap-Eye every 4 weeks (0.5Q4); n=304 • 2 mg VEGF Trap-Eye every 8 weeks (2Q8); n=303 • 0.5 mg ranibizumab every 4 weeks (RQ4); n=306	The proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score compared to baseline.	• Change from baseline in the BCVA score over time up to week 52 • Proportion of subjects who gained ≥15 letters in the BCVA score at week 52 compared with baseline
311523 (VIEW 2; VGFT-OD-0618)	Multi-center, double-masked, randomized study, conducted primarily in Europe, Asia, Australia and Latin America. The study duration is 2 years with primary efficacy evaluation conducted at one year.	The study population consisted of men and women ≥ 50 years of age diagnosed with neovascular AMD.	• 2 mg VEGF Trap-Eye every 4 weeks (2Q4); n=313 • 0.5 mg VEGF Trap-Eye every 4 weeks (0.5Q4); n=311 • 2 mg VEGF Trap-Eye every 8 weeks (2Q8); n=313 • 0.5 mg ranibizumab every 4 weeks (RQ4); n=303	The proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score compared to baseline.	• Change from baseline in the BCVA score over time up to week 52 • Proportion of subjects who gained ≥15 letters in the BCVA score at week 52 compared with baseline

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Patient Disposition

Study VIEW 1 enrolled a total of 1217 subjects from 154 sites in USA and Canada. These subjects were randomized to one of 4 dosing regimens:

- 2 mg VEGF Trap-Eye administered every 4 weeks (2Q4; N=304),
- 0.5 mg VEGF Trap-Eye administered every 4 weeks (0.5Q4; N=304),
- 2 mg VEGF Trap-Eye administered every 8 weeks (2Q8; N=303), and
- 0.5 mg ranibizumab administered every 4 weeks (RQ4; N=306).

Almost 93% of subjects completed the first year of the study. Among the 87 subjects who discontinued from the study prematurely, the primary reason for discontinuation was "withdrawal by the subject" (30 subjects), followed by 'adverse events' (16 subjects) and 'death' (13 subjects). The reasons for and incidence of premature discontinuation from the study were comparable among the treatment groups (Table 4).

Table 4: Study VIEW 1 - Subject Disposition (All randomized subjects)

	Ranibizumab		VEGF Trap-Eye		
Disposition/Reason	**0.5Q4**	**2Q4**	**0.5Q4**	**2Q8**	**Total**
Randomized	306 (100%)	304 (100%)	304 (100%)	303 (100%)	1217 (100%)
Treated	304 (99.3%)	304 (100%)	304 (100%)	303 (100%)	1215 (99.8%)
Safety Analysis Set	304 (99.3%)	304 (100%)	304 (100%)	303 (100%)	1215 (99.8%)
Full Analysis Set	304 (99.3%)	304 (100%)	301 (99.0%)	301 (99.3%)	1210 (99.4%)
Per Protocol Set	269 (87.9%)	285 (93.8%)	270 (88.8%)	265 (87.5%)	1089 (89.5%)
Completed First Year of Study	284 (92.8%)	293 (96.4%)	277 (91.1%)	276 (91.1%)	1130 (92.9%)
Discontinuation from Study within First Year	22 (7.2%)	11 (3.6%)	27 (8.9%)	27 (8.9%)	87 (7.1%)
Adverse Event	4	3	5	4	16
Death	3	1	2	7	13
Withdrawal by Subject	10	5	7	8	30
Protocol Deviation	3	0	3	1	7
Lost-to-Follow-up	1	2	4	4	11
Treatment Failure	0	0	2	2	4
Other	1	0	4	1	6

Source: Tables 7 and 9, Study VGFT-OD-0605 CSR.

In study VIEW 2, conducted primarily in Europe, Asia, Australia and Latin America, a total of 1240 subjects from 186 study sites were randomized to one of 4 dosing regimens:

- 2 mg VEGF Trap-Eye administered every 4 weeks (2Q4; N=313),
- 0.5 mg VEGF Trap-Eye administered every 4 weeks (0.5Q4; N=311),
- 2 mg VEGF Trap-Eye administered every 8 weeks (2Q8; N=303), and
- 0.5 mg ranibizumab administered every 4 weeks (RQ4; N=313).

Slightly less than 90% of subjects completed the first year of the study (Table 5). Among the 125 subjects who discontinued from the study prematurely, the primary reason for discontinuation

was "withdrawal by the subject" (50 subjects) as in study VIEW 1. Subjects treated with VEGF Trap-Eye were more likely to discontinue from study due to 'adverse events' (6, 8, and 9 subjects, respectively) compared to subjects treated with ranibizumab (2 subjects).

Table 5: Study VIEW 2 - Subject Disposition (All Randomized Subjects)

	Ranibizumab		VEGF Trap-Eye		
Disposition/Reason	**0.5Q4**	**2Q4**	**0.5Q4**	**2Q8**	**Total**
Randomized	303 (100%)	313 (100%)	311 (100%)	313 (100%)	1240 (100%)
Treated	291 (96.0%)	309 (98.7%)	297 (95.5%)	307 (98.1%)	1204 (97.1%)
Safety Analysis Set	291 (96.0%)	309 (98.7%)	297 (95.5%)	307 (98.1%)	1204 (97.1%)
Full Analysis Set	291 (96.0%)	309 (98.7%)	296 (95.2%)	306 (97.8%)	1202 (96.9%)
Per Protocol Set	269 (88.8%)	274 (87.5%)	268 (86.2%)	270 (86.3%)	1081 (87.2%)
Completed First Year of Study	276 (91.1%)	281 (89.8%)	274 (88.1%)	284 (90.7%)	1115 (89.9%)
Discontinuation from Study within First Year	27 (8.9%)	32 (10.2%)	37 (11.9%)	29 (9.3%)	125 (10.1%)
Adverse Event	2	6	8	9	25
Death	1	3	2	1	7
Withdrawal by Subject	11	15	13	11	50
Protocol Deviation	2	1	1	0	4
Lost-to-Follow-up	4	1	2	2	9
Treatment Failure	0	0	1	1	2
Other	7	6	10	5	28

Source: Tables 7 and 9, Study 311523 CSR.

The number of subjects in each analysis set is included in the above tables. The proportion of subjects included in each analysis set was similar across treatment groups in both studies. The following analysis sets were defined for the purpose of analyses.

The full analysis set (FAS) included all randomized subjects who received any study medication and had a baseline and at least 1 post-baseline BCVA assessment. The FAS was used for all hypothesis tests of superiority. For completeness, statistical evaluation of non-inferiority was also constructed using the FAS.

The per protocol set (PPS) included all subjects in the FAS who received at least 9 doses of study drug (sham injections were counted as doses administered), and attended at least 9 scheduled visits during the first year, except for those who were excluded because of major protocol deviations. A major protocol deviation was one that might have affected the interpretation of the study results (e.g., missing 2 consecutive injections before administration of the 9th injection). The PPS also included subjects who discontinued the study because of treatment failure, without a major protocol deviation, at any time during the first 52 weeks.

Treatment failure during the first 52 weeks of the study was defined as a decrease from baseline in BCVA by 15 or more letters at 2 consecutive assessments, 4 weeks apart. A subject who qualified as a treatment failure could be, but was not required to be, discontinued from the study. If a subject did withdraw, he or she was required to complete the year 2 end-of-study/early termination visit procedures.

The PPS was used for the primary analysis (statistical evaluation of non-inferiority). Analysis of superiority using the PPS was also done for supportive analyses.

All efficacy analyses were conducted with subjects as randomized.

The safety analysis set (SAF) was used for safety analyses. The SAF included all subjects who received any study medication. Safety analyses were conducted with subjects as treated.

3.2.2.2 Demographic and Baseline Characteristics

The demographic characteristics were comparable among the treatment groups for subjects in the FAS of study VIEW 1 (Table 6). Subjects were 49 to 99 years old, with a mean of 78.1 years. Most subjects were white (96.6%), non Hispanic or Latino (96.6%), approximately half were female (58.8%), and most had non-dark eye colors (65.5%).

Similar observation was made for the demographic characteristics of the subjects in study VIEW 2 (Table 7). In the FAS, approximately half of the subjects (55.5%) were female. Subjects aged between 50 and 93 year with a mean of 78.1 years. The majority of subjects was White (72.8%), not of Hispanic or Latino (82.4%), and had dark eye color (60.1%).

Table 6: Study VIEW 1 - Demographics and baseline characteristics (Full analysis set)

	Ranibizumab 0.5Q4 (N=304)	VEGF Trap-Eye 2Q4 (N=304)	VEGF Trap-Eye 0.5Q4 (N=301)	VEGF Trap-Eye 2Q8 (N=301)	Total (N=1210)
Age (years)					
Mean (SD)	78.2 (7.60)	77.7 (7.93)	78.4 (8.08)	77.9 (8.39)	78.1 (8.00)
Median	79.0	79.0	80.0	79.0	79.0
Min : Max	56 : 99	51 : 94	50 : 94	49* : 94	49* : 99
Sex (n [%])					
Female	172 (56.6%)	194 (63.8%)	167 (55.5%)	178 (59.1%)	711 (58.8%)
Male	132 (43.4%)	110 (36.2%)	134 (44.5%)	123 (40.9%)	499 (41.2%)
Race (n [%])					
White	296 (97.4%)	295 (97.0%)	291 (96.7%)	287 (95.3%)	1169 (96.6%)
Black	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	3 (0.2%)
Asian	0	3 (1.0%)	5 (1.7%)	4 (1.3%)	12 (1.0%)
American Indian or Alaska Native	2 (0.7%)	0	2 (0.7%)	1 (0.3%)	5 (0.4%)
Native Hawaiian or Pacific Islander	1 (0.3%)	0	0	1 (0.3%)	2 (0.2%)
Not Reported	4 (1.3%)	5 (1.6%)	3 (1.0%)	6 (2.0%)	18 (1.5%)
Multiple	0	0	0	1 (0.3%)	1 (<0.1%)
Eye Color (n [%])					
Dark (Black/brown)	101 (33.2%)	107 (35.2%)	106 (35.2%)	99 (32.9%)	413 (34.1%)
Other	203 (66.8%)	195 (64.1%)	194 (64.5%)	201 (66.8%)	793 (65.5%)
Missing	0	2	1	1	4
Weight (kg)					
Mean (SD)	75.9 (17.75)	74.2 (16.32)	77.0 (17.87)	74.4 (17.67)	75.39 (17.43)
Median	74.8	73.5	74.8	72.6	73.5
Min : Max	40 : 135	41 : 137	36 : 172	41 : 143	36 : 172
Height (cm)					
Mean (SD)	166.4 (9.83)	164.7 (10.01)	166.3 (10.24)	165.0 (10.55)	165.6 (10.18)
Median	165.1	165.1	165.1	165.1	165.1
Min : Max	144 : 196	135 : 191	142 : 196	135 : 188	135 : 196
Body Mass Index (kg/m^2)					
Mean (SD)	27.3 (5.21)	27.4 (5.50)	27.8 (5.66)	27.2 (5.75)	27.4 (5.53)
Median	26.8	26.4	27.0	26.6	26.6
Min : Max	15 : 45	15 : 47	17 : 56	17 : 71	15 : 71

Source: Table 12, Study VGFT-OD-0605 CSR.

Table 7: Study VIEW 2 - Demographics and baseline characteristics (Full analysis set)

Parameter/variable	Ranibizumab	VEGF Trap-Eye			Total
	0.5Q4 (N = 291)	2Q4 (N = 309)	0.5Q4 (N = 296)	2Q8 (N = 306)	(N = 1202)
Age (years)					
Mean (SD)	73.0 (9.0)	74.1 (8.5)	74.7 (8.6)	73.8 (8.6)	73.9 (8.7)
Median	74.0	75.0	76.0	75.0	75.0
Min: Max	[50; 92]	[50; 93]	[51; 93]	[50; 93]	[50; 93]
P-value [a] / P-value [b]		0.10 / 0.06	0.02 / 0.01	0.26 / 0.16	0.12 / 0.08
Sex (n [%])					
Female	169 (58.1)	176 (57.0)	147 (49.7)	175 (57.2)	667 (55.5)
Male	122 (41.9)	133 (43.0)	149 (50.3)	131 (42.8)	535 (44.5)
P-value [c] / P-value [d]		0.78 / 0.86	0.04 / 0.04	0.83 / 0.91	0.14 / 0.11
Race (n [%])					
White	213 (73.2)	226 (73.1)	219 (74.0)	217 (70.9)	875 (72.8)
Black or African American	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.7)	4 (0.3)
Asian	60 (20.6)	67 (21.7)	61 (20.6)	69 (22.5)	257 (21.4)
Missing	17 (5.8)	16 (5.2)	15 (5.1)	18 (5.9)	66 (5.5)
Ethnicity (n [%])					
Not Hispanic or Latino	239 (82.1)	259 (83.8)	241 (81.4)	251 (82.0)	990 (82.4)
Hispanic or Latino	52 (17.9)	50 (16.2)	55 (18.6)	55 (18.0)	212 (17.6)
Eye color (n [%])					
Dark (black/brown)	177 (60.8)	117 (57.3)	176 (59.5)	193 (63.1)	723 (60.1)
Other	114 (39.2)	132 (42.7)	120 (40.5)	113 (36.9)	479 (39.9)
Weight (kg)					
Mean (SD)	69.83 (15.00)	70.29 (14.35)	70.54 (14.38)	69.56 (14.36)	70.05 (14.51)
Median	68.0	69.0	70.0	68.0	68.0
Min: Max	[40.0; 133.0]	[32.0; 140.0]	[37.0; 125.0]	[41.0; 123.0]	[32.0; 140.0]
P-value [a] / P-value [b]		0.69 / 0.64	0.55 / 0.56	0.82 / 0.90	0.84 / 0.86
Height (cm)					
Mean (SD)	162.5 (9.38)	163.3 (9.19)	163.8 (9.34)	162.8 (9.22)	163.1 (9.28)
Median	162.6	163.0	163.4	163.0	163.0
Min: Max	[127; 184]	[144; 195]	[140; 198]	[143; 190]	[127; 198]
P-value [a] / P-value [b]		0.31 / 0.29	0.11 / 0.11	0.75 / 0.71	0.38 / 0.38
Body mass index (kg/m^2)					
Mean (SD)	26.34 (4.80)	26.32 (4.89)	26.22 (4.49)	26.18 (4.51)	26.26 (4.67)
Median	25.97	25.59	25.57	25.62	25.71
Min: Max	[15.8; 57.6]	[14.2; 60.4]	[15.6; 42.8]	[17.1; 39.2]	[14.2; 60.4]

a P-value in VEGF Trap-Eye column pair wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group as fixed factor.

b P-value in VEGF Trap-Eye column pair wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group and region as fixed factors.

c P-value in VEGF Trap-Eye column pair wise comparison versus ranibizumab (Chi-square test) and in total column all 4 treatment groups (Chi-square test)

d P-value in VEGF Trap-Eye column CMH-test region adjusted (pair wise comparison versus ranibizumab) and in total column CMH-test region adjusted (all 4 treatment groups)

Source: Table 13, Study 311523 CSR.

In the FAS of study VIEW 1, the baseline disease characteristics were balanced among the treatment groups (Table 8). The overall mean baseline BCVA score in the study eye was 55.1. The most common lesion type was occult. The mean retinal thickness was 266.1 µm, and the mean CNV area was 6.6 mm^2. Subjects in PPS had similar baseline disease characteristics to those in the FAS.

Table 8: Study VIEW 1 - Baseline disease characteristics in the study eye (Full analysis set)

	Ranibizumab 0.5Q4 (N=304)	VEGF Trap-Eye 2Q4 (N=304)	VEGF Trap-Eye 0.5Q4 (N=301)	VEGF Trap-Eye 2Q8 (N=301)	Total (N=1210
Visual Acuity Letter Score					
n	304	304	301	301	1210
Mean (SD)	54.0 (13.41)	55.2 (13.15)	55.6 (13.07)	55.7 (12.77)	55.1 (13.11)
Median	56.0	58.0	58.0	56.0	57.0
Min : Max	10 : 78	11 : 81	18 : 85	15 : 83	10 : 85
Retinal Thickness (um)					
n	304	303	300	301	1208
Mean (SD)	266.8 (126.73)	261.8 (122.42)	266.7 (139.15)	269.0 (133.34)	266.1 (130.40)
Median	233.5	236.0	234.0	238.0	235.0
Min : Max	51 : 822	65 : 71	66 : 1257	60 : 845	51 : 1257
Area of CNV (mm^2)					
n	298	302	300	300	1200
Mean (SD)	6.5 (5.25)	6.6 (5.05)	6.5 (4.45)	6.6 (5.14)	6.6 (4.98)
Median	5.2	5.6	5.9	5.4	5.5
Min : Max	0 : 29	0 : 30	0 : 25	0 : 33	0 : 33
Lesion Type					
Occult	115 (37.8%)	110 (36.2%)	121 (40.2%)	118 (39.2%)	464 (38.3%)
Minimally Classic	101 (33.2%)	105 (34.5%)	97 (32.2%)	110 (36.5%)	413 (34.1%)
Predominantly Classic	82 (27.0%)	87 (28.6%)	81 (26.9%)	71 (23.6%)	321 (26.5%)
Total Lesion Size					
n	298	302	300	301	1201
Mean (SD)	6.99 (5.493)	6.98 (5.388)	6.95 (4.725)	6.89 (5.225)	6.95 (5.210)
Median	5.52	5.86	6.23	5.64	5.86
Min:Max	0.1 : 29.0	0.2 : 29.6	0.2 : 24.9	0.0 : 32.6	0.0 : 32.6
NEI VFQ-25 Total Score					
n	303	300	297	293	1193
Mean (SD)	71.8 (17.16)	70.4 (16.60)	71.1 (17.77)	69.6 (16.83)	70.7 (17.09)
Median	74.8	72.1	74.5	71.6	73.4
Min : Max	25 : 99	25 : 99	7 : 100	21 : 97	7 : 100

Source: Table 13, Study VGFT-OD-0605 CSR.

In the FAS of study VIEW 2, the baseline disease characteristics were similar across the treatment groups (Table 9). The lesion type in the study eye was "occult" in 38.4% of the subjects, "minimally classic" in 35.4% of the subjects, and "predominantly classic" in 25.8% of the subjects. The overall mean baseline BCVA score in the study eye was 52.4. The mean retinal thickness was 332.5 μm, and the mean CNV area was 7.8 mm^2. Subjects in PPS had similar baseline disease characteristics to those in the FAS.

Comparing to subjects in study VIEW 1, subjects in VIEW 2 had lower baseline BCVA score, but greater baseline retinal thickness, CNV area, and lesion size.

Table 9: Study VIEW 2 - Baseline Disease Characteristics in the Study Eye (Full Analysis Set)

Parameter/variable	Ranibizumab	VEGF Trap-Eye			Total
	0.5Q4 (N = 291)	2Q4 (N = 309)	0.5Q4 (N = 296)	2Q8 (N = 306)	(N = 1202)
BCVA (ETDRS letter score)					
n	291	309	296	306	1202
Mean (SD)	53.8 (13.5)	52.8 (13.9)	51.6 (14.2)	51.6 (13.9)	52.4 (13.9)
Median	56.0	55.0	54.0	52.0	55.0
Min: Max	[10; 83]	[10; 79]	[12; 79]	[16; 76]	[10; 83]
P-value [a] / P-value [b]		0.38 / 0.39	0.06 / 0.06	0.06 / 0.06	0.17 / 0.17
Central retinal thickness (µm)					
n	290	308	294	302	1194
Mean (SD)	325.9 (111.0)	334.6 (119.8)	326.5 (116.5)	342.6 (124.0)	332.5 (118.0)
Median	309.5	309.0	313.5	327.5	315.0
Min: Max	[139; 810]	[103; 805]	[107; 793]	[107; 868]	[103; 868]
P-value [a] / P-value [b]		0.37 / 0.37	0.95 / 0.95	0.08 / 0.09	0.26 / 0.27
Total lesion size (mm^2)					
n	290	307	296	305	1198
Mean (SD)	8.01 (5.74)	8.72 (6.14)	8.17 (5.51)	8.22 (5.87)	8.28 (5.82)
Median	6.60	7.30	7.10	6.70	7.00
Min: Max	[0.1; 28.8]	[0.1; 30.0]	[0.1; 26.6]	[0.0; 26.7]	[0.0; 30.0]
P-value [a] / P-value [b]		0.14 / 0.13	0.74 / 0.73	0.67 / 0.68	0.48 / 0.47
Area of CNV (mm^2)					
n	291	308	296	305	1200
Mean (SD)	7.59 (5.34)	8.25 (5.77)	7.70 (5.26)	7.75 (5.52)	7.83 (5.48)
Median	6.40	6.70	6.85	6.40	6.60
Min: Max	[0.1; 28.8]	[0.1; 26.9]	[0.1; 26.6]	[0.0; 24.9]	[0.0; 28.8]
P-value [a] / P-value [b]		0.14 / 0.14	0.81 / 0.80	0.71 / 0.72	0.46 / 0.45
Lesion type					
Predominantly classic	70 (24.1)	72 (23.3)	80 (27.0)	88 (28.8)	310 (25.8)
Minimally classic	104 (35.7)	112 (36.2)	103 (34.8)	106 (34.6)	425 (35.4)
Occult	116 (39.9)	123 (39.8)	113 (38.2)	110 (35.9)	462 (38.4)
Missing	1 (0.3)	2 (0.6)	0 (0.0)	2 (0.7)	5 (0.4)
P-value [c] / P-value [d]		0.98 / 0.98	0.72 / 0.72	0.39 / 0.40	0.78 / 0.78
NEI VFQ-25 total score					
n	291	309	295	306	1201
Mean (SD)	72.90 (19.09)	70.27 (19.41)	74.04 (18.22)	71.30 (19.06)	72.10 (18.99)
Median	78.60	74.80	78.40	73.70	77.00
Min: Max	[12.0; 98.2]	[7.8; 98.2]	[14.8; 98.2]	[19.4; 98.0]	[7.8; 98.2]
P-value [a] / P-value [b]		0.09 / 0.08	0.47 / 0.49	0.30 / 0.32	0.07 / 0.07
EQ-5D score					
n	291	308	295	306	1200
Mean (SD)	0.80 (0.21)	0.78 (0.22)	0.79 (0.22)	0.81 (0.19)	0.80 (0.21)
Median	0.80	0.80	0.80	0.80	0.80
Min: Max	[-0.1; 1.0]	[-0.2; 1.0]	[-0.3; 1.0]	[-0.1; 1.0]	[-0.3; 1.0]
P-value [a] / P-value [b]		0.24 / 0.22	0.82 / 0.77	0.34 / 0.32	0.19 / 0.16

a P-value in VEGF Trap-Eye column pair wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group as fixed factor.

b P-value in VEGF Trap-Eye column pair wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group and region as fixed factors.

c P-value in VEGF Trap-Eye column pair wise comparison versus ranibizumab (Chi-square test) and in total column all 4 treatment groups (Chi-square test)

d P-value in VEGF Trap-Eye column CMH-test region adjusted (pair wise comparison versus ranibizumab) and in total column CMH-test region adjusted (all 4 treatment groups)

Source: Table 14, Study 311523 CSR.

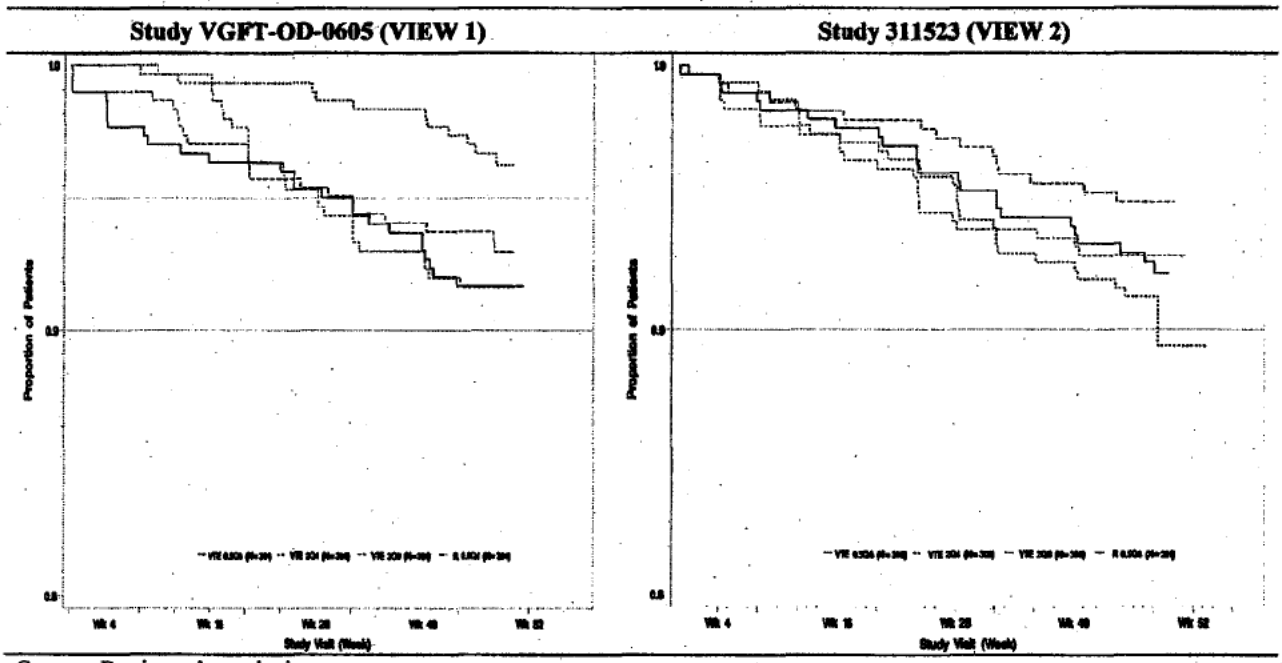
3.2.3 Statistical Methodologies

Efficacy data were analyzed as randomized following the intent-to-treat principle.

For the primary and secondary endpoints, missing data at week 52 were imputed using the last observation carried forward (LOCF) method. Baseline values were not carried forward. A subject who withdrew from the study before week 36 due to treatment failure was considered a non-responder. Otherwise, the last observation carried forward (LOCF) approach was used to impute missing values.

The proportion of subjects completing the first year of the study was above or near 90%. The proportion of subjects remaining in the study by visits is displayed in Figure 2 for full analysis set in studies VIEW 1 and VIEW 2. The number of subjects attending each visit is presented in Table 10.

Figure 2: Proportion of subjects remaining in the study by visits (Full analysis set)



Source: Reviewer's analysis.

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Table 10: Number of subjects attending the study visits (Full analysis set)

		Week													
	BL	1	4	8	12	16	20	24	28	32	36	40	44	48	52
Study VGFT-OD-0605 (VIEW 1)															
R 0.5Q4 (N=304)	304	304	295	293	293	288	284	285	279	280	277	271	272	273	273
VTE 0.5Q4 (N=301)	301	301	290	290	285	285	282	282	280	275	274	274	266	266	263
VTE 2Q4 (N=304)	304	304	300	298	294	294	294	290	293	288	293	291	287	284	285
VTE 2Q8 (N=301)	301	301	298	295	291	294	286	281	280	270	270	272	263	269	266
Study 311523 (VIEW 2)															
R 0.5Q4 (N=291)	291	291	290	287	287	284	281	277	276	275	272	272	274	270	273
VTE 0.5Q4 (N=296)	296	296	294	289	288	288	284	287	279	278	275	277	271	272	268
VTE 2Q4 (N=309)	309	309	308	305	301	295	296	293	290	290	281	281	281	275	276
VTE 2Q8 (N=306)	306	306	305	301	295	294	288	288	287	280	280	278	277	280	278

BL: baseline, Day 1.
Source: Reviewer's analysis.

Both studies employed an Independent Data Monitoring Committee (IDMC) to review periodically the ongoing safety of subjects. To preserve the overall probability of a Type I error at 5%, a correction of 0.1% was made to the significance level in study VIEW 1 to account for the IDMC safety assessments. However, the correction was not made in study VIEW 2.

To reflect the IDMC safety assessments performed during the study conduct and be consistent across studies, an alpha adjustment of 0.1% was adopted in Reviewer's analyses. The 2-sided p-values will be compared to $\alpha = 0.049$ and if applicable, two-sided 95.1% confidence intervals for the treatment difference between VEGF Trap-Eye treatment group and ranibizumab will be reported. Nevertheless, the correction of 0.1% makes negligible difference in the CIs.

3.2.3.1 Primary Efficacy Analyses

The primary analysis was to demonstrate the non-inferiority of VEGF Trap-Eye treatment regimens to 0.5 mg ranibizumab with respect to maintaining vision at Week 52. Maintenance of vision was defined as a loss of <15 letters in the ETDRS letter score from baseline at week 52. The non-inferiority margin was set at 10%. The analysis included a step-wise conditional calculation of the 95.1% CIs of the difference in the proportion of subjects who maintained vision at week 52 between the group treated with 0.5 mg ranibizumab and each of the groups treated with VEGF Trap-Eye. The conditional sequence was: 2Q4, 0.5Q4, and then 2Q8 compared to RQ4. The 95.1% CIs were used to account for an alpha adjustment of 0.1% as a result of the IDMC safety assessments.

VEGF Trap-Eye was considered to be non-inferior to ranibizumab if the CI of the difference (ranibizumab minus VEGF Trap-Eye) lay entirely below 10%, where a negative difference favored VEGF Trap-Eye. Once the non-inferiority was demonstrated, the superiority of VEGF Trap-Eye to ranibizumab was examined. VEGF Trap-Eye was considered to be superior to ranibizumab if the CI of the difference lay entirely below zero.

According to Applicant's analyses, the proportion of subjects who maintained vision was >94% in all treatment groups at week 52 in the PPS for both studies (Table 11). All VEGF Trap-Eye

treatment groups were non-inferior to the ranibizumab treatment group (RQ4) as demonstrated by the observation that the upper bound of the 95.1% CI was below the pre-specified non-inferiority margin of 10%. However, the studies didn't show superiority of any VEGF Trap-Eye treatment group to the ranibizumab treatment group. These results were confirmed by the Reviewer.

Table 11: Proportion of Subjects who Maintained Vision at Week 52 (Per Protocol Set)

Study VGFT-OD-0605 (VIEW 1)				
	Ranibizumab	**VEGF Trap-Eye**		
	0.5Q4	**2Q4**	**0.5Q4**	**2Q8**
	(N = 269)	**(N = 285)**	**(N = 270)**	**(N = 265)**
Subjects with Maintained Vision at Week 52 [1]	254 (94.4%)	271 (95.1%)	259 (95.9%)	252 (95.1%)
Difference (%) (95.1% CI) [2]				
First non-inferiority test		–0.7 (–4.4, 3.1)		
Second non-inferiority test			–1.5 (–5.1, 2.1)	
Third non-inferiority test				–0.7 (–4.5, 3.1)
Study 311523 (VIEW 2)				
	Ranibizumab	**VEGF Trap-Eye**		
	0.5Q4	**2Q4**	**0.5Q4**	**2Q8**
	(N = 269)	**(N = 274)**	**(N = 268)**	**(N = 270)**
Subjects with Maintained Vision at Week 52 [1]	254 (94.4%)	262 (95.6%)	258 (96.3%)	258 (95.6%)
Difference (%) (95.1% CI) [2]				
First non-inferiority test		-1.2 (-4.9, 2.5)		
Second non-inferiority test			–1.8 (–5.4, 1.7)	
Third non-inferiority test				–1.1 (–4.8, 2.6)

Note: Maintenance of vision was defined as a loss of <15 letters in the ETDRS letter score.
[1]: LOCF (baseline values were not carried forward)
[2]: Difference is ranibizumab minus VEGF Trap-Eye; CI was calculated using a normal approximation.
Source: Table 18, Study VGFT-OD-0605 CSR; Table 19, Study 311523 CSR; and Reviewer's analysis for 95.1% CI for Study 311523.

The analyses based on FAS yielded similar results (Table 12).

Table 12: Proportion of subjects who maintained vision at week 52 (Full analysis set)

Study VGFT-OD-0605 (VIEW 1)				
	Ranibizumab 0.5Q4 (N = 304)	VEGF Trap-Eye 2Q4 (N = 304)	VEGF Trap-Eye 0.5Q4 (N = 301)	VEGF Trap-Eye 2Q8 (N = 301)
Subjects with Maintained Vision at Week 52 [1]	285 (93.8%)	289 (95.1%)	286 (95.0%)	284 (94.4%)
Difference (%) (95.1% CI) [2]		-1.3 (-5.0 2.4)	-1.3(-4.9, 2.4)	-0.6 (-4.4, 3.2)
Study 311523 (VIEW 2)				
	Ranibizumab 0.5Q4 (N = 291)	VEGF Trap-Eye 2Q4 (N = 309)	VEGF Trap-Eye 0.5Q4 (N = 296)	VEGF Trap-Eye 2Q8 (N = 306)
Subjects with Maintained Vision at Week 52 [1]	276 (94.9%)	292 (94.5%)	282 (95.3%)	292 (95.4%)
Difference (%) (95.1% CI) [2]		0.4 (-3.3, 4.0)	-0.4 (-4.0, 3.1)	-0.6 (-4.1, 2.9)

Note: Maintenance of vision was defined as a loss of <15 letters in the ETDRS letter score.
[1]: LOCF (baseline values were not carried forward)
[2]: Difference is ranibizumab minus VEGF Trap-Eye; CI was calculated using a normal approximation.
Source: Table 20, Study VGFT-OD-0605 CSR; Table 21, Study 311523 CSR; and Reviewer's analysis for 95.1% CI for Study 311523.

In the Applicant's analyses, CI was calculated using a normal approximation without adjusting for any baseline covariates. In BLA 125156 for ranibizumab, the proportions of subjects maintaining vision were compared between each of the two ranibizumab dose groups and the sham group using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline CNV classification (Occult with No Classic CNV, Minimally Classic CNV or Predominantly Classic CNV) and baseline BCVA score (≤54, >54 letters).

The Reviewer's reanalysis of the proportion of subjects who maintained vision at week 52 using CMH test adjusting for baseline CNV classification (Occult, Minimally Classic CNV, Predominantly Classic CNV) and baseline BCVA score (≤54 letters, >54 letters) showed results similar to the Applicant's analysis based on a normal approximation without adjusting for any baseline covariates (Table 13 for PPS and Table 14 for FAS). There were no remarkable differences among treatment groups with respect to outcomes for CNV type or baseline VA. This is similar to the observation made with ranibizumab that the visual-acuity benefit associated with ranibizumab was independent of the lesion type or baseline visual acuity.

Table 13: Reviewer's analysis of proportion of subjects who maintained vision at week 52 [1] using CMH test (Per protocol set)

Study VGFT-OD-0605 (VIEW 1)					
		Ranibizumab	VEGF Trap-Eye		
Baseline CNV Classification	Baseline BCVA Score	0.5Q4 (N=269)	2Q4 (N=285)	0.5Q4 (N = 270)	2Q8 (N = 265)
Occult	≤54 Letters	34/36 (94.4%)	29/29 (100%)	24/24 (100%)	29/30 (96.7%)
Minimally Classic	≤54 Letters	40/40 (100%)	38/43 (88.4%)	35/37 (94.6%)	46/48 (95.8%)
Predominantly Classic	≤54 Letters	40/44 (90.9%)	48/51 (94.1%)	48/50 (96.0%)	37/41 (90.2%)
Occult	>54 Letters	63/65 (96.9%)	72/73 (98.6%)	81/83 (97.6%)	68/72 (94.4%)
Minimally Classic	>54 Letters	46/52 (88.5%)	54/58 (93.1%)	48/51 (94.1%)	47/49 (95.9%)
Predominantly Classic	>54 Letters	27/28 (96.4%)	28/29 (96.6%)	23/25 (92.0%)	25/25 (100%)
Difference (%) (95.1% CI) [2]			-0.8 (-4.6, 3.0)	-1.5 (-5.2, 2.2)	-0.6 (-4.4, 3.2)

Study 311523 (VIEW 2)					
		Ranibizumab	VEGF Trap-Eye		
Baseline CNV Classification	Baseline BCVA Score	0.5Q4 (N=269)	2Q4 (N=274)	0.5Q4 (N = 268)	2Q8 (N = 270)
Occult	≤54 Letters	31/33 (93.9%)	31/33 (93.9%)	37/38 (97.4%)	43/44 (97.7%)
Minimally Classic	≤54 Letters	38/40 (95.0%)	45/48 (93.8%)	54/57 (94.7%)	49/51 (96.1%)
Predominantly Classic	≤54 Letters	39/42 (92.9%)	42/43 (97.7%)	40/42 (95.2%)	43/45 (95.6%)
Occult	>54 Letters	70/74 (94.6%)	74/77 (96.1%)	62/63 (98.4%)	51/55 (92.7%)
Minimally Classic	>54 Letters	53/54 (98.1%)	46/49 (93.9%)	35/38 (92.1%)	37/39 (94.9%)
Predominantly Classic	>54 Letters	23/25 (92.0%)	22/22 (100%)	30/30 (100%)	33/34 (97.1%)
Difference (%) (95.1% CI) [2]			-0.7 (-4.3, 3.0)	-1.4 (-5.0, 2.2)	-0.7 (-4.5, 3.1)

[1]: Maintenance of vision was defined as a loss of <15 letters in the ETDRS letter score. Missing data was imputed using LOCF (baseline values were not carried forward).
[2]: Difference is ranibizumab minus VEGF Trap-Eye; CI was calculated using a Cochran-Mantel-Haenszel test.
Source: Reviewer's analysis.

Table 14: Reviewer's analysis of proportion of subjects who maintained vision at week 52 [1] using CMH test (Full analysis set)

Study VGFT-OD-0605 (VIEW 1)					
		Ranibizumab	VEGF Trap-Eye		
Baseline CNV Classification	Baseline BCVA Score	0.5Q4 (N=304)	2Q4 (N=304)	0.5Q4 (N=301)	2Q8 (N=301)
Occult	≤54 Letters	36/40 (90.0%)	31/31 (100%)	30/31 (96.8%)	33/34 (97.1%)
Minimally Classic	≤54 Letters	46/47 (97.9%)	38/43 (88.4%)	40/42 (95.2%)	54/57 (94.7%)
Predominantly Classic	≤54 Letters	47/51 (92.2%)	52/55 (94.5%)	53/55 (96.4%)	39/43 (90.7%)
Occult	>54 Letters	72/75 (96.0%)	78/79 (98.7%)	87/90 (96.7%)	79/84 (94.0%)
Minimally Classic	>54 Letters	48/54 (88.9%)	57/62 (91.9%)	50/55 (90.9%)	51/53 (96.2%)
Predominantly Classic	>54 Letters	30/31 (96.8%)	31/32 (96.9%)	24/26 (92.3%)	27/28 (96.4%)
Difference (%) (95.1% CI) [2]			-1.3 (-5.0, 2.4)	-1.3 (-5.0, 2.4)	-0.9 (-4.6, 2.9)

Study 311523 (VIEW 2)					
		Ranibizumab	VEGF Trap-Eye		
Baseline CNV Classification	Baseline BCVA Score	0.5Q4 (N=291)	2Q4 (N=309)	0.5Q4 (N=296)	2Q8 (N=306)
Occult	≤54 Letters	35/37 (94.6%)	35/39 (89.7%)	43/44 (97.7%)	49/50 (98.0%)
Minimally Classic	≤54 Letters	43/45 (95.6%)	54/57 (94.7%)	56/61 (91.8%)	59/61 (96.7%)
Predominantly Classic	≤54 Letters	42/45 (93.3%)	47/49 (95.9%)	45/47 (95.7%)	50/52 (96.2%)
Occult	>54 Letters	75/79 (94.9%)	81/84 (96.4%)	68/69 (98.6%)	55/60 (91.7%)
Minimally Classic	>54 Letters	58/59 (98.3%)	50/55 (90.9%)	38/42 (90.5%)	43/45 (95.6%)
Predominantly Classic	>54 Letters	23/25 (92.0%)	23/23 (100%)	32/33 (97.0%)	34/36 (94.4%)
Difference (%) (95.1% CI) [2]			0.9 (-2.7, 4.5)	-0.2 (-3.8, 3.3)	-0.2 (-3.7, 3.4)

[1]: Maintenance of vision was defined as a loss of <15 letters in the ETDRS letter score. Missing data was imputed using LOCF (baseline values were not carried forward).
[2]: Difference is ranibizumab minus VEGF Trap-Eye; CI was calculated using a Cochran-Mantel-Haenszel test.
Source: Reviewer's analysis.

The Applicant conducted various sensitivity analyses on both the PPS and FAS to assess the robustness of the main analysis results. These analyses used different approaches to handle missing data, including using observed values, Worst Observation Carried Forward (WOCF) method, and counting all drop-outs and treatment failures as non-responders. These sensitivity analyses generated results similar to those in the PPS LOCF and supported the non-inferiority of VEGF Trap-Eye treatment regimens to 0.5 mg ranibizumab with respect to maintaining vision at Week 52.

Instead of filling in a single value for each missing value using LOCF or WOCF, multiple imputation (MI) was explored as an alternative approach to handle the missing data. MI replaces each missing BCVA score with a set of plausible values that represent the uncertainty about the right value to impute. The multiply imputed data sets were then analyzed as complete data and the results from these analyses are combined. Table 15 (PPS) and Table 16 (FAS) display the results from analyses after MI. A total of 10 complete data sets were generated using MI procedure. The Markov Chain Monte Carlo (MCMC) method was used with a parametric method that assumes multivariate normality for the distribution of repeated BCVA measures. These results were in general comparable to those from analyses using LOCF, even though the CIs tended to be wider and p-values were bigger. These are expected because MI incorporated greater uncertainty in missing values.

Table 15: Reviewer's Analysis of Proportion of Subjects who Maintained Vision at Week 52 [1] Using Multiple Imputation (Per Protocol Set)

	Study VGFT-OD-0605 (VIEW 1)			
	Ranibizumab		**VEGF Trap-Eye**	
	0.5Q4 (N = 269)	**2Q4 (N = 285)**	**0.5Q4 (N = 270)**	**2Q8 (N = 265)**
Subjects with Maintained Vision at Week 52 [1]	94.6%	95.1%	96.0%	94.8%
Difference (%) (95.1% CI) [2]		-0.4 (-4.1, 3.3)	-1.3 (-5.0, 2.4)	-0.1 (-4.0, 3.7)
	Study 311523 (VIEW 2)			
	Ranibizumab		**VEGF Trap-Eye**	
	0.5Q4 (N = 269)	**2Q4 (N = 274)**	**0.5Q4 (N = 268)**	**2Q8 (N = 270)**
Subjects with Maintained Vision at Week 52 [1]	94.3%	95.6%	96.2%	95.7%
Difference (%) (95.1% CI) [2]		-1.3 (-5.1, 2.4)	-2.0 (-5.6, 1.7)	-1.4 (-5.2, 2.4)

[1]: Maintenance of vision was defined as a loss of <15 letters in the ETDRS letter score. Missing data was handled using multiple imputation.
[2]: Difference is ranibizumab minus VEGF Trap-Eye. CI was calculated using a normal approximation.
Source: Reviewer's analysis.

Table 16: Reviewer's Analysis of Proportion of Subjects who Maintained Vision at Week 52 [1] Using Multiple Imputation (Full Analysis Set)

Study VGFT-OD-0605 (VIEW 1)				
	Ranibizumab		**VEGF Trap-Eye**	
	0.5Q4 (N = 304)	**2Q4 (N = 304)**	**0.5Q4 (N = 301)**	**2Q8 (N = 301)**
Subjects with Maintained Vision at Week 52 [1]	94.4%	95.0%	95.3%	94.1%
Difference (%) (95.1% CI) [2]		-0.6 (-4.3, 3.1)	-0.9 (-4.6, 2.8)	0.4 (-3.5, 4.2)

Study 311523 (VIEW 2)				
	Ranibizumab		**VEGF Trap-Eye**	
	0.5Q4 (N = 291)	**2Q4 (N = 309)**	**0.5Q4 (N = 296)**	**2Q8 (N = 306)**
Subjects with Maintained Vision at Week 52 [1]	94.5%	94.5%	95.3%	95.2%
Difference (%) (95.1% CI) [2]		-0.1 (-3.9, 3.8)	-0.8 (-4.5, 2.8)	-0.7 (-4.4, 2.9)

[1]: Maintenance of vision was defined as a loss of <15 letters in the ETDRS letter score. Missing data was handled using multiple imputation.
[2]: Difference is ranibizumab minus VEGF Trap-Eye. CI was calculated using a normal approximation.
Source: Reviewer's analysis.

3.2.3.2 Secondary Efficacy Analyses

The secondary endpoint analyses were performed in the FAS and tested for superiority of VEGF Trap-Eye over ranibizumab. Secondary efficacy endpoints included the following at Week 52:

- Change from baseline in BCVA as measured by ETDRS letter score,
- Proportion of subjects who gain at least 15 letters of vision from baseline,
- Change in total NEI VFQ-25 score from baseline,
- Change in CNV area from baseline.

The following sequence of analyses for superiority of VEGF Trap-Eye over ranibizumab was to be performed if non-inferiority of all 3 groups treated with VEGF Trap-Eye to ranibizumab was demonstrated (Table 17).

Table 17: Testing order of secondary efficacy variables in pivotal studies (VIEW 1, VIEW 2)

	Endpoint category			
	Visual acuity		Quality-of-life	Morphology
Testing order	**BCVA as measured by ETDRS letter score:** Change from baseline to Week 52	**Proportion of subjects who gained 15 or more letters** from baseline to Week 52	**Total NEI-VFQ-25 score:** Change from baseline to Week 52	**Change in CNV area:** Change from baseline to Week 52
1	2.0 mg Q4			
2		2.0 mg Q4		
3			2.0 mg Q4	
4	0.5 mg Q4			
5		0.5 mg Q4		
6			0.5 mg Q4	
7	2.0 mg Q8			
8		2.0 mg Q8		
9			2.0 mg Q8	
10				2.0 mg Q4
11				0.5 mg Q4
12				2.0 mg Q8

Note: Entries denote the VEGF Trap-Eye dose group to be tested against 0.5 mg ranibizumab Q4

Analysis of proportions used the Pearson's Chi-Square test for the pair-wise comparisons of 2Q4, 0.5Q4, and 2Q8 to RQ4. Analyses of continuous variables used analysis of covariance (ANCOVA) model including the baseline measure as a covariate.

If applicable, two-sided 95.1% confidence intervals for the treatment difference of each VEGF Trap-Eye treatment group minus ranibizumab and two-sided nominal p-values will be reported for the secondary analyses. The p-values will be compared to $\alpha = 0.049$ after an adjustment for the IDMC safety assessments.

Change from baseline in BCVA at week 52

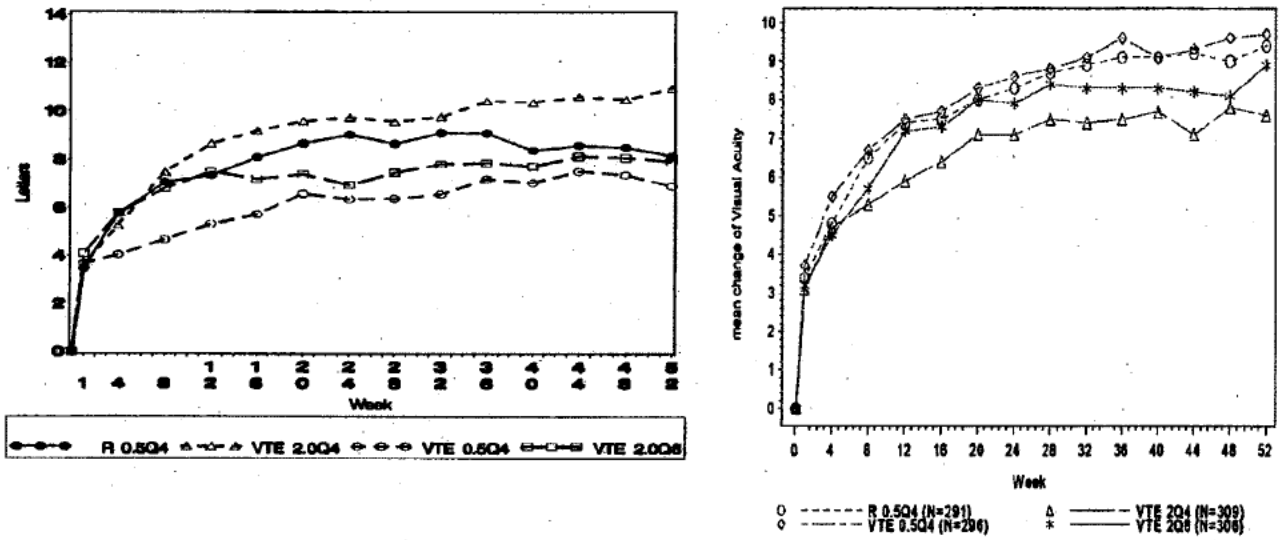
BCVA score was comparable at baseline among treatment groups in the FAS. For all treatment groups, improvement in BCVA was seen as early as week 1. The improvement approached the peak around week 24 and was maintained throughout week 52 (Figure 3, Table 18). A summary of BCVA score and the change in BCVA score by visit is provided in Table A.1 and Table A.2.

At week 52 in study VIEW 1, the VEGF Trap-Eye 2Q4 showed a superior improvement in the ETDRS letter score compared to the RQ4 group (a mean of 10.9 letters; LS mean 10.97 letters versus a mean of 8.1 letters; LS mean 7.82 letters) (LS mean difference = 3.15; 95.1% CI = 0.92 to 5.37; p = 0.0054). The improvement in BCVA score for 0.5Q4 and 2Q8 groups were numerically lower than that of RQ4, but the difference was not statistically significant.

By Week 52 in study VIEW 2, BCVA score had increased in all treatment groups. Based on the least-squares means calculated from the ANCOVA adjusting for baseline BCVA scores, the differences between the 3 VEGF Trap-Eye groups and the ranibizumab group were in favor of the ranibizumab treatment. However, the difference was not statistically significant. Thus, the sequential hypothesis testing for superiority of VEGF Trap-Eye to ranibizumab in a confirmatory manner had to stop after the first step (comparison of 2Q4 vs. R05Q4) failed to show statistically significant difference. Therefore, any subsequent statistical tests no longer served any confirmatory statistical hypothesis testing. They gave only descriptive indications for potential treatment differences.

The changes of 8.1 letters and 9.4 letters in RQ4 group in these two studies were in line with the observation made previously for ranibizumab.

Figure 3: Mean change from baseline through week 52 in ETDRS letter score (LOCF) (Full analysis set)



Source: Figure 3, Study VGFT-OD-0605 CSR; Figure 4, Study 311523 CSR.

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Table 18: Change from baseline to week 52 in ETDRS letter score (LOCF) (Full analysis set)

Study VGFT-OD-0605 (VIEW 1)

	Ranibizumab 0.5Q4 (N = 304)	VEGF Trap-Eye 2Q4 (N = 304)	VEGF Trap-Eye 0.5Q4 (N = 301)	VEGF Trap-Eye 2Q8 (N = 301)
Baseline				
n	304	304	301	301
Mean (SD)	54.0 (13.41)	55.2 (13.15)	55.6 (13.07)	55.7 (12.77)
Median	56.0	58.0	58.0	56.0
Min:Max	10.0:78.0	11.0:81.0	18.0:85.0	15.0:83.0
Week 52				
n	304	304	301	301
Mean (SD)	62.1 (17.71)	66.1 (16.17)	62.4 (16.45)	63.6 (16.85)
Median	67.0	71.0	65.0	68.0
Min:Max	0.0:88.0	8.0:98.0	11.0:89.0	11.0:93.0
Change from baseline at week 52				
n	304	304	301	301
Mean (SD)	8.1 (15.25)	10.9 (13.77)	6.9 (13.41)	7.9 (15.00)
Median	9.0	11.0	7.0	9.0
Min:Max	–75.0:56.0	–37.0:61.0	–46.0:56.0	–48.0:54.0
LS mean difference [1]		3.15	-0.80	0.26
95.1% C.I. for difference		(0.92 , 5.37)	(–3.03, 1.43)	(–1.97, 2.49)
p-value vs. RQ4 [2]		0.0054	0.4793	0.8179

Study 311523 (VIEW 2)

	Ranibizumab 0.5Q4 (N = 291)	VEGF Trap-Eye 2Q4 (N = 309)	VEGF Trap-Eye 0.5Q4 (N = 296)	VEGF Trap-Eye 2Q8 (N = 306)
Baseline				
n	291	309	296	306
Mean (SD)	53.8 (13.5)	52.8 (13.9)	51.6 (14.2)	51.6 (13.9)
Median	56.0	55.0	54.0	52.0
Min:Max	10.0:83.0	10.0:79.0	12.0:79.0	16.0:76.0
Week 52				
n	291	309	296	306
Mean (SD)	63.1 (16.6)	60.4 (18.3)	61.3 (17.8)	60.5 (17.5)
Median	67.0	65.0	65.0	64.0
Min:Max	8.0:90.0	4.0:92.0	0:89.0	7.0:93.0
Change from baseline at week 52				
n	291	309	296	306
Mean (SD)	9.4 (13.5)	7.6 (12.6)	9.7 (14.1)	8.9 (14.4)
Median	10.0	8.0	10.0	9.0
Min:Max	–47.0:56.0	–37.0:42.0	–52.0:45.0	–63.0:50.0
LS mean difference [1]		-1.95	-0.06	-0.90
95.1% C.I. for difference		(-4.11; 0.21)	(-2.25; 2.13)	(-3.07; 1.27)
p-value vs. RQ4 [2]		0.0760	0.9555	0.4131

[1]: Difference is VEGF Trap-Eye minus ranibizumab. CI calculated using normal approximation.
[2]: ANCOVA main effect model, including baseline BCVA as a covariate.
Source: Table 22, Study VGFT-OD-0605 CSR; Table 24, Study 311523 CSR; and Reviewer's analysis for 95.1% CI for Study 311523.

The multiply imputed data sets mentioned earlier were analyzed for the change in BCVA from baseline at week 52 by using ANCOVA model for complete data and the results from these analyses were combined. Table 19 displays the results from analyses after missing data was imputed with MI procedure. A total of 10 complete data sets were generated using MI procedure. As observed before, these results were in general comparable to those from analyses using LOCF, even though the CIs tended to be wider and p-values were bigger.

Table 19: Change from baseline to week 52 in ETDRS letter score (multiple imputation) (Full analysis set)

Study VGFT-OD-0605 (VIEW 1)				
	Ranibizumab 0.5Q4 (N = 304)	**VEGF Trap-Eye**		
		2Q4 (N = 304)	**0.5Q4 (N = 301)**	**2Q8 (N = 301)**
Change from baseline at week 52				
LS mean	8.07	11.06	7.31	7.96
LS mean difference [1]		2.98	-0.77	-0.12
95.1% C.I. for difference		(0.72 , 5.24)	(–3.05, 1.52)	(–2.41, 2.17)
p-value vs. RQ4 [2]		0.0094	0.5083	0.9184
Study 311523 (VIEW 2)				
	Ranibizumab 0.5Q4 (N = 291)	**VEGF Trap-Eye**		
		2Q4 (N = 309)	**0.5Q4 (N = 296)**	**2Q8 (N = 306)**
Change from baseline at week 52				
LS mean	9.70	7.79	9.93	9.04
LS mean difference [1]		-1.90	0.10	-0.74
95.1% C.I. for difference		(-4.14; 0.33)	(-2.12; 2.32)	(-2.93; 1.45)
p-value vs. RQ4 [2]		0.0939	0.9261	0.5072

[1]: Difference is VEGF Trap-Eye minus ranibizumab. CI calculated using normal approximation.
[2]: ANCOVA main effect model, including baseline BCVA as a covariate.
Source: Reviewer's analysis.

Proportion of subjects who gained at least 15 letters of vision from baseline at week 52

In study VIEW 1, The proportion of subjects who experienced a gain in vision of ≥ 15 letters at week 52 was slightly higher in the VEGF Trap-Eye group dosed 2 mg monthly (2Q4) compared to the RQ4 group (37.5% versus 30.9%). However, the difference between the treatment groups was not statistically significant. As a result, the pre-specified conditional sequence of statistical hypothesis tests for superiority of VEGF Trap-Eye was interrupted for this study. All p-values for the subsequent hypothesis tests were provided for descriptive purposes only.

The 2Q8 group was similar to the RQ4 group, and the 0.5Q4 group had the fewest 15-letter gainers.

The proportion of 15-letter gainers was similar in study VIEW 2. No statistically significant difference between the VTE Trap-Eye treatment groups and RQ4 treatment group was observed.

Table 20: Proportion of subjects who gained ≥15 letters in the ETDRS letter score at Week 52 (LOCF) (Full snalysis set)

Study VGFT-OD-0605 (VIEW 1)				
	Ranibizumab 0.5Q4 (N = 304)	**VEGF Trap-Eye**		
		2Q4 (N = 304)	**0.5Q4 (N = 301)**	**2Q8 (N = 301)**
Subjects who gained ≥ 15 letters at week 52 (n [%])	94 (30.9)	114 (37.5)	75 (24.9%)	92 (30.6%)
Difference (%) vs. RQ4 [1]		6.6	-6.0	-0.4
95.1% CI for difference		(-1.0, 14.1)	(-13.2, 1.2)	(-7.7, 7.0)
p-value vs. RQ4 [2]		0.0873	0.0998	0.9244
Study 311523 (VIEW 2)				
	Ranibizumab 0.5Q4 (N = 291)	**VEGF Trap-Eye**		
		2Q4 (N = 309)	**0.5Q4 (N = 296)**	**2Q8 (N = 306)**
Subjects who gained ≥ 15 letters at week 52 (n [%])	99 (34.0)	91 (29.4)	103 (34.8)	96 (31.4)
Difference (%) vs. RQ4 [1]		-4.6	0.8	-2.7
95.1% CI for difference		(-12.1, 2.9)	(-6.9, 8.5)	(-10.2, 4.9)
p-value vs. RQ4 [2]		0.2290	0.8430	0.4904

[1] Difference is VEGF Trap-Eye minus ranibizumab. CI calculated using normal approximation.
[2] Chi-Square Test (2-Sided).

Source: Table 23, Study VGFT-OD-0605 CSR; Table 25, Study 311523 CSR; and Reviewer's analysis for 95.1% CI for Study 311523.

The proportion of 15-letter gainers was analyzed using the multiply imputed data sets. The analysis produced comparable results to those from analyses using LOCF for study VIEW 1. In study VIEW 2, the proportion of 15-letter gainers was higher for VTE 2Q4, but lower for VTE 0.5Q4 when the multiply imputed data sets were used and compared to LOCF results (Table 21).

Table 21: Proportion of subjects who gained ≥15 letters in the ETDRS letter score at week 52 (multiple imputation) (Full analysis set)

Study VGFT-OD-0605 (VIEW 1)				
	Ranibizumab		**VEGF Trap-Eye**	
	0.5Q4	**2Q4**	**0.5Q4**	**2Q8**
	(N = 304)	**(N = 304)**	**(N = 301)**	**(N = 301)**
Subjects who gained ≥ 15 letters at week 52 (%)	32.1%	38.2%	25.3%	30.8%
Difference (%) vs. RQ4 [1]		6.1	-6.8	-1.3
95.1% CI for difference		(-1.7, 14.0)	(-14.3, 0.8)	(-9.0, 6.3)
p-value vs. RQ4 [2]		0.1243	0.0790	0.7295
Study 311523 (VIEW 2)				
	Ranibizumab		**VEGF Trap-Eye**	
	0.5Q4	**2Q4**	**0.5Q4**	**2Q8**
	(N = 291)	**(N = 309)**	**(N = 296)**	**(N = 306)**
Subjects who gained ≥ 15 letters at week 52 (n [%])	34.3%	29.9%	35.1%	32.4%
Difference (%) vs. RQ4 [1]		-4.5	-0.7	-1.9
95.1% CI for difference		(-12.2, 3.3)	(-7.2, 8.6)	(-9.6, 5.8)
p-value vs. RQ4 [2]		0.2570	0.8540	0.6250

[1] Difference is VEGF Trap-Eye minus ranibizumab. CI calculated using normal approximation.
[2] Chi-Square Test (2-Sided).

Source: Table 23, Study VGFT-OD-0605 CSR; Table 25, Study 311523 CSR; and Reviewer's analysis for 95.1% CI for Study 311523.

3.2.4 Results and Conclusions

The Phase-3, randomized, double masked, active comparator (0.5 mg ranibizumab) controlled studies, VGFT-OD-0605 (VIEW 1) and 311523 (VIEW 2), provided the clinical data to assess the efficacy of VEGF Trap-Eye. The Applicant conducted the primary and secondary efficacy analyses according to pre-specified statistical methodology.

These two studies demonstrated that VEGF Trap-Eye is non-inferior to 0.5 mg ranibizumab with respect to the proportion of subjects who maintained vision at week 52, based on a pre-determined non-inferiority margin of 10%. In both studies, nearly 94% of subjects treated with VEGF Trap-Eye and 0.5 mg ranibizumab maintained vision at week 52.

Results from the analysis of secondary efficacy endpoints, including BCVA change from baseline at week 52 and the proportion of subjects who gained at least 15 letters in the BCVA score at week 52 compared with baseline, further supported the efficacy of VEGF Trap-Eye compared to 0.5 mg ranibizumab. Both VEGF Trap-Eye regimens and 0.5 mg ranibizumab were associated with fairly similar change in BCVA score and proportion of subjects who gained at least 15 letters in the BCVA score at week 52 compared with baseline.

The Reviewer concurred with the pre-specified statistical methodology and confirmed the primary efficacy and key secondary efficacy results for visual acuity. Additional analyses employing different statistical approach or different method to handle missing data were performed by the Reviewer. The results from these analyses were similar to those presented in the submission.

Therefore, the efficacy of VEGF Trap-Eye regimens was supported by a non-inferiority comparison to 0.5 mg ranibizumab for the proportion of subjects who maintained vision at week 52. Similar efficacy results observed with VEGF Trap-Eye and 0.5 mg ranibizumab in the secondary visual acuity endpoints further substantiated the efficacy of VEGF Trap-Eye compared to 0.5 mg ranibizumab for treatment of neovascular AMD.

3.3 Evaluation of Safety

For the evaluation of safety, please refer to medical officer Dr. Sonal Wadhwa's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were performed for the following visual acuity efficacy variables:

- Proportion of subjects who maintained vision (<15 letters lost) (PPS and FAS),
- Change from baseline in BCVA at week 52 (FAS),
- Proportion of subjects who gained at least 15 letters of vision at week 52 (FAS).

The subgroups were defined by age (<65 years, ≥65 years to <75 years, ≥75 years), gender, race (white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander; OR: white or non-white), ethnicity, baseline VA (better than 20/100 [≥50 letters]), between 20/100 and 20/200 (≥35 to <50 letters), worse than 20/200 (<35 letters), lesion size (>10.16 mm^2 to ≤10.16 mm^2, equivalent to 4 DAs [2.54 mm^2 = 1 DA]), and lesion type (predominantly classic, minimally classic, and occult), and country in study VIEW 2.

The results of the subgroup analyses were overall consistent with those in the total population.

Assessment of treatment-by-site interaction was performed using ANCOVA for continuous variables, Pearson Chi-Square test for proportion. Pooling of sites was used to evaluate treatment effect by site.

4.2 Other Special/Subgroup Populations

No other special populations or subgroups were considered in this review.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The Reviewer didn't find any major statistical issues that impacted the analyses and overall conclusions. The Applicant conducted the primary and secondary efficacy analyses in the pivotal Phase-3 studies according to pre-specified statistical methodology. The Reviewer generally concurred with the pre-specified statistical methodology and confirmed the primary efficacy and key secondary efficacy results for visual acuity. Additionally, the Reviewer's analyses employing different statistical approach or different method to handle missing data yielded results similar to those presented in the submission.

Both Phase-3 studies were designed as non-inferiority trials to demonstrate that VEGF Trap-Eye regimens was not inferior to 0.5 mg ranibizumab by 10% or more with respect to the proportion of subjects maintaining vision at Week 52. The selection of the 10% margin could be justified using pivotal ranibizumab clinical trial data. However, the justification was not provided in either study protocols, or the BLA submission.

An IDMC was used to conduct safety assessments. Study VIEW 1 made an alpha correction of 0.1% for the efficacy analyses. Even though the same safety assessment procedure was implemented in study VIEW 2, an alpha correct was not made. This caused discrepancy in presenting the confidence intervals in two identically designed and analyzed studies.

5.2 Conclusions and Recommendations

The BLA application was mainly supported by the clinical data from two Phase-3 studies, VGFT-OD-0605 (VIEW 1) and 311523 (VIEW 2). These studies demonstrated that VEGF Trap-Eye is non-inferior to 0.5 mg ranibizumab with respect to the proportion of subjects who maintained vision at week 52, based on a non-inferiority margin of 10%. In both studies, nearly 94% of subjects treated with VEGF Trap-Eye and 0.5 mg ranibizumab maintained vision at week 52. The findings for 0.5 mg ranibizumab were similar to those from the pivotal ranibizumab studies used to support its registration. Furthermore, the design and conduct of both non-inferiority studies for the VEGF Trap-Eye program are considered adequate.

Results from the analysis of secondary efficacy endpoints, including BCVA change from baseline at week 52 and the proportion of subjects who gained at least 15 letters in the BCVA score at week 52 compared with baseline, also supported the efficacy of VEGF Trap-Eye compared to 0.5 mg ranibizumab. Both VEGF Trap-Eye regimens and 0.5 mg ranibizumab were associated with fairly similar change in BCVA score and proportion of subjects who gained at least 15 letters in the BCVA score at week 52 compared with baseline.

In Reviewer's view, the efficacy of VEGF Trap-Eye compared to 0.5 mg ranibizumab for treatment of neovascular AMD had been adequately demonstrated in the Phase-3 studies included in the application.

6 APPENDICES

Table A.1: Summary Statistics for ETDRS Letter Score, Observed Values (VIEW 1; Full Analysis Set)

Treatment Group	Visit	Value at visit								Change from baseline at visit							
		n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
R 0.5Q4 (N = 304)	SCREENING	304	55.2	12.59	16.0	49.0	57.5	65.5	75.0								
	BASELINE (DAY 1)	304	54.0	13.41	10.0	46.5	56.0	64.0	78.0								
	WEEK 1	297	57.4	13.40	0.0	51.0	60.0	68.0	85.0	297	3.5	8.05	-44.0	-1.0	3.0	7.0	31.0
	WEEK 4	295	59.8	13.23	22.0	52.0	62.0	70.0	87.0	295	5.8	8.73	-22.0	1.0	5.0	9.0	43.0
	WEEK 8	293	61.0	13.33	20.0	53.0	63.0	71.0	86.0	293	7.1	9.95	-24.0	1.0	7.0	11.0	46.0
	WEEK 12	293	61.4	14.23	14.0	54.0	64.0	72.0	86.0	293	7.5	10.80	-33.0	2.0	6.0	12.0	52.0
	WEEK 16	288	62.2	14.63	16.0	53.0	65.0	74.0	90.0	288	8.3	11.28	-29.0	2.0	8.0	14.0	56.0
	WEEK 20	284	62.5	15.00	11.0	53.0	65.0	74.0	88.0	284	8.8	11.58	-46.0	2.0	8.0	15.5	50.0
	WEEK 24	285	63.2	15.11	0.0	54.0	67.0	75.0	90.0	285	9.3	12.03	-25.0	2.0	9.0	16.0	54.0
	WEEK 28	279	63.2	15.47	15.0	53.0	66.0	75.0	89.0	279	9.0	12.46	-34.0	3.0	8.0	16.0	52.0
	WEEK 32	280	63.7	15.04	7.0	54.5	66.0	75.0	90.0	280	9.5	12.39	-29.0	3.0	9.0	16.0	53.0
	WEEK 36	277	63.4	15.80	0.0	53.0	66.0	76.0	88.0	277	9.2	12.87	-35.0	2.0	9.0	16.0	55.0
	WEEK 40	271	63.1	15.80	11.0	54.0	66.0	76.0	92.0	271	8.9	13.03	-38.0	2.0	9.0	15.0	55.0
	WEEK 44	272	63.2	16.44	8.0	53.0	67.0	76.5	91.0	272	9.0	13.56	-36.0	2.0	9.0	16.0	59.0
	WEEK 48	273	63.1	16.97	0.0	52.0	67.0	76.0	90.0	273	8.9	15.05	-72.0	3.0	9.0	17.0	56.0
	WEEK 52	273	62.6	17.22	0.0	53.0	68.0	75.0	88.0	273	8.6	15.20	-75.0	2.0	9.0	17.0	56.0

Treatment Group	Visit	Value at visit								Change from baseline at visit							
		n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
VTE 2Q4 (N = 304)	SCREENING	302	56.9	11.34	27.0	50.0	59.0	66.0	77.0								
	BASELINE (DAY 1)	303	55.2	13.17	11.0	46.0	58.0	65.0	81.0								
	WEEK 1	299	58.8	12.73	8.0	51.0	60.0	68.0	85.0	299	3.6	7.76	-24.0	-1.0	3.0	8.0	47.0
	WEEK 4	300	60.5	13.49	9.0	53.0	62.0	71.0	86.0	300	5.3	9.48	-37.0	0.0	4.0	10.0	49.0
	WEEK 8	298	62.6	14.06	7.0	54.0	64.0	73.0	86.0	298	7.5	10.00	-27.0	1.0	6.5	13.0	45.0
	WEEK 12	294	63.9	14.15	15.0	57.0	66.0	74.0	89.0	294	8.8	10.60	-30.0	2.0	8.0	15.0	50.0
	WEEK 16	294	64.3	14.77	16.0	54.0	67.0	75.0	93.0	294	9.2	11.69	-30.0	2.0	9.0	15.0	59.0
	WEEK 20	294	64.8	15.00	11.0	55.0	69.0	76.0	94.0	294	9.8	12.11	-33.0	3.0	9.0	17.0	59.0
	WEEK 24	290	65.3	15.37	7.0	57.0	69.0	77.0	91.0	290	10.2	11.90	-24.0	4.0	10.0	17.0	51.0
	WEEK 28	293	64.8	16.26	10.0	57.0	69.0	78.0	89.0	293	9.9	13.03	-40.0	2.0	10.0	18.0	55.0
	WEEK 32	288	65.0	16.21	8.0	57.0	69.0	77.0	89.0	288	9.9	12.98	-39.0	3.0	10.0	18.0	55.0
	WEEK 36	293	65.5	15.54	11.0	58.0	69.0	77.0	94.0	293	10.6	12.77	-39.0	4.0	10.0	18.0	51.0
	WEEK 40	291	65.5	16.08	10.0	59.0	69.0	78.0	90.0	291	10.5	13.10	-40.0	4.0	10.0	18.0	60.0
	WEEK 44	287	65.8	16.06	8.0	58.0	70.0	78.0	94.0	287	10.7	13.13	-42.0	3.0	10.0	19.0	56.0
	WEEK 48	284	65.6	15.97	12.0	56.5	69.0	77.0	97.0	284	10.4	13.43	-36.0	4.0	10.0	19.0	56.0
	WEEK 52	285	66.3	16.28	8.0	59.0	71.0	78.0	98.0	285	11.1	13.86	-37.0	4.0	11.0	19.0	61.0

Treatment Group	Visit	Value at visit								Change from baseline at visit							
		n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
VTE 0.5Q4 (N = 301)	SCREENING	298	56.1	12.23	23.0	51.0	59.0	65.0	75.0								
	BASELINE (DAY 1)	298	55.6	13.14	18.0	48.0	58.0	65.0	85.0								
	WEEK 1	293	59.4	13.17	15.0	52.0	61.0	69.0	84.0	293	3.7	7.73	-29.0	-1.0	3.0	8.0	38.0
	WEEK 4	290	59.6	14.25	15.0	51.0	62.0	71.0	85.0	290	4.1	9.13	-29.0	-1.0	4.0	8.0	45.0
	WEEK 8	290	60.1	15.13	8.0	51.0	62.0	72.0	86.0	290	4.8	10.86	-33.0	-1.0	4.0	10.0	47.0
	WEEK 12	285	61.3	14.66	15.0	52.0	64.0	73.0	86.0	285	5.8	10.91	-29.0	0.0	5.0	11.0	50.0
	WEEK 16	285	61.8	15.24	15.0	51.0	66.0	73.0	89.0	285	6.2	11.42	-30.0	0.0	6.0	12.0	50.0
	WEEK 20	282	62.2	15.41	11.0	52.0	66.0	74.0	89.0	282	6.9	11.67	-37.0	0.0	7.5	14.0	53.0
	WEEK 24	282	62.2	15.66	15.0	52.0	66.0	74.0	90.0	282	6.6	12.39	-39.0	-1.0	7.0	14.0	56.0
	WEEK 28	280	62.6	15.76	11.0	53.0	66.0	74.5	94.0	280	6.8	12.36	-47.0	0.5	6.0	14.0	59.0
	WEEK 32	275	63.2	15.45	17.0	53.0	67.0	75.0	90.0	275	7.3	12.30	-41.0	1.0	8.0	14.0	54.0
	WEEK 36	274	63.3	15.61	14.0	54.0	67.0	75.0	89.0	274	7.9	12.70	-41.0	1.0	9.0	15.0	58.0
	WEEK 40	274	63.4	15.94	20.0	54.0	66.5	77.0	87.0	274	7.8	13.19	-46.0	0.0	9.0	15.0	49.0
	WEEK 44	266	64.3	14.86	16.0	53.0	68.0	76.0	89.0	266	8.5	12.22	-35.0	0.0	9.0	15.0	55.0
	WEEK 48	266	64.5	15.07	18.0	54.0	69.0	76.0	91.0	266	8.7	12.59	-33.0	3.0	9.0	16.0	59.0
	WEEK 52	263	63.7	15.66	15.0	55.0	66.0	76.0	89.0	263	8.0	12.70	-36.0	1.0	8.0	15.0	56.0

Table A.1: Summary Statistics for ETDRS Letter Score, Observed Values (VIEW 1; Full Analysis Set)

Treatment Group	Visit	Value at visit								Change from baseline at visit							
		n	Mean	SD	Min	Q1	Medi an	Q3	Max	n	Mean	SD	Min	Q1	Medi an	Q3	Max
VTE 2Q8 (N = 301)	SCREENING	296	56.8	11.96	22.0	50.0	59.0	66.5	83.0								
	BASELINE (DAY 1)	297	55.9	12.65	15.0	50.0	57.0	65.0	83.0								
	WEEK 1	293	59.8	12.92	16.0	53.0	61.0	69.0	87.0	293	4.1	7.71	-23.0	0.0	3.0	8.0	37.0
	WEEK 4	298	61.5	13.12	22.0	54.0	64.0	71.0	87.0	298	5.8	9.46	-50.0	1.0	4.0	11.0	45.0
	WEEK 8	295	62.5	14.50	17.0	54.0	65.0	74.0	90.0	295	6.8	11.16	-54.0	1.0	7.0	12.0	42.0
	WEEK 12	291	63.3	14.60	9.0	54.0	67.0	74.0	95.0	291	7.6	11.99	-50.0	1.0	7.0	13.0	51.0
	WEEK 16	294	63.2	15.22	11.0	54.0	66.0	74.0	92.0	294	7.5	11.89	-48.0	1.0	7.0	14.0	50.0
	WEEK 20	286	63.4	15.34	14.0	55.0	66.0	76.0	92.0	286	7.5	12.13	-53.0	2.0	7.0	14.0	47.0
	WEEK 24	281	63.6	15.12	18.0	53.0	67.0	75.0	92.0	281	7.4	13.06	-50.0	0.0	7.0	16.0	49.0
	WEEK 28	280	64.1	15.32	14.0	55.0	67.5	76.0	94.0	280	8.1	13.07	-46.0	1.5	7.5	16.0	45.0
	WEEK 32	270	64.6	15.27	6.0	56.0	68.0	76.0	93.0	270	8.4	13.21	-45.0	1.0	8.0	16.0	53.0
	WEEK 36	270	65.3	15.32	3.0	57.0	67.0	78.0	88.0	270	9.3	13.20	-48.0	2.0	9.0	17.0	52.0
	WEEK 40	272	65.1	15.58	2.0	56.0	69.0	77.0	94.0	272	8.9	13.91	-49.0	2.0	8.5	17.0	52.0
	WEEK 44	263	65.4	15.68	4.0	57.0	68.0	78.0	91.0	263	9.7	13.65	-47.0	3.0	10.0	16.0	52.0
	WEEK 48	269	65.5	15.40	20.0	57.0	69.0	77.0	91.0	269	9.5	13.94	-45.0	2.0	10.0	17.0	53.0
	WEEK 52	266	65.1	15.91	11.0	56.0	69.0	77.0	93.0	266	9.2	14.20	-44.0	2.0	9.5	17.0	54.0

Source: VGFT-OD-0605 (VIEW 1) CSR Post-text Table 14.2.2/12.

Table A.2: Summary Statistics for ETDRS Letter Score, Observed Values (VIEW 2; Full Analysis Set)

Treatment group	Visit	Value at Visit								Change from Baseline							
		n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
R 0.5Q4 (N=291)	SCREENING	289	55.0	12.5	25	49.0	57.0	65.0	79	289	1.0	5.2	-32	-2.0	1.0	3.0	19
	BASELINE	291	53.8	13.5	10	45.0	56.0	64.0	83								
	WEEK 1	286	57.2	13.3	20	50.0	60.0	67.0	85	286	3.4	5.8	-17	0.0	3.0	6.0	34
	WEEK 4	290	58.6	13.9	17	50.0	60.0	69.0	84	290	4.8	7.4	-19	0.0	5.0	10.0	40
	WEEK 8	287	60.2	14.5	16	51.0	62.0	71.0	92	287	6.5	8.6	-18	1.0	6.0	12.0	40
	WEEK 12	287	61.2	15.0	6	52.0	63.0	73.0	88	287	7.5	9.3	-28	2.0	7.0	14.0	42
	WEEK 16	284	61.3	15.1	15	53.0	63.0	73.5	85	284	7.6	10.4	-40	1.0	8.0	14.0	47
	WEEK 20	281	62.0	14.8	23	53.0	64.0	74.0	87	281	8.1	10.5	-30	2.0	8.0	14.0	42
	WEEK 24	277	62.1	15.4	15	52.0	64.0	75.0	87	277	8.3	10.9	-22	2.0	8.0	15.0	43
	WEEK 28	275	62.8	15.3	20	53.0	65.0	75.0	89	275	9.1	10.9	-39	3.0	9.0	16.0	43
	WEEK 32	275	62.9	15.5	6	54.0	66.0	75.0	93	275	9.1	11.9	-34	2.0	9.0	17.0	48
	WEEK 36	272	63.1	15.8	17	54.5	66.0	75.0	94	272	9.4	11.8	-40	2.5	10.0	17.0	45
	WEEK 40	272	63.1	16.1	16	52.5	67.0	76.0	92	272	9.4	12.6	-40	2.0	10.0	17.0	44
	WEEK 44	274	63.3	16.0	4	54.0	67.0	76.0	92	274	9.6	12.6	-42	3.0	10.0	17.0	48
	WEEK 48	269	63.3	16.8	10	53.0	67.0	76.0	91	269	9.5	13.9	-49	3.0	11.0	17.0	49
	WEEK 52	272	63.6	16.6	8	54.0	67.5	76.0	90	272	9.9	13.6	-47	2.5	10.0	18.0	56
VTE 2Q4 (N=309)	SCREENING	308	53.6	13.3	25	45.0	56.0	64.0	73	308	0.9	5.3	-24	-2.0	0.0	3.0	19
	BASELINE	309	52.8	13.9	10	43.0	55.0	63.0	79								
	WEEK 1	305	55.8	14.6	10	47.0	58.0	67.0	80	305	3.1	6.6	-20	0.0	2.0	6.0	30
	WEEK 4	307	57.5	15.5	17	48.0	60.0	68.0	92	307	4.7	8.3	-22	-1.0	5.0	9.0	40
	WEEK 8	305	58.0	16.5	0	50.0	60.0	70.0	87	305	5.3	9.2	-50	1.0	5.0	10.0	31
	WEEK 12	301	58.6	16.5	8	50.0	61.0	71.0	90	301	5.9	9.2	-22	1.0	5.0	11.0	29
	WEEK 16	295	59.4	16.7	8	50.0	62.0	73.0	88	295	6.4	9.9	-37	1.0	6.0	12.0	36
	WEEK 20	296	60.1	17.3	6	50.5	63.0	73.0	90	296	7.1	10.6	-29	2.0	7.0	13.0	41
	WEEK 24	293	60.3	16.8	8	50.0	64.0	73.0	92	293	7.3	10.6	-28	2.0	8.0	13.0	38
	WEEK 28	290	60.6	17.1	11	50.0	64.0	73.0	92	290	7.6	11.2	-27	1.0	8.0	14.0	40
	WEEK 32	289	60.9	17.2	14	52.0	64.0	74.0	89	289	7.7	11.3	-32	2.0	8.0	15.0	44
	WEEK 36	281	60.7	17.3	14	50.0	64.0	74.0	90	281	7.6	11.4	-29	1.0	8.0	15.0	41
	WEEK 40	281	61.2	17.1	13	50.0	65.0	74.0	91	281	8.0	11.8	-33	1.0	9.0	15.0	43
	WEEK 44	281	60.4	17.9	0	50.0	64.0	74.0	93	281	7.3	12.6	-40	0.0	7.0	15.0	41
	WEEK 48	275	60.8	17.7	8	48.0	65.0	74.0	90	275	7.9	12.2	-31	1.0	8.0	15.0	41
	WEEK 52	276	60.5	18.1	4	48.5	65.0	75.0	92	276	7.7	12.7	-37	0.0	8.0	15.5	42

Table A.2: Summary Statistics for ETDRS Letter Score, Observed Values (VIEW 2; Full Analysis Set)

		Value at Visit								Change from Baseline							
Treatment group	Visit	n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
VTE 0.5Q4 (N=296)	SCREENING	295	52.5	13.5	12	44.0	55.0	63.0	73	295	0.8	6.7	-21	-2.0	0.0	4.0	28
	BASELINE	296	51.6	14.2	12	41.0	54.0	62.0	79								
	WEEK 1	293	55.3	14.5	13	46.0	58.0	67.0	84	293	3.7	7.1	-24	0.0	3.0	7.0	32
	WEEK 4	292	57.1	14.7	8	48.0	58.0	69.0	85	292	5.5	8.7	-23	0.5	5.0	10.0	51
	WEEK 8	289	58.3	14.6	11	50.0	59.0	70.0	84	289	6.8	8.9	-17	2.0	6.0	11.0	40
	WEEK 12	288	59.3	15.3	17	50.0	61.5	72.0	86	288	7.8	9.8	-19	2.0	7.0	13.0	40
	WEEK 16	288	59.7	16.2	12	49.0	63.0	73.0	90	288	8.1	11.0	-46	2.5	8.0	14.0	44
	WEEK 20	284	60.5	16.2	10	50.0	63.0	73.0	89	284	8.6	11.5	-48	3.0	9.0	14.0	45
	WEEK 24	287	60.6	16.7	1	50.0	65.0	74.0	88	287	9.0	12.3	-57	2.0	10.0	15.0	45
	WEEK 28	279	60.8	17.0	1	50.0	64.0	74.0	90	279	9.3	12.7	-57	3.0	9.0	15.0	46
	WEEK 32	278	61.3	16.9	3	51.0	64.0	75.0	93	278	9.8	12.7	-55	3.0	10.0	16.0	45
	WEEK 36	275	61.8	17.0	4	52.0	66.0	75.0	89	275	10.2	12.5	-54	3.0	11.0	16.0	46
	WEEK 40	277	61.3	18.0	0	51.0	65.0	75.0	94	277	9.8	13.5	-53	3.0	10.0	17.0	44
	WEEK 44	271	61.6	17.6	0	51.0	65.0	76.0	94	271	10.0	13.5	-50	3.0	11.0	17.0	45
	WEEK 48	272	61.9	17.7	0	51.5	67.0	75.5	89	272	10.4	13.7	-50	3.0	11.0	18.0	45
	WEEK 52	268	62.4	17.3	6	53.0	66.0	76.0	89	268	10.7	13.5	-52	3.0	11.0	19.0	45
VTE 2Q8 (N=306)	SCREENING	305	52.1	13.3	25	43.0	53.0	63.0	73	305	0.5	5.7	-35	-2.0	0.0	3.0	20
	BASELINE	306	51.6	13.9	16	42.0	52.0	63.0	76								
	WEEK 1	298	54.8	14.6	15	46.0	55.5	67.0	86	298	3.2	6.8	-21	-1.0	2.0	7.0	23
	WEEK 4	305	56.2	15.7	14	46.0	58.0	68.0	87	305	4.5	8.5	-45	0.0	4.0	10.0	35
	WEEK 8	301	57.3	16.3	16	47.0	58.0	71.0	90	301	5.7	10.0	-56	0.0	5.0	12.0	38
	WEEK 12	295	58.9	17.1	5	50.0	61.0	72.0	94	295	7.4	11.0	-59	0.0	7.0	14.0	44
	WEEK 16	294	59.3	16.5	5	50.0	61.0	73.0	87	294	7.5	11.4	-61	1.0	8.0	15.0	45
	WEEK 20	288	60.0	16.7	5	50.5	62.5	73.0	89	288	8.2	11.9	-62	2.0	8.5	15.0	45
	WEEK 24	288	59.7	17.4	8	50.0	62.0	73.5	90	288	8.2	12.9	-60	2.0	9.0	15.0	46
	WEEK 28	287	60.1	17.0	8	50.0	62.0	74.0	93	287	8.4	12.3	-55	2.0	9.0	16.0	46
	WEEK 32	280	60.0	17.0	7	51.0	63.0	73.0	89	280	8.4	13.0	-64	2.0	8.0	16.0	46
	WEEK 36	280	60.2	17.4	6	51.0	63.0	74.5	90	280	8.4	13.6	-65	1.0	9.0	17.0	45
	WEEK 40	278	60.5	17.5	5	51.0	63.5	74.0	88	278	8.8	13.7	-59	1.0	10.0	18.0	44
	WEEK 44	277	60.3	17.4	7	50.0	63.0	74.0	90	277	8.7	14.2	-62	2.0	10.0	17.0	51
	WEEK 48	280	60.0	17.4	10	50.0	63.0	73.0	94	280	8.4	14.4	-61	1.0	9.0	17.0	45
	WEEK 52	278	61.0	17.4	7	51.0	64.0	75.0	93	278	9.4	14.5	-63	3.0	10.0	18.0	50

Source: 311523 (VIEW 2) CSR Post-text Table 14.2.2/7.

7 SIGNATURES/DISTRIBUTION LIST

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