VEGF TRAP-EYE
(aflibercept ophthalmic solution)

OPHTHALMOLOGIC DRUGS ADVISORY COMMITTEE

JUNE 17, 2011

Regeneron Pharmaceuticals, Inc.

EXECUTIVE SUMMARY

Synopsis

Age-related macular degeneration (AMD) is the most common cause of legal blindness in the elderly population of the developed world. A major paradigm shift occurred with the suggestion that vascular endothelial growth factor (VEGF), a growth factor known to promote both vascular growth and permeability, might be driving the abnormal choroidal neovascularization (CNV) and retinal edema that lead to loss of vision in AMD. Approval by the FDA in 2006 of intravitreal (IVT) injections of 0.5 mg ranibizumab, a humanized monoclonal antibody fragment that blocks VEGF, changed the standard-of-care for this blinding disease: based on large pivotal studies, monthly injections of ranibizumab have been shown to provide the best visual outcome and anatomic correction, and on average lead not only to maintenance of vision, but to gains in visual acuity (VA). Because of the marked treatment burden of monthly monitoring visits and injections on the elderly AMD patient population and their caregivers, there has been extensive effort to decrease the frequency of patient visits and injections; however, it has been difficult to replicate the visual gains and anatomic benefit of monthly ranibizumab using such approaches.

VEGF Trap-Eye is a soluble decoy receptor fusion protein created using Trap technology that may have theoretical and mechanistic advantages. Most importantly, the binding affinity to VEGF-A is substantially greater than that of ranibizumab, leading to the mathematical modeling suggestion that it might still be active in the eye for 10 to 12 weeks after a single intravitreal injection, with the binding activity of 2 mg VEGF Trap-Eye at 83 days estimated to be comparable to the activity of 0.5 mg ranibizumab at 30 days (Stewart 2008).

The current application is for the IVT administration of VEGF Trap-Eye for the treatment of wet AMD. The recommended regimen is 2 mg VEGF Trap-Eye administered IVT every 2 months following 3 initial monthly doses. Based on the primary analysis in two large Phase 3 studies comparing the endpoint of maintenance of vision, this dosing regimen provided efficacy that was numerically similar, statistically non-inferior and clinically equivalent to the current standard of care, ranibizumab 0.5 mg monthly; this dosing regimen also produced similar average gains in vision to monthly ranibizumab in both Phase 3 studies, and similar anatomic benefit. Administration of VEGF Trap-Eye was also associated with a safety profile similar to that of ranibizumab, in terms of both ocular and systemic adverse events (AEs). As the major safety risks with anti-VEGF therapy in wet AMD are serious ocular AEs related to the IVT injection procedure (e.g., endophthalmitis, retinal detachments, traumatic cataract, and increased intraocular pressure [IOP]), it is anticipated that reducing the number of IVT injections by about half will result in a corresponding decrease in the number of these rare but serious AEs. Moreover, eliminating the need for not only monthly injections but also for mandatory monthly monitoring of patients could substantially reduce the treatment burden on patients, caregivers, and the health care system, without sacrificing patient benefit.

Introduction and Unmet Medical Need

Age-related macular degeneration is the most common degenerative disease of the macula, and is the most common cause of legal blindness in the elderly population of the developed world. Evidence suggests that 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to

85 years, show signs of AMD (Phillips 2009). The most severe form of AMD is the wet form, so-called because it is marked by abnormal CNV and associated vascular leak and retinal edema. The new, pathological blood vessels in the retina leak lipids, fluid and blood, leading to edema and retinal thickening that can profoundly impair VA, particularly when the macula is affected. Without treatment, patients can on average lose on the order of one letter a month (corresponding to over 10 letters a year) when evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual chart (The Early Treatment Diabetic Retinopathy Study Group 1985).

A major paradigm shift occurred in the field with the suggestion that VEGF, a growth factor known to promote both vascular growth and permeability, might be driving the abnormal CNV and retinal edema that leads to vision loss in AMD (Adamis 1994, Aiello 1994). Since the 1990s, evidence from both animal and clinical studies has accumulated in support of the critical role of VEGF in ocular neovascularization.

Today, anti-VEGF therapy is the standard of care in the treatment of wet AMD. The first anti-VEGF therapy evaluated for clinical efficacy in AMD patients was an RNA-based aptamer known as pegaptanib sodium (Macugen®, Eyetech) that bound and blocked only one isoform of VEGF with relatively low affinity. Though pegaptanib served as the ground-breaking pioneer both for anti-VEGF therapies and for approaches involving regular IVT injections, its efficacy was modest. Pegaptanib did not provide vision gains nor did it stabilize vision, but instead it served to slow the rate of ongoing visual deterioration. The next major advance in the field involved the clinical testing of a much broader and higher-affinity VEGF-blocking agent, known as ranibizumab (Lucentis®, Genentech and Novartis). Ranibizumab is an IVT-injected antibody fragment that binds all VEGF-A isoforms (Lowe 2007). Ranibizumab proved highly efficacious in wet AMD when administered monthly. Data from the MARINA (Rosenfeld 2006) and ANCHOR (Brown 2006) Phase 3 studies showed that monthly ranibizumab resulted not only in maintenance of vision, but also in marked average vision gains. Approval of monthly IVT injections of ranibizumab by the FDA in 2006 changed the standard-of-care for this blinding disease.

Monthly IVT injections, however, present both a risk and a burden to patients. First, there is the potential for serious risk associated with each IVT injection procedure, including endophthalmitis, retinal detachments, traumatic cataract, and increased IOP. Second, monthly treatment or even monthly monitoring, which may continue for a patient's lifetime, is a substantial burden to patients, their caregivers, ophthalmologists and the healthcare system. This burden is more than just an inconvenience. These elderly patients frequently require the assistance of a family member to come to the ophthalmologist. And this family member is frequently somebody with a full-time job who needs to miss a day of work to help the patient. Thus there are hidden economic and quality-of-life costs associated with monthly visits.

To date, the gold standard treatment for wet AMD, based on the pivotal studies, is monthly injections of ranibizumab. However, because of the safety risks and treatment burden of monthly injections, as well as the cost of this expensive new therapeutic, physicians have been extensively exploring other treatment options. Physicians have attempted to decrease the safety risk and treatment burden by exploring less frequent dosing strategies, and they have tried to reduce the cost burden by substituting a related, off-label anti-VEGF agent, bevacizumab (Avastin®, Genentech and Roche); bevacizumab is a humanized full-length antibody derived from the same parent antibody as the ranibizumab antibody-fragment, and it is approved for

cancer treatment and must be re-aliquotted by compounding pharmacies for use in the eye. Despite extensive efforts to develop alternative treatment strategies with ranibizumab that would decrease the frequency of patient visits and injections without sacrificing patient benefit, most of these efforts have had difficulty matching the vision gains and anatomic benefit seen with monthly ranibizumab dosing. Fixed quarterly dosing with ranibizumab failed to stabilize vision from the onset of this dosing regimen (Regillo 2008), while studies testing "as needed" (PRN) ranibizumab, without requiring monthly monitoring visits, also could not stabilize vision (Boyer 2009, Awh 2008).In addition, though monthly and PRN bevacizumab usage has been widely adopted because of the cost benefit, particularly for patients whose health-care coverage could not cover ranibizumab, definitive data comparing the effectiveness of these regimens to monthly ranibizumab was not available.

To compare the benefit of monthly ranibizumab with bevacizumab, as well as to explore less frequent dosing regimens, the NIH performed the CATT study which compared monthly and PRN regimens of ranibizumab and bevacizumab. Importantly, in contrast to previous PRN attempts that did not require monthly monitoring, the CATT study mandated monthly monitoring at which time treatment with PRN injection was to be performed if there was any evidence of retinal fluid as judged by Optical Coherance Tomography (OCT). The primary endpoint was mean change in visual acuity at 1 year. Analysis of the primary endpoint showed that monthly ranibizumab and monthly bevacizumab resulted in numerically similar mean visual acuity gains at 1 year (8.5 letters for monthly ranibizumab vs. 8.0 letters for monthly bevacizumab), and that monthly bevacizumab was noninferior to monthly ranibizumab based on the prespecified non-inferiority criteria. Ranibizumab given PRN as specified in the protocol (which required an average of 6.9 injections during the first year and yielded a mean change in VA of 6.8 letters) also met the non-inferiority criterion compared to monthly ranibizumab. However, the PRN regimen for Bevacizumab (which required an average of 7.9 injections in the first year and yielded a mean change in VA of 5.9 letters) failed to demonstrate non-inferiority to either of the monthly regimens (Figure 1). With respect to several ways of assessing anatomic correction of the disease and the decrease in retinal swelling and fluid, monthly ranibizumab was significantly better than monthly bevacizumab or either of the PRN regimens; it will be important to understand if differences in these anatomic endpoints will ultimately correlate with longer term problems in vision and/or other aspects of disease control. The interpretation of these results is therefore complex. However a particular clinical practice might interpret CATT in terms of affecting their usage of ranibizumab versus bevacizumab, or PRN compared to monthly dosing, it is important to note that all of the regimens studied in the CATT trial still required patients to come in for mandatory monthly visits and exams during which difficult treatment decisions had to be made based on anatomic surrogates whose predictive value for clinical outcomes is not completely understood. Thus, there remains an unmet need for new therapies that will provide efficacy equivalent to monthly ranibizumab treatment but that reduce the burden and risk of monthly injections, and also avoid the burden of mandatory monthly monitoring visits; it would also be desirable to have such therapies that not only provide similar numerical benefit in terms of vision gains, but also provide similar anatomical control of disease activity as heretofore has only been demonstrated by monthly ranibizumab, while also avoiding the need to make "as needed" treatment decisions based on anatomic surrogates whose relevance to ultimate outcome is not completely understood.

Non Clinical Overview and Clinical Pharmacology

The VEGF Trap is a soluble decoy receptor fusion protein that may have theoretical and mechanistic advantages for use in the eye. The VEGF Trap was created using Trap technology (Economides 2002, Holash 2002) also used to create an Interleukin-1 Trap, rilonacept ARCALYST®, Regeneron), which was recently approved to treat a rare cold-induced auto-inflammatory disease (Arcalyst US package insert) and has been shown in Phase 3 studies to reduce the incidence of gout flares in patients initiating urate lowering therapy (Regeneron, data on file). In particular, the VEGF Trap was created by fusing DNA sequences encoding the second Ig domain of human VEGF receptor 1 (VEGFR-1) to the third Ig domain of human VEGF receptor 2 (VEGFR-2), which is in turn fused to the constant region of human IgG1 (Holash 2002); as is also the case with the Interleukin-1 Trap, the VEGF Trap binds to its cognate ligands with substantially higher affinity than do the native receptors from which it was constructed. Recombinant VEGF Trap protein is expressed in Chinese hamster ovary (CHO) K1 cells, and then purified by a combination of filtration and chromatographic techniques. VEGF Trap-Eye is specially purified and specifically formulated for IVT injection.

A unique characteristic of VEGF Trap is its high binding affinities to all isoforms of VEGF as well as to the highly related placental growth factor (PlGF); e.g., the equilibrium dissociation constant (K_D) for VEGF Trap binding to human VEGF-A_{165} is 0.5 pM, to human VEGF-A_{121}, is 0.36 pM, and to human PlGF-2 is 39 pM (Holash 2002). Research with VEGF Trap in several different animal models of ophthalmologic disorders has shown that VEGF Trap can substantially inhibit retinal and choroidal neovascularization, as well as the formation of retinal edema (Section 3.2).

Most importantly, the binding affinity of VEGF Trap to VEGF-A is substantially greater than that of ranibizumab, leading to the mathematical modeling suggestion that because low VEGF Trap concentrations can still provide potent blockade it might still be active in the eye for 10 to 12 weeks after a single intravitreal injection, with the binding activity of 2 mg VEGF Trap-Eye at 83 days estimated to be comparable to that of 0.5 mg ranibizumab at 30 days (Stewart 2008). Thus, the high-affinity blocking properties of VEGF Trap may allow for an extended dosing interval compared to ranibizumab (Stewart 2008).

In our clinical program we sought to test whether a molecule with these characteristics, VEGF Trap-Eye, would allow for similar efficacy to the standard of care while requiring less frequent IVT dosing.

Early clinical development demonstrated that IVT doses in the range of 0.5 to 2 mg provided maximal clinical benefit in patients suffering from wet AMD, in terms of initially improving visual activity and then maintaining these gains. Greater doses (i.e., 4 mg IVT) did not provide greater effects. The Phase 2 data as well as modeling data (Stewart, 2008), suggested that the q8 interval may allow sufficient activity to provide maintenance of visual gains.

VEGF Trap is slowly absorbed from the eye into the systemic circulation after IVT administration and is predominately observed in the systemic circulation as an inactive, stable complex with VEGF; however only “free VEGF Trap” is able to bind endogenous VEGF. It is estimated that after IVT administration of 2 mg to patients, the mean maximum plasma concentration of free VEGF Trap is more than 100-fold lower than the concentration of VEGF Trap required to half-maximally bind systemic VEGF. Therefore, systemic PD effects

using the IVT doses of interest are unlikely. Consistent with this, there was no evidence in early clinical trials that IVT VEGF Trap-Eye was associated with the most sensitive indicator of systemic effects, i.e. induction of increases in blood pressure, in these early studies.

Phase 3 AMD Program: VIEW 1 and VIEW 2

The safety and efficacy of VEGF Trap-Eye were assessed in two similarly-designed, randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with VEGF Trap-Eye) in the two studies (VIEW 1 and VIEW 2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4); 2) VEGF Trap-Eye administered 2 mg every 4 weeks (VEGF Trap-Eye 2Q4); 3) VEGF Trap-Eye 0.5 mg administered every 4 weeks (VEGF Trap-Eye 0.5Q4); and 4) VEGF Trap-Eye administered 2 mg every 8 weeks following 3 initial monthly doses (VEGF Trap-Eye 2Q8). Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set (PPS) who maintained vision, defined as losing fewer than 15 letters of VA, (measured by ETDRS letter score) at week 52 compared to baseline. The primary analysis was an evaluation of the non-inferiority of VEGF Trap-Eye to ranibizumab with a pre-specified non-inferiority margin of 10%. Secondary efficacy endpoints included change from baseline to week 52 in best corrected visual acuity (BCVA) letter score, proportion of subjects who gained 15 or more letters from baseline to week 52, change from baseline to week 52 in total National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25) total score, and change from baseline to week 52 in CNV area. A conditional sequence of testing controlled overall alpha at the 5% level; the every 8 week dosing paradigm was chosen to be last in the conditional sequence as achieving success with this longer-interval dosing regimen was considered to be most challenging. Aspects of the study design, including the primary analysis and non-inferiority margin, were developed in conjunction with discussions with the FDA as part of a Special Protocol Assessment. Although not in the analysis plan for the study, in a separate communication, the FDA further explained that, whereas the 10% confidence interval would be used to assess non-inferiority, a 5% confidence interval would be used to assess clinical equivalence.

Phase 3 Efficacy

In both pivotal studies (VIEW 1, VIEW 2), all three VEGF Trap-Eye dosing regimens, including the every 8 week dosing regimen, were numerically similar and were consistently shown to be non-inferior to ranibizumab with regard to the pre-specified primary efficacy analysis, i.e., the proportion of subjects maintaining vision after one year of treatment, analyzed for the pre-specified PPS using the last-observation-carried forward (LOCF) approach (VIEW 1: 94.4% for ranibizumab, and 95.9, 95.1, and 95.1% for VEGF Trap-Eye 2Q4, 0.5Q4, and 2Q8, respectively; VIEW 2: 94.4 for ranibizumab and 96.3, 95.6, and 95.6% for VEGF Trap-Eye 2Q4, 0.5Q4, and 2Q8, respectively). In fact, in each study and for all comparisons, the actual upper limit of the confidence interval (CI) of the difference between ranibizumab and VEGF Trap-Eye ($\leq$ 3.1%) was substantially below the pre-specified, clinically meaningful non-inferiority margin of 10% and also below 5%. All sensitivity analyses conducted to assess the robustness of these results confirmed the findings of the primary analysis. The validity of these findings is further supported by the fact that, as is desirable for non-inferiority studies, the active comparator in

both pivotal VEGF Trap-Eye studies behaved in a manner entirely consistent with its clinical experience: i.e., the active comparator ranibizumab yielded success rates for the primary efficacy variable (94.4% of all subjects maintained vision in both VIEW 1 and VIEW 2) that were very similar to those obtained in the pivotal studies ANCHOR (Brown 2006) and MARINA (Rosenfeld 2006) that had been used to support the registration of ranibizumab. The extensive number of secondary and pharmacoynamic variables examined, provide a very robust and compelling picture. Most notably, all VEGF Trap-Eye dosing regimens, including the every 8 week regimen, resulted in similar gains to ranibizumab in the key secondary endpoint of change from baseline to week 52 in change in best corrected visual acuity (BCVA), with mean gains ranging from 7.6 to 10.9 letters in all three regimens across the two studies; the 2 mg VEGF Trap-Eye dosed every 4 weeks demonstrated the largest gain (10.9 letters) and was statistically superior to ranibizumab in VIEW 1, but not in VIEW 2. Similarly, other minor differences seen in VIEW 1 among the three VEGF Trap-Eye dosing regimens were not reproduced in VIEW 2, further suggesting that all three dosing regimens indeed had rather similar efficacy. This conclusion was supported by a pre-specified integrated analysis combining the two studies in which all dosing regimens resulted in 52 week BCVA outcomes within a letter of each other (from 8.3 to 9.3 letters). In addition to VA outcomes, all 3 VEGF Trap-Eye dosing regimens, including 2 mg VEGF Trap-Eye dosed every 8 weeks, also similarly improved anatomic outcomes as compared to monthly ranibizumab. Consistency was found for both primary and secondary endpoints (i) across all clinical studies designed to assess efficacy of VEGF Trap-Eye, (ii) between analysis sets, i.e. per-protocol set (PPS) versus full-analysis set (FAS), (iii) between original analysis and, where performed, sensitivity analyses and (iv) across all subgroups assessed (e.g. age, gender, race, baseline visual acuity, lesion type, CNV area).

Importantly, these results established that all 3 VEGF Trap-Eye dose regimens, and, in particular, 2 mg VEGF Trap-Eye dosed every 8 weeks, provided efficacy that was clinically equivalent to ranibizumab 0.5 mg dosed every 4 weeks. Moreover, because data from examinations conducted at non-dosing visits in the 2Q8 arm could not be used for clinical decision making (other than for withdrawal of patients) and was only collected for analytic purposes, the results demonstrate that these benefits can be achieved without the need for between-visit monitoring for patients treated with VEGF Trap-Eye 2 mg every 2 months. Thus, VEGF Trap-Eye 2Q8 can be given on a regular every two month dosing schedule and yield similar vision gains and anatomic disease control as monthly ranibizumab, without the need for intervening monitoring visits, and without the need for making "as needed" treatment decisions based on anatomic surrogates whose relevance to long-term outcomes is not well understood.

Phase 3 Safety

VEGF Trap-Eye was well tolerated with an acceptable safety profile and without notable differences compared to ranibizumab 0.5Q4 in ocular or non-ocular treatment emergent AEs (TEAEs). The most common (>5%) adverse events not related to the underlying disease reported in patients receiving VEGF Trap-Eye were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased IOP. Serious adverse reactions related to the injection procedure have occurred in <0.1% of IVT injections with either VEGF Trap-Eye or ranibizumab and included endophthalmitis, traumatic cataract, and transient increased IOP. The incidence of SAEs, fatal events, and withdrawals due to AEs was balanced between treatment groups, as was the incidence of adjudicated arterial thromboembolic events based on the definition used by the Anti-Platelet Trialists' Collaboration (APTC). APTC events (non-fatal

myocardial infarctions, non-fatal strokes, and fatal vascular events) are the most clinically important arterial thromboembolic events because they represent irreversible morbidity or mortality. There was no dose-response across VEGF Trap-Eye groups with regards to APTC events or serious AEs potentially related to systemic VEGF inhibition and the frequencies of these were low across treatment groups and, in the VEGF Trap-Eye groups, consistent with those previously reported for ranibizumab.

Risk/Benefit and Conclusion

All three regimens of VEGF Trap-Eye demonstrated non-inferiority to the current optimal standard of care, i.e. monthly ranibizumab, in two rigorously designed Phase 3 studies. The data support that all 3 regimens provide essentially the same efficacy as ranibizumab. In clinical studies, VEGF Trap-Eye had an excellent safety profile similar to that of ranibizumab. Therefore, it is reasonable to conclude that the benefit of VEGF Trap-Eye outweighs the potential risks.

The 2Q8 regimen for VEGF Trap-Eye has additional potential benefits by allowing substantially less frequent injections compared to monthly dosing regimens and less frequent monitoring compared to PRN regimens that require monthly monitoring. These additional potential benefits include (i) decreased risk for adverse injection-related events, (ii) eliminated need for interim monitoring visits during which difficult treatment decisions have to be made based on anatomic surrogates whose predictive value for clinical outcomes is not completely understood and thus (iii) decreased burden on the patients, their caregivers and physicians, and the overall healthcare system. These additional potential benefits do not have associated additional risks. Visual acuity, anatomic endpoints, and functional endpoints at 52 weeks are not compromised by a fixed 2Q8 regimen and there is little reason to believe that interim monitoring visits would meaningfully improve patient safety.

In summary, dosing of VEGF Trap-Eye has a clearly positive benefit / risk balance in patients with wet AMD and the regimen of VEGF Trap-Eye every two months (after 3 initial dosing) provides additional potential benefit over current therapies. For those instances where it may be clinically warranted, VEGF Trap-Eye may be dosed as frequently as once per month.

Therefore, VEGF Trap-Eye treatment should be initiated with one injection per month for three consecutive months, followed by one injection every 2 months.

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Ab	Antibody
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AEI	AE of interest
AMD	Age-related macular degeneration
APTC	Anti-Platelet Trialists' Collaboration
ATE	Arterial thromboembolic events
BCVA	Best corrected visual acuity
BMI	Body mass index
CDC	Complement dependent cytotoxicity
CI	Confidence interval
CNV	Choroidal neovascularization
CR/LT	Central Retinal/Lesion Thickness
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CSR	Clinical study report
CVA	Cerebrovascular accident
DLT	Dose limiting toxicity
DME	Diabetic macular edema
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein angiography
Fc	Fragment, crystallizable region or constant
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
Ig	Immunoglobulin
IOP	Intraocular pressure
IV	Intravenous
IVT	Intravitreal
LOAEL	Lowest-observable-adverse-effect level
LOCF	Last observation carried forward
MTD	Maximum tolerated dose
NEI-VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
NOAEL	No-observed-adverse-effect level
OCT	Optical coherence tomography
PD	Pharmacodynamic
PK	Pharmacokinetics
PlGF	Placental growth factor
PT	Preferred term
QOL	Quality of Life
Regeneron	Regeneron Pharmaceuticals, Inc.
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class

T1/2	Terminal half-life
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VA	Visual acuity

1. PROPOSED INDICATION AND DOSING

1.1. Proposed Indication

The proposed indication is for the treatment of neovascular age-related macular degeneration (AMD).

1.2. Rationale for Dosing Regimen in Proposed Labeling

VEGF Trap-Eye was designed to be administered intravitreally (IVT) to maximize local clinical effects (improvement in visual acuity [VA]) while minimizing the systemic effects (e.g. increases in blood pressure) related to systemic vascular endothelial growth factor (VEGF) inhibition.

Indications of the efficacy of VEGF Trap-Eye were seen in all phases of the clinical development program. Early clinical development demonstrated that doses less than 0.5 mg IVT resulted in sub-maximal and/or short-lived effects. Doses of 0.5 mg and 2 mg IVT provided equivalent effects up to 1 month on VA and on pharmacodynamic (PD) markers of efficacy such as central retinal lesion thickness or choroidal neovascularization (CNV) area. No additional benefit was seen with a 4 mg dose.

Based on these observations, the dose regimens selected for Phase 3 were 0.5 mg IVT every 4 weeks, 2 mg IVT every 4 weeks, and 2 mg IVT every 8 weeks (after three initial monthly doses), with the hope that the higher 2 mg dose would allow for the same clinical benefit with longer-interval dosing, as suggested by mathematical modeling analysis (Stewart 2008). These regimens were compared with ranibizumab 0.5 mg every 4 weeks, the dose and interval endorsed by the FDA in the ranibizumab prescribing information, and which seems to be associated with the optimal clinical benefit. The 3 dosing regimens of VEGF Trap-Eye were compared to monthly 0.5 mg ranibizumab in two phase 3 studies of essentially identical design (VIEW 1 and VIEW 2; the design of VIEW 1 was discussed with FDA in a Special Protocol Assessment). These two studies together included over 2400 patients with approximately 1800 patients being dosed with VEGF Trap-Eye. In both studies, the primary analysis was an evaluation of the non-inferiority of VEGF Trap-Eye to monthly ranibizumab in terms of the proportion of patients who maintained vision, with a pre-specified non-inferiority margin of 10%, using a conditional sequence in which the every 8 week dosing paradigm was chosen to be last in the sequence. Achieving success with this longer-interval dosing regimen was considered to be most challenging. The statistical approach also allowed comparison with a 5% margin that, in a separate communication, the FDA explained would be used to assess clinical equivalence. Key secondary efficacy endpoints included change from baseline to week 52 in mean BCVA letter score.

In both pivotal studies (VIEW 1, VIEW 2), all three VEGF Trap-Eye dosing regimens, including the every 8 week dosing regimen, were numerically similar and were consistently shown to be non-inferior to ranibizumab with regard to the pre-specified primary efficacy analysis (the proportion of subjects maintaining vision after one year of treatment, analyzed for the pre-specified PPS using the last-observation-carried forward (LOCF) approach (VIEW 1: 94.4% for ranibizumab, and 95.9, 95.1, and 95.1% for VEGF Trap-Eye 2Q4, 0.5Q4, and 2Q8,

respectively; VIEW 2: 94.4 for ranibizumab and 96.3, 95.6, and 95.6% for VEGF Trap-Eye 2Q4, 0.5Q4, and 2Q8, respectively). In each study and for all comparisons, the actual upper limit of the CI of the difference between ranibizumab and VEGF Trap-Eye (≤ 3.1%) was substantially below the pre-specified, clinically meaningful non-inferiority margin of 10% and also below 5%. All sensitivity analyses conducted to assess the robustness of these results confirmed the findings of the primary analysis. The validity of these findings is further supported by the fact that, as is desirable for non-inferiority studies, the active comparator in both pivotal VEGF Trap-Eye studies behaved in a manner entirely consistent with its clinical experience: i.e., the active comparator ranibizumab yielded success rates for the primary efficacy variable (> 94% of all subjects maintained vision) that were very similar to those obtained in the pivotal, sham-controlled studies ANCHOR (Brown 2006) and MARINA (Rosenfeld 2006) that had been used to support the registration of ranibizumab. The extensive number of secondary and PD variables examined provide a very robust and compelling picture. Most notably, all 3 VEGF Trap-Eye dosing regimens, including the every 8 week regimen, resulted in similar gains to ranibizumab in the key secondary endpoint of change from baseline to week 52 in BCVA letter score, with mean gains ranging from 7.6 to 10.9 letters with all three regimens across the two studies; the 2 mg VEGF Trap-Eye dosed every 4 weeks demonstrated the largest gain (10.9 letters) and was statistically superior to ranibizumab in VIEW 1, but not in VIEW 2. Similarly, other minor differences seen in VIEW 1 among the three VEGF Trap-Eye dosing regimens were not reproduced in VIEW 2, further suggesting that all three dosing regimens indeed had rather similar efficacy. This conclusion was supported by a pre-specified integrated analysis combining the two studies in which all dosing regimens resulted in 52 week BCVA outcomes within a letter of each other (from 8.3 to 9.3 letters). In addition to VA outcomes, all 3 VEGF Trap-Eye dosing regimens, including 2 mg VEGF Trap-Eye dosed every 8 weeks, also similarly improved anatomic outcomes as compared to monthly ranibizumab. Consistency was found in the primary as well as secondary endpoints (i) across all clinical studies designed to assess efficacy of VEGF Trap-Eye, (ii) between analysis sets, i.e. PPS versus FAS, (iii) between original analysis and, where performed, sensitivity analyses and (iv) across all subgroups assessed (e.g. age, gender, race, baseline VA, lesion type, CNV area).

Importantly, these results established that all 3 VEGF Trap-Eye dose regimens, and, in particular, 2 mg VEGF Trap-Eye dosed every 8 weeks, provided efficacy that was clinically equivalent to ranibizumab 0.5 mg dosed every 4 weeks. A key finding that should be of important benefit to patients was that the dosing interval of IVT VEGF Trap-Eye injections can be as long as every two months (i.e., q8 weeks) – twice as long as the recommended dosing interval of optimal (i.e., q4 weeks or monthly) ranibizumab – with equivalent efficacy. In particular, because subjects in the VEGF Trap-Eye 2 mg every two months group were not permitted to receive an injection at the intervening visit between doses and, in general, because the monthly monitoring data in VIEW 1 and VIEW 2 could not be used for clinical decision making (other than withdrawal of patients from the study) and was only collected for analytic purposes, the results demonstrate that monthly monitoring is not necessary with the VEGF Trap-Eye 2 mg every two month regimen. Thus, VEGF Trap-Eye 2Q8 can be given on a regular every two month dosing schedule and yield similar vision gains and anatomic disease control as monthly ranibizumab, without the need for intervening monitoring visits, and without the need for making difficult "as needed" treatment decisions based on anatomic surrogates whose relevance to long-term outcomes is not well understood. For those instances where it may

be clinically warranted, the safety data support that VEGF Trap-Eye may be dosed as frequently as once per month.

Based on the above, we propose that the optimal regimen for VEGF Trap-Eye is 2 mg every two months (after three initial monthly loading doses) for the following reasons:

1. The efficacy of this dosing regimen of VEGF Trap-Eye is similar to that of the current standard-of-care, monthly ranibizumab
2. The current optimal standard-of-care requiring monthly visits and injections results in a large treatment burden for this elderly patient population, their caregivers, as well as the health care system, and this burden could be substantially lowered by allowing for regular every two month injections without the need for monthly monitoring visits
3. The main safety risk associated with the treatment of wet AMD is the IVT injection procedure itself, and thus safety issues should decrease with less frequent injections.

2. INTRODUCTION AND UNMET MEDICAL NEED

Age-related macular degeneration is the most common cause of legal blindness in the elderly population of the developed world, and involves loss of central vision due to progressive pathology in the central portion of the retina known as the macula. Age-related macular degeneration is a disease of the elderly, and evidence suggests that 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to 85 years, show signs of AMD (Phillips 2009).

There are two forms of AMD, the dry and the wet form. The dry form is less aggressive and accounts for 90% of all AMD cases, but only for 10% of cases of blindness due to AMD. Wet AMD affects 10% of the AMD patients and is the more aggressive form, which, if untreated, leads to rapid severe visual impairment and in many cases legal blindness.

Summary of AMD Pathophysiology

The pathology in AMD involves the three layers that underlie the neural retina – the retinal pigment epithelium (RPE), Bruch's membrane, and the choroid; these layers are involved in transporting metabolic waste products from the retina and RPE to the choroid vasculature. In the aging eye, Bruch's membrane can thicken and its composition can change, impeding the transport of waste products, and this is thought to result in abnormal deposits. Such deposits are visible during retinal examination as drusen, which, from a clinical perspective, mark the start of AMD. Drusen contain lipofuscin, including the photophore A2E and other toxic waste products of metabolism.

The first symptoms of wet AMD are often self-reported vision-related changes including blurred vision, metamorphopsia, and difficulties with reading. Clinically, wet AMD usually progresses slowly but often inexorably, so that without treatment, patients lose on average about one letter per month (as evaluated using the standardized Early Treatment Diabetic Retinopathy Study [ETDRS] vision testing chart) and about 10 letters per year; however, acute vision loss may result from subretinal bleeding. One or both eyes may be affected, at the same time or sequentially.

Dry AMD

In the dry form, contrary to the wet form, no abnormal neovascularization occurs in the subretinal space, and therefore there is no exudate. Drusen deposits are clustered in and around the macula, and these become larger and more numerous over time.

Dry AMD with drusen only is typically asymptomatic, but some patients also may report blurred vision. If, in addition to drusen, dry AMD patients also develop retinal geographic atrophy involving the fovea, it can significantly reduce near and distance vision. There may also be a blind spot in the middle of their visual field. The blind spot may be small initially, but it can slowly grow over time.

Currently, there is no approved treatment for dry AMD. Antioxidants and vitamins have been shown in certain subgroups to have some mild prophylactic effects, i.e. reducing the risk of AMD progression (AREDS, report no. 8, 2001).

Wet AMD

Dry AMD may develop into wet AMD, also known as neovascular or exudative AMD, which is less prevalent. Only about 10% of AMD patients have the wet form; however, 80% to 90% of patients with severe vision loss due to AMD have wet AMD. In wet AMD, damage to Bruch's membrane is associated with a localized inflammatory response and induction of CNV. The CNV consists of abnormal, hyperpermeable blood vessels, growing from the choroid through the defects in Bruch's membrane underneath the RPE and the retina. These new, immature blood vessels leak lipids, fluid and blood. This causes edema, swelling and disturbance of the retinal architecture, resulting in blurring and distortion of vision. The onset of visual dysfunction in wet AMD is acute, and then inexorably progresses. Rarely, it can progress in more accelerated fashion, particularly if subretinal bleeding occurs. With bleeding under the macula or persistent edema, the loss of central vision may become permanent. Typically, patients develop difficulty in their ability to read, watch TV, drive a car or recognize faces.

Prior to 2000, the only treatment for neovascular wet AMD was laser ablation to the affected retina to limit the expanding lesion in the central vision (Gelfand 1997). Patients were offered this therapy which, when applied to the central retina, often resulted in immediate and irreversible vision loss. Studies demonstrated that after 2 to 3 years, patients would often have been better off if they had had no treatment at all. Laser ablation treatment for AMD was replaced by photodynamic therapy with verteporfin, which was approved by the FDA in 2000 (Bressler 2001; Tap Report; 1999). Unfortunately for patients at the time, this therapy did not stabilize vision, but merely slowed the rate of inexorable deterioration.

Anti-VEGF Therapies Provide a Paradigm Shift in the Treatment of wet AMD Treatment

A major paradigm shift occurred with the suggestion that VEGF, a growth factor known to promote both vascular growth and permeability, might be driving the abnormal CNV and retinal edema seen in AMD (Adamis 1994, Aiello 1994). This led to testing of the first anti-VEGF therapy in AMD, i.e. IVT administration of an RNA aptamer known as pegaptanib sodium (Macugen®, Eyetech), which was approved in 2004. Although an improvement over previous therapies, pegaptanib did not stabilize vision but only slowed vision loss on average. This may be because pegaptanib only blocks some of the active isoforms of VEGF and with relatively low affinity. In 2006, two phase 3 studies (MARINA [Rosenfeld 2006] and ANCHOR

[Brown 2006]) showed that monthly IVT injections of 0.3 mg or 0.5 mg ranibizumab (Lucentis®, Genentech and Novartis), a humanized monoclonal antibody fragment that blocks all isoforms of VEGF, not only prevented vision loss in the large majority of patients, but also led to significant visual gain in approximately one-third of patients. The ranibizumab development program thus established that, in comparison to pegaptanib, a pan-isoform higher-affinity anti-VEGF treatment is more effective in wet AMD. The safety of the treatment was also established, with the most notable safety findings related to the injection procedure, as ultimately noted in the product label, "Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections, including endophthalmitis, rhegmatogenous retinal detachments, and iatrogenic traumatic cataracts." Approval of monthly IVT injections of ranibizumab by the FDA in 2006 changed the standard-of-care for this blinding disease.

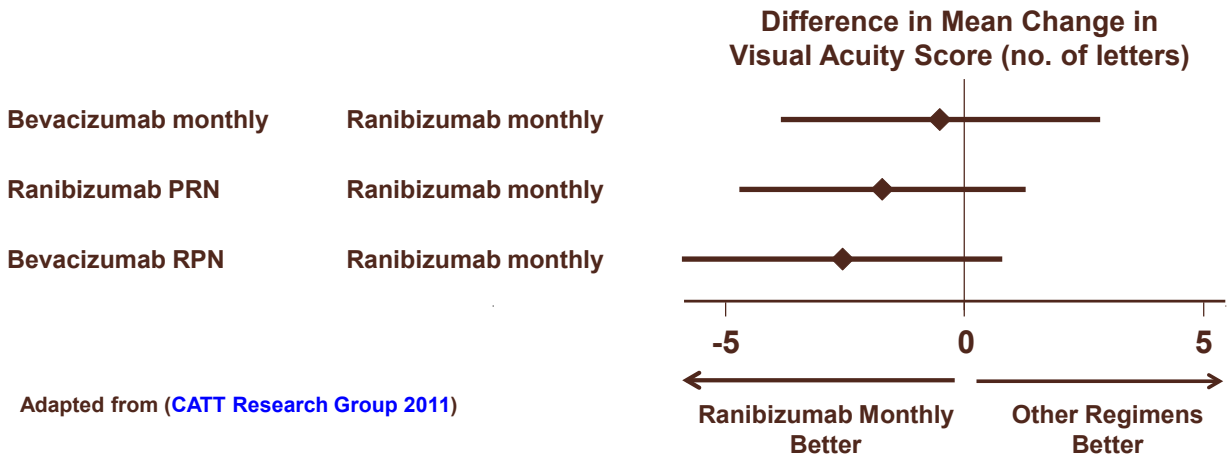
Monthly IVT injections, however, present both a risk and a burden to patients. First, there is the potential for serious risk associated with each IVT injection procedure, including endophthalmitis, retinal detachments, traumatic cataract, and increased IOP. Second, monthly treatment or even monthly monitoring, which may continue for a patient's lifetime, is a substantial burden to patients, their caregivers, ophthalmologists and the healthcare system. This burden is more than just an inconvenience. These elderly patients frequently require the assistance of a family member to come to the ophthalmologist. And this family member is frequently somebody with a full-time job who needs to miss a day of work to help the patient. Thus there are hidden economic and quality-of-life costs associated with monthly visits.

To date, the gold standard treatment for wet AMD, based on the pivotal studies, is monthly injections of ranibizumab. However, because of the safety risks and treatment burden of monthly injections, as well as the cost of this expensive new therapeutic, physicians have been extensively exploring other treatment options. Physicians have attempted to decrease the safety risk and treatment burden by exploring less frequent dosing strategies, and they have tried to reduce the cost burden by substituting a related, off-label anti-VEGF agent, bevacizumab (Avastin®, Genentech and Roche); bevacizumab is a humanized full-length antibody derived from the same parent antibody as the ranibizumab antibody-fragment, and it is approved for cancer treatment and must be re-aliquotted by compounding pharmacies for use in the eye. Despite extensive efforts to develop alternative treatment strategies with ranibizumab that would decrease the frequency of patient visits and injections without sacrificing patient benefit, most of these efforts have had difficulty matching the vision gains and anatomic benefit seen with monthly ranibizumab dosing. Fixed quarterly dosing with ranibizumab failed to stabilize vision from the onset of this dosing regimen (Regillo 2008), while studies testing "as needed" (PRN) ranibizumab, without requiring monthly monitoring visits, also could not stabilize vision (Boyer 2009, Awh 2008).In addition, though monthly and PRN bevacizumab usage has been widely adopted because of the cost benefit, particularly for patients whose health-care coverage could not cover ranibizumab, definitive data comparing the effectiveness of these regimens to monthly ranibizumab was not available.

To compare the benefit of monthly ranibizumab with bevacizumab, as well as to explore less frequent dosing regimens, the NIH performed the CATT study which compared monthly and PRN regimens of ranibizumab and bevacizumab. Importantly, in contrast to previous PRN attempts that did not require monthly monitoring, the CATT study mandated monthly monitoring at which time treatment with PRN injection was to be performed if there was any evidence of

retinal fluid as judged by Optical Coherence Tomography (OCT). The primary endpoint was mean change in visual acuity at 1 year. Analysis of the primary endpoint showed that monthly ranibizumab and monthly bevacizumab resulted in numerically similar mean visual acuity gains at 1 year (8.5 letters for monthly ranibizumab vs. 8.0 letters for monthly bevacizumab), and that monthly bevacizumab was noninferior to monthly ranibizumab based on the prespecified non-inferiority criteria. Ranibizumab given PRN as specified in the protocol (which required an average of 6.9 injections during the first year and yielded a mean change in VA of 6.8 letters) also met the non-inferiority criterion compared to monthly ranibizumab. However, the PRN regimen for Bevacizumab (which required an average of 7.9 injections in the first year and yielded a mean change in VA of 5.9 letters) failed to demonstrate non-inferiority to either of the monthly regimens (Figure 1). With respect to several ways of assessing anatomic correction of the disease and the decrease in retinal swelling and fluid, monthly ranibizumab was significantly better than monthly bevacizumab or either of the PRN regimens; it will be important to understand if differences in these anatomic endpoints will ultimately correlate with longer term problems in vision and/or other aspects of disease control. The interpretation of these results is therefore complex. However a particular clinical practice might interpret CATT in terms of affecting their usage of ranibizumab versus bevacizumab, or PRN compared to monthly dosing, it is important to note that all of the regimens studied in the CATT trial still required patients to come in for mandatory monthly visits and exams during which difficult treatment decisions had to be made based on anatomic surrogates whose predictive value for clinical outcomes is not completely understood. Thus, there remains an unmet need for new therapies that will provide efficacy equivalent to monthly ranibizumab treatment but that reduce the burden and risk of monthly injections, and also avoid the burden of mandatory monthly monitoring visits; it would also be desirable to have such therapies that not only provide similar numerical benefit in terms of vision gains, but also provide similar anatomical control of disease activity as heretofore has only been demonstrated by monthly ranibizumab, while also avoiding the need to make “as needed” treatment decisions based on anatomic surrogates whose relevance to ultimate outcome is not completely understood.

Figure 1: CATT Study – Change from Baseline in Visual Acuity at 52 Weeks for Ranibizumab Monthly vs. Other Regimens



Adapted from (CATT Research Group 2011)

Another major concern with treatment regimens involving PRN dosing is that while some patients can achieve periods of apparent quiescence after initial anti-VEGF therapy, the disease can unpredictably recur with catastrophic manifestations such as submacular hemorrhage; these catastrophic events do not appear to be predicted by monitoring exams, but have been reported occur if the patient is not continuing to receive regular anti-VEGF treatment (Levine 2009, Barbazetto 2010). It is a reasonable assumption that a fixed dosing paradigm of demonstrated efficacy would not only serve to maintain initial vision gains, but also reduce the risk of rare catastrophic events such as submacular hemorrhages.

Both ranibizumab and bevacizumab act by binding IVT VEGF-A, and both agents are derived from a mouse antibody specific to VEGF-A. This application presents data on a new anti-VEGF agent: VEGF Trap-Eye. VEGF Trap-Eye is a fusion protein composed of key domains from human VEGF receptors 1 and 2, fused to human IgG Fc, which is then specifically purified and formulated for intraocular injection. Most importantly, VEGF Trap-Eye has a binding affinity to VEGF-A 40 to 50 times greater than either bevacizumab or ranibizumab (Holash 2002; and Regeneron, data on file). Mathematical modeling suggests that because of the higher affinity, VEGF Trap-Eye may maintain significant IVT VEGF biologic activity for 10 to 12 weeks after a single injection, with the biologic activity of 2 mg at 83 days estimated to be comparable to the activity of ranibizumab 0.5 mg at 30 days (Stewart, 2008). The development program for VEGF Trap-Eye thus sought to determine whether it might represent a novel product with clinical efficacy at least as good as monthly IVT ranibizumab but with an IVT dosing interval longer than once monthly.

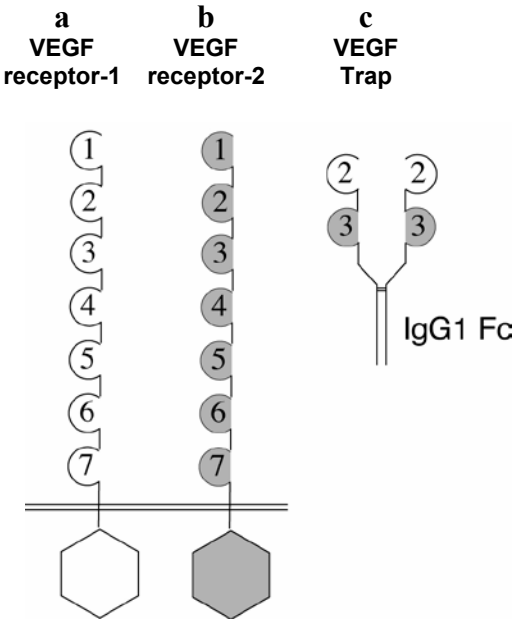
3. NONCLINICAL OVERVIEW AND CLINICAL PHARMACOLOGY

3.1. Trap Technology and VEGF Trap-Eye

Traps are based on a proprietary technology developed at Regeneron in which portions of two receptors are fused together along with an immunoglobulin constant region (Fc) to create a soluble decoy receptor that possesses more potent binding to their cognate ligands than the individual receptors (Economides 2002; Holash 2002). Rilonacept (ARCALYST™) is the Interleukin-1 Trap that received regulatory approval for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) - a rare cold-induced autoinflammatory disorder.

VEGF Trap was created by fusing DNA sequences encoding the second Ig domain of human VEGFR-1 to the third Ig domain of human VEGFR-2, which is in turn fused to the constant region of human IgG1, which serves to create a homodimer of the fusion protein (Holash 2002) (Figure 2). VEGF Trap binds to human VEGF-A with a Kd of 0.497 pM, and binds all isoforms of VEGF-A. As is the case with Interleukin-1 Trap, the VEGF Trap binds to VEGF with greater affinity than the binding between VEGF and its cognate receptors. VEGF Trap is a homodimeric glycoprotein possessing a protein molecular weight of 97 kilodaltons (kDa) along with approximately 15% by weight of N-linked oligosaccharide chains; the total molecular weight of the VEGF Trap homodimer is approximately 115 kDa. Recombinant VEGF Trap protein is expressed in CHO K1 cells, and then purified by a combination of filtration and chromatographic techniques. This formulation of VEGF Trap, which is specially purified and specifically formulated for IVT injection, is called VEGF Trap-Eye.

Figure 2: Structure of VEGF Trap



VEGF receptor-1 (**a**) and VEGF receptor-2 (**b**) are related receptors that have 7 extracellular Ig domains, and an intracellular tyrosine kinase domain.

VEGF Trap (**c**) contains the Ig domain 2 of VEGF receptor-1 fused to the Ig domain 3 of VEGF receptor-2, which is in turn fused to the IgG1 Fc.

3.1.1. VEGF Trap binds to VEGF to form a stable inert complex, and systemic levels of this complex can be used to predict systemic biologic effects

In vitro BiaCore studies demonstrated that VEGF Trap binds with picomolar affinity to mouse, rat, rabbit, monkey and human VEGF-A, and to the related angiogenic molecules, human PlGF-1 and mouse and human PlGF-2, but not to human VEGF-C and VEGF-D, which are primarily involved in lymphangiogenesis (Alitalo 2002). VEGF Trap binds both human VEGF-A and PlGF-2 homodimers *in vitro* as a one-to-one binding complex with equilibrium dissociation constants (K_D) of 0.497 pM and of 38.8 pM, respectively. This affinity is higher than that measured for the native receptors binding to these factors. Moreover, the association rate constant for VEGF binding to VEGF Trap is greater than 10^7 M^{-1} s^{-1}, which is very fast for a protein:protein interaction; this fast association and tight binding facilitate potent blockade of VEGF bioactivity even at low concentrations of VEGF Trap. In cell-based assays, VEGF Trap inhibited VEGF-dependent receptor phosphorylation and subsequent calcium mobilization. VEGF Trap functions solely through binding and sequestration of VEGF and potentially other VEGFR ligands, as determined by the absence of demonstrable complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) *ex vivo* using either HUVEC or various tumor cell lines.

An inactive stable complex of VEGF:VEGF Trap is formed upon ligand binding (Holash 2002; Rudge 2007); importantly, this complex is not analogous to an antibody-antigen complex and

does not have the propensity to aggregate and form high-molecular weight immune complexes. In vivo, the VEGF:VEGF Trap complex accumulates as the Trap binds to its ligand. The level of systemic VEGF:VEGF Trap complex becomes maximal at doses of VEGF Trap that are sufficient to bind all of the VEGF synthesized by the body. As the VEGF Trap dose is further increased, one observes a dose-dependent increase in the levels of free VEGF Trap because there is no more VEGF available to bind. In animals, the level of systemic complex, and of excess free VEGF Trap, correlate with systemic efficacy readouts. That is, effects due to systemic VEGF blockade are only notable when high levels of complex and sufficient excess free VEGF Trap are systemically available; with low doses of VEGF Trap, mostly complex is observed, and only a small portion of the body's VEGF activity is blocked, and thus systemic effects of such blockade are not notable. The most sensitive indicator of systemic VEGF blockade is an increase in blood pressure because ambient VEGF activity seems to have an ongoing anti-hypertensive role; such blockade can be correlated with systemic levels of free as well as complexed VEGF Trap. As discussed in more detail below, the levels of systemic VEGF Trap achieved following IVT doses that are sufficient to be efficacious in the eye do not approach the systemic levels required for inducing blood pressure increases or any other systemic biologic effects due to VEGF blockade, and consistent with this, lead to only very low observed levels of systemic VEGF Trap complex.

3.2. Nonclinical Pharmacology: VEGF Trap-Eye is efficacious in animal models of ocular disease

In nonclinical pharmacological studies, VEGF Trap was effective in an assortment of animal models of ocular disease, whether small doses were injected directly into the eye or whether larger doses were administered systemically; local injection avoided other systemic effects.

Importantly for AMD, the VEGF Trap effectively inhibited neovascularization and/or pathological vascular leak in all animal models of ocular neovascular disease and vascular leak tested to date. VEGF Trap inhibited the development of pathological neovascularization and/or edema in rodent models of diabetic and ischemic retinopathy, and corneal injury, as well as in rodent and primate models of CNV that resemble the neovascular or 'wet' form of AMD. Of particular relevance, IVT administration of VEGF Trap rapidly resolved existing vascular leak in the retinas of diabetic rodents, and in primates with active, laser-induced CNV. Moreover, VEGF Trap ameliorated the associated ocular inflammation in the above models, for experiments in which this endpoint was evaluated. The anti-inflammatory effect of VEGF Trap is likely attributable to its ability to bind VEGF-A and/or PlGF, which are known to mediate leukocyte chemotaxis via VEGFR-1 expressed on the surface of subpopulations of leukocytes, particularly macrophages and neutrophils (Cao 2009).

In the above models, VEGF Trap was found to be effective whether administered directly into the vitreous of the eye, or systemically (e.g. by subcutaneous [SC], intraperitoneal or intravenous [IV] routes). However, compared to IVT administration, much higher doses of systemically administered VEGF Trap were required to ameliorate pathological vascular leak and neovascularization in the eye. For example, VEGF Trap prevented the development of active CNV when given at an IVT dose of 50 µg/eye every other week. This IVT regimen was as effective as VEGF Trap 3 mg/kg or 10 mg/kg given IV weekly. The latter systemic doses were previously shown to be required to effectively neutralize the whole-body pool of endogenous VEGF in both normal and tumor-bearing mice, and humans (Rudge 2007). Specifically, in mice,

VEGF Trap was shown to substantially suppress the growth of most tumor xenografts only at doses ≥2.5 mg/kg (SC, twice weekly), with maximal suppression of tumor growth generally seen at doses ≥10 mg/kg (SC, twice weekly).

Similarly, SC doses of VEGF Trap ≥10 mg/kg were required to achieve maximal elevations in blood pressure in telemetered rats. Maximal increases in blood pressure were attained when circulating levels of free VEGF Trap reached approximately 10 μg/mL, and blood pressure remained elevated above pre-treatment levels until concentrations of free VEGF Trap in the circulation fell below approximately 1-2 μg/mL. VEGF Trap did not produce detectable elevations in blood pressure at doses < 0.5 mg/kg. In humans, hypertension is also a prominent side effect and perhaps the most sensitive indicator of the anti-VEGF activity of the humanized anti-VEGF antibody, bevacizumab, and is now known to be an on-target class effect of drugs that inhibit VEGF/VEGFR signaling. It is believed that this effect is related to the role of the VEGF pathway in blood pressure homeostasis (Izzedine 2009; Vaklavas 2010). Thus, the animal pharmacology studies indicated that for efficacy of VEGF Trap in eye models, systemic doses had to be used which were similar to those having more widespread systemic actions, whereas much lower doses could be given locally via the IVT route, thus avoiding systemic actions and side effects.

3.3. Toxicology

The toxicity of VEGF Trap was evaluated in the most relevant species, the cynomolgus monkey, using the clinically relevant IVT route of administration directly into the eye. These studies included an exploratory 13-week study, three good laboratory practice (GLP) 13-week studies to support clinical IVT formulation optimization, and an 8-month pivotal study to support long-term IVT dosing with the current clinical formulation.

In general, ocular findings were consistent across all GLP IVT studies and consisted primarily of mild and transient ocular inflammation. The occurrence of transient and minor inflammatory responses tended to be more frequent and more severe in VEGF Trap-treated eyes than in controls but did not affect electroretinographic evaluation. Intraocular pressure changes observed in controls and all dose groups are likely a result of the IVT administration procedure and the volumes of vehicle and test article administered. The lowest observable adverse effect level (LOAEL) in the 8-month study, was 2 mg/eye based on microscopic observations of mild erosions and ulcerations of the respiratory epithelium of the nasal turbinates in individual animals. When normalized for eye volume, the maximum of 4 mg/eye that can be administered to a monkey eye, which has a volume of 1.5 mL, is approximately 6-fold greater than the 2 mg dose administered to the human eye (4 to 4.5 mL total volume). Although inflammation of the nasal turbinates was observed, these microscopic findings were not seen in the recovery phase monkeys after a 4-month treatment-free period. Although this lesion may be the result of general systemic exposure to VEGF Trap following entry of the IVT dose into circulation (which is much higher in monkeys as compared to humans based on body size differences), it more likely resulted from local exposure of the nasal epithelium to VEGF Trap by way of anastamoses between the ophthalmic and nasal venous plexuses, or leakage from the IVT injection site into the nasal lacrimal duct. As described in Section 4.8.4.3, during a specific Phase 3 clinical assessment there was no evidence to suggest a signal for the occurrence of nasal erosions after IVT administration of VEGF Trap-Eye to humans. Finally, there were no changes in any other

organs related to the IVT administration of VEGF Trap, as assessed by clinical observations, clinical pathology and histopathology. In the 8-month study, the no observed adverse effect level (NOAEL) was determined to be 0.5 mg/eye.

Additional chronic and reproductive toxicology studies, as well as safety pharmacology studies were also performed using systemic delivery of VEGF Trap, which resulted in systemic drug exposures that were thousands of times higher than those observed following IVT administration to humans. In systemic repeat dose toxicity studies in cynomolgus monkey, the target organs of toxicity were bone, kidney, testes, ovary, and the respiratory and olfactory epithelium of nasal turbinates. These findings can be related to the known mode of action of VEGF.

As expected for a drug that inhibits VEGF, high levels of systemic VEGF Trap produced embryo-fetal toxicity in an embryo-fetal development study in pregnant rabbits with intravenous (IV) administration (3 to 60 mg/kg). The maternal NOAEL was at the dose of 3 mg/kg. At this dose, the systemic exposures based on peak concentration (C_{max}) and area under the curve (AUC) for free aflibercept were approximately 2900- and 600-fold higher, respectively, when compared to corresponding values observed in humans after an IVT dose of 2 mg.

3.4. Systemic administration Phase 1 studies

The initial AMD development program investigated VEGF Trap administered systemically by the IV route. The first study was a Phase I, double-masked, placebo-controlled, sequential-group, dose-escalating, safety, tolerability, and biological effect study of IV administered VEGF Trap in patients with neovascular AMD. Groups of eight patients who met the eligibility criteria for having subfoveal CNV related to AMD were assigned VEGF Trap dose levels: 0.3, 1, 3, 5, 7, or 10 mg/ kg once every two weeks (total of four IV infusions) over an 8-week period. Patients received active VEGF Trap or placebo in a ratio of 3:1 in each cohort. In patients with AMD, ocular PD effects observed at the higher dose groups (1 and 3 mg/kg) included small improvements in VA, excess retinal thickness, foveal thickness, and macular volume. The study was terminated at the VEGF Trap 3 mg/kg dose level after the identification of dose-limiting toxicities (DLTs; Grade 2 proteinuria in a single patient and Grade 4 treatment-related malignant hypertension in a single patient) at the 3 mg/kg level.

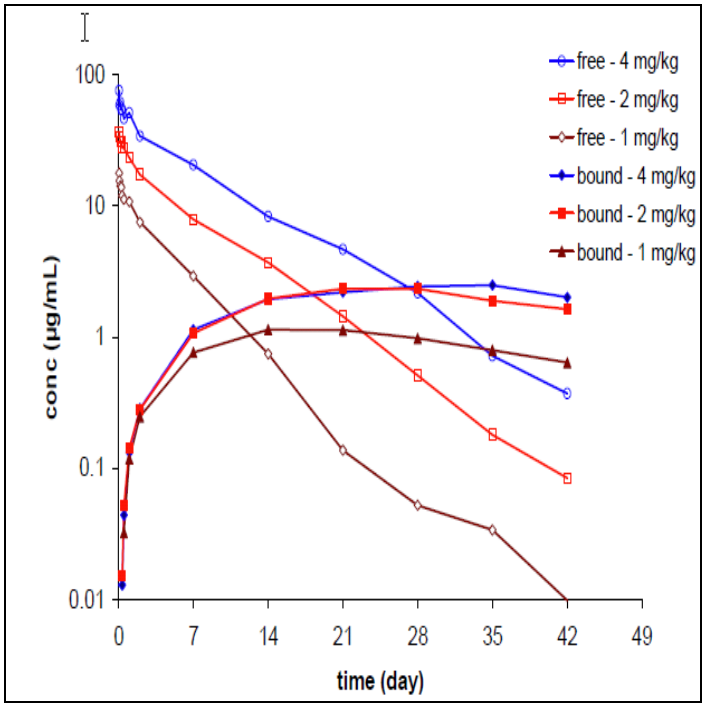
In Phase I studies, the safety and tolerability of VEGF Trap was also assessed in healthy volunteers with single doses of 1 to 4 mg/kg. Intravenous administration of VEGF Trap resulted in dose-related transient systemic effects (as measured by blood pressure).

These studies allowed the characterization of the pharmacokinetics (PK) of systemically administered VEGF Trap and also an assessment of the relationship between systemic PK and systemic PD effects. Free VEGF Trap exhibits nonlinear PK consistent with saturable, target-mediated drug disposition. VEGF Trap is cleared by specific and saturable high affinity binding to VEGF (i.e., conversion of free VEGF Trap to the inert bound VEGF Trap complex) as well as via non-saturable clearance mechanisms, including catabolic degradation by proteolysis. The terminal elimination half-life ($t_{1/2}$) of free systemic VEGF Trap was approximately 1.9 days following an IV dose of 0.3 mg/kg, and increased with increasing doses, reaching $t_{1/2}$ estimates of 5 to 6 days after IV administration of doses of 2 to 4 mg/kg VEGF Trap.

As had been described in preclinical studies, systemic pharmacologic effects were only observed after sufficient drug had been administered to bind all systemic VEGF. The extent of VEGF

blockade can be estimated by assessing systemic levels of free and bound VEGF Trap (Figure 3). In humans, formation of the systemic bound VEGF Trap complex is approximately dose proportional at low systemic VEGF Trap doses. At higher systemic VEGF Trap doses, bound systemic VEGF Trap concentrations reach a plateau one to two weeks after dosing. The terminal observed $t_{1/2}$ of bound VEGF Trap is approximately 21 days. The dose at which VEGF Trap binding is saturated reflects the level of VEGF Trap administration at which all systemic VEGF has been bound. The administration of higher doses of VEGF Trap thus result in higher levels of free VEGF but no higher levels of bound VEGF Trap.

Figure 3: Mean Free and Bound VEGF Trap Concentration-Time Profiles (µg/mL) in Healthy Volunteers



After IV doses ≥2 mg/kg, binding of systemic VEGF is saturated or nearly saturated as evidenced by the fact that the amount of bound complex does not further increase with higher dose, (Figure 3), suggesting that doses ≥2 mg/kg bind the majority of available systemic VEGF and these doses should demonstrate near maximal systemic PD effects (as measured by changes in blood pressure). The clinical PK data were used to derive the Michaelis–Menten constant Km which represents the time averaged concentration needed for an agent to bind 50% of the maximum amount of a ligand an agent is capable of binding. In other words, a drug's Km represents the concentration need to achieve half-maximal binding of its ligand. For free VEGF Trap binding to human VEGF the systemic concentration needed to achieve half-maximal binding was calculated to be 2.91 µg/mL (Thai 2010).

3.5. Intravitreal Administration Phase 1 and Phase 2 studies

The Phase 1 and Phase 2 IVT studies established a dose range for testing in Phase 3 and established the systemic PK of VEGF Trap-Eye after IVT administration.

With respect to PK, VEGF Trap is slowly absorbed from the eye into the systemic circulation after IVT administration and is predominately observed in the systemic circulation as low levels of inactive, stable complex with VEGF; since only "free VEGF Trap" is able to bind endogenous VEGF, these levels of complex should not bind or block systemically available VEGF. It is estimated that after IVT administration of 2 mg to patients, the mean maximum plasma concentration of free VEGF Trap is more than a 100-fold lower than the concentration of VEGF Trap required to half-maximally bind systemic VEGF. Therefore, systemic PD effects are unlikely.

With respect to dose ranging, early clinical development demonstrated that IVT doses in the range of 0.5 to 2 mg provided maximal clinical benefit. Greater doses (i.e., 4 mg IVT) did not provide greater effects. The Phase 2 data as well as modeling data suggested that the q8 week interval may allow sufficient activity to provide maintenance of visual gains. The Phase 3 program with VEGF Trap-Eye therefore sought to extend the previous dose ranging studies by examining 3 different regimens:

- VEGF Trap-Eye 2 mg every 4 weeks (2Q4)
- VEGF Trap-Eye 0.5 mg every 4 weeks (0.5Q4)
- VEGF Trap-Eye 2 mg every 8 weeks following 3 initial monthly doses (2Q8).

3.5.1. Summary of Phase 1 IVT Studies

The initial clinical development of VEGF Trap-Eye with IVT administration for the treatment of wet AMD was initiated with Phase 1 study VGFT-OD-0502. Twenty-one subjects received a single treatment with VEGF Trap-Eye (0.05 mg [3 subjects], 0.15 mg [3 subjects], 0.5 mg [3 subjects], 1 mg [6 subjects], 2 mg [3 subjects], or 4 mg [3 subjects]) on Day 1 and primary efficacy was assessed on Day 43. The primary efficacy variable was the percentage change in central retinal lesion thickness (CR/LT) (as assessed by optical coherence tomography [OCT]) from baseline at Day 43. Secondary efficacy endpoints included the change and percentage change in CR/LT from baseline at each scheduled visit; changes from baseline in total macular volume, lesion size, area of CNV, area of classic CNV, and the assessment of efficacy by VA (i.e., best corrected visual acuity [BCVA] letter score); and proportion of subjects experiencing vision gain or loss. The primary analysis was a paired t-test (Day 43 compared to Baseline) conducted on the combined treatment group. As specified in the Statistical Analysis Plan (SAP), an analysis of covariance (ANCOVA) model with baseline CR/LT as a covariate and treatment as the main effect was conducted among the six individual dose groups and among the following three combined groups: Group A = 0.05, 0.15, and 0.5 mg dose groups; Group B = 1 mg dose group; and Group C = 2 and 4 mg dose groups. The percent change from baseline in CR/LT for the combined treatment group was -16.5% ± 28.7 ($p = 0.0185$) with an evident dose response across the treatment groups. Although change from baseline in ETDRS letter score was not statistically significant (4.4 ± 18 letters for all groups combined), a dose response was again evident (0.6 ± 5.4 letters Group A; 1.2 ± 11.0 letters Group B; 13.5 ±15.7 letters Group C).

This study provided the first evidence of a dose-response in the bioeffects of IVT administered VEGF Trap-Eye. At the higher single doses VEGF Trap-Eye was associated with improvements in BCVA and improvements in morphologic characteristics of the CNV lesion. These improvements, which were evident for at least one month after a single injection, provided the first evidence of the durability of the effect of IVT VEGF Trap-Eye in patients with wet AMD.

In the dose-escalation phase of this study, there were no ocular serious adverse events (SAEs) and no evidence of inflammation. There were also no systemic SAEs or changes in laboratory values. There was no DLT and a maximum tolerated dose (MTD) was not identified.

3.5.2. Summary of Phase 2 IVT Studies

VGFT-OD-0508 was primarily a dose-finding study and assessed the efficacy of different doses (0.5 mg, 2 mg and 4 mg) and dosing regimens (every 4 or every 12 weeks depending on dose) of IVT VEGF Trap-Eye in subjects with subfoveal CNV secondary to wet AMD. A total of 159 subjects were randomized and 157 were treated across 33 participating sites in the US. Key eligibility criteria were men and women 50 years of age or older with subfoveal CNV secondary to wet AMD, CR/LT of least 300 microns as measured by OCT, and a BCVA (using the ETDRS chart) of 73 to 34 letters. This Phase 2 study comprised a fixed-dosing phase of day 1 through week 12 followed by a flexible-dosing phase from weeks 16 through 52. Subjects were randomly assigned in a 1:1:1:1:1 ratio to one of five dose groups:

- 0.5 mg Day 1 and Week 12 (0.5Q12) (32 subjects)
- 0.5 mg Day 1 and Weeks 4, 8, and 12 (0.5Q4) (32 subjects)
- 2 mg Day 1 and Week 12 (2Q12) (31 subjects)
- 2 mg Day 1 and Weeks 4, 8, and 12 (2Q4) (31 subjects)
- 4 mg Day 1 and Week 12 (4Q12) (31 subjects)

The primary efficacy variable was the change from baseline in CR/LT and the primary efficacy endpoint was assessed at week 12 (prior to any dosing with study drug at that visit). The primary analysis was a paired t-test (1-sample test) of the significance of change in CR/LT from baseline at week 12 in a pool of the five treatment groups. Secondary efficacy variables included the change in BCVA (ETDRS letter score), proportion of subjects who gained or lost letters, and effects on CNV lesion characteristics and fluorescein leakage as assessed by fluorescein angiography (FA).

Mean decreases from baseline in CR/LT after administration of a 0.5 and 2 mg/eye dose at a Q4 dosing interval demonstrated a dose-dependent improvement in CR/LT over the entire duration of fixed treatment period (Figure 4). At a dosing interval of Q12, improvement in CR/LT measurements did not persist over the duration of the dosing interval at any dose level studied. Compared to the 2 mg dose, there was no additional benefit with the 4 mg dose.

Figure 4: VGFT-OD-0508 – Mean Change from Baseline Central Retinal / Lesion Thickness

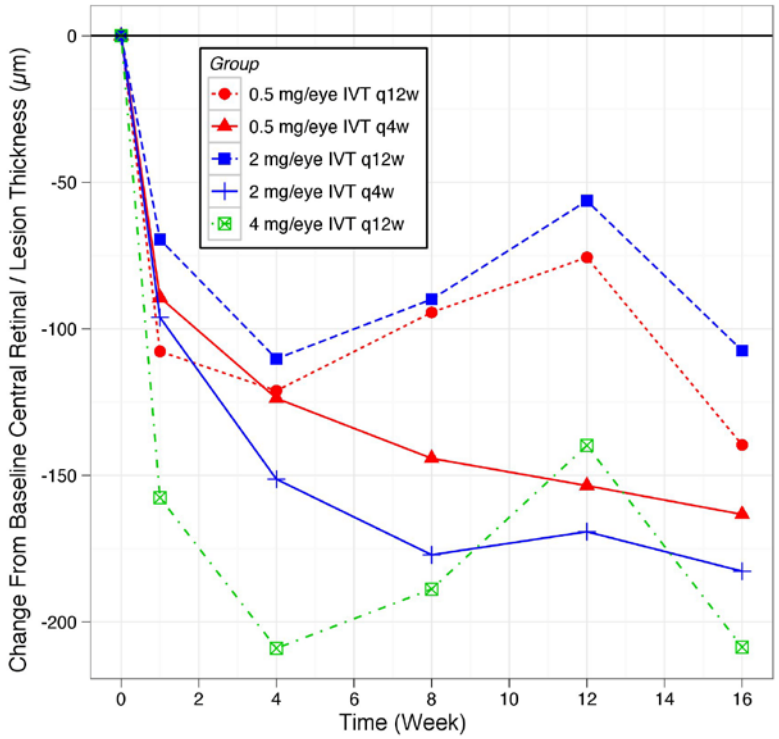
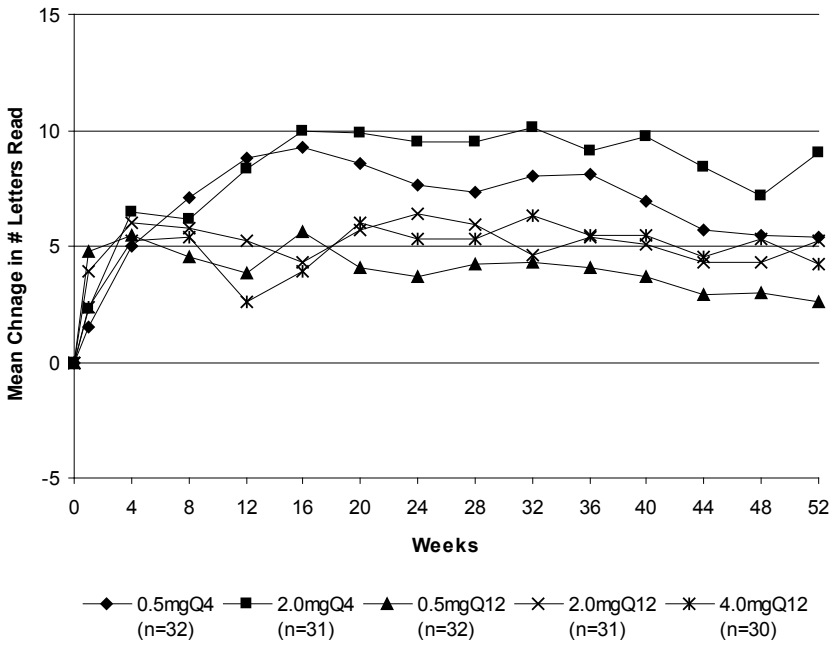


Figure 5: VGFT-OD-0508 – Mean Change in BCVA (LOCF, FAS)



BCAV = Best corrected visual acuity; LOCF = Last observation carried forward; FAS = full analysis set

All treatment groups experienced improvements in VA as early as week 1 and these improvements were maintained through week 12 (time point for the assessment of the primary efficacy endpoint) (Figure 5). However, the monthly dosing groups had a greater improvement in visual acuity at 3 months, with a mean improvement greater than 8 letters, an advantage that was maintained throughout the PRN phase of the trial. This suggested that an initial dosing regimen consisting of 3 monthly doses is worthwhile. The single 2 mg and 0.5 mg dose groups revealed improvement in retinal thickness and vision out to 8 weeks, which began to wane by 12 weeks. This was the basis for our studying an 8-week dosing interval in Phase 3 and not a 12-week interval. During the PRN phase, the 2 mg dose cohort experienced better visual acuity than the 0.5 mg dose group. This supported our decision in Phase 3 to only study the 2 mg dose at the longer, 8-week interval. Overall, the 4 mg dose group did not show an advantage over the 2 mg group. Thus, in Phase 3, the highest dose studied was 2 mg.

A summary of adverse experiences in the Phase 2 study is provided in (Table 1). The number of patients with systemic treatment emergent adverse events (TEAEs) was similar among treatment groups. The most commonly-reported systemic TEAE was urinary tract infection. Two deaths (pancreatic carcinoma [2Q4], and pulmonary hypertension [4 q12]) were reported during the study and both were assessed as unrelated to study drug. Seven patients withdrew from the study due to AEs: 1 due to Non-Hodgkin's lymphoma (0.5Q4); 1 due to hip fracture, 1 due to retinal hemorrhage and VA reduced, and 1 due to colon cancer (0.5Q12); 1 due to retinal edema and 1 due to bronchitis (2Q12), and 1 due to IOP increased (4Q12).

Table 1: VGFT-OD-0508 – Summary of Number and Percent of Patients with Adverse Events during the Fixed and Continued Dosing Phases (Safety Analysis Set [SAF])

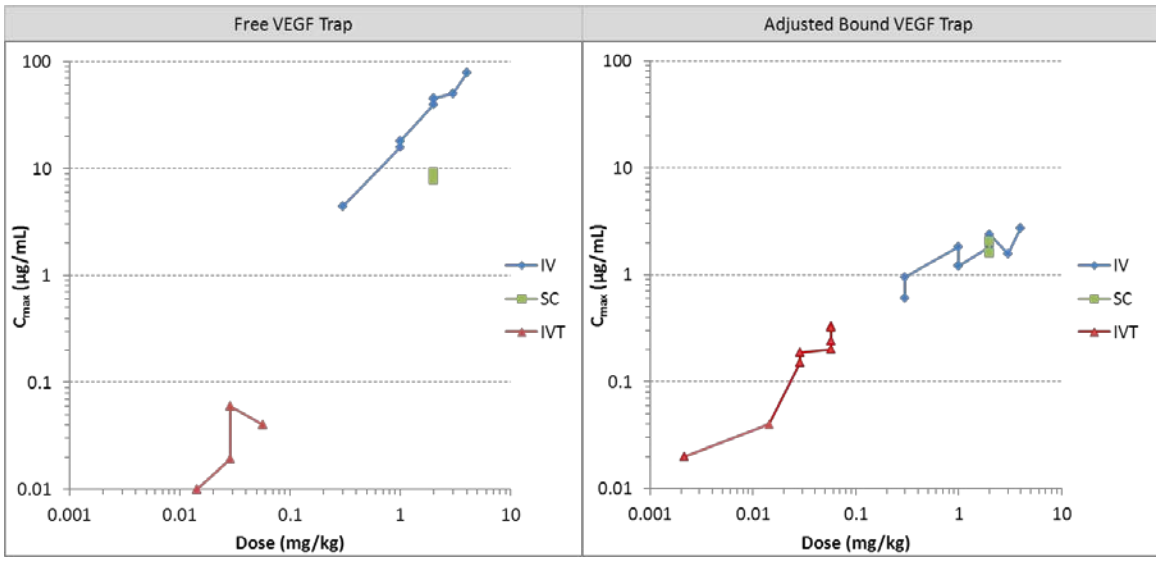
Events	0.5q4 n = 32	0.5q12 n = 32	2Q4 n = 31	2Q12 n = 31	4q12 n = 31	All n = 157
Systemic TEAEs	27 (84.4)	25 (78.1)	28 (90.3)	24 (77.4)	25 (80.6)	129 (82.2)
Ocular TEAEs (study eye)	29 (90.6)	26 (81.3)	26 (83.9)	25 (80.6)	28 (90.3)	134 (85.4)
TEAEs related to study treatment	5 (15.6)	3 (9.4)	4 (12.9)	5 (16.1)	2 (6.5)	19 (12.1)
TEAEs resulting in withdrawal	1 (3.1)	3 (9.4)	0 (0)	2 (6.5)	1 (3.2)	7 (4.5)
Treatment-emergent SAEs	11 (34.4)	5 (15.6)	10 (32.3)	7 (22.6)	2 (6.5)	35 (22.3)
Deaths	0	0	1	0	1	2

3.5.3. Pharmacokinetics after IVT Administration

After IVT administration, VEGF Trap is slowly absorbed into the systemic circulation. Free VEGF Trap plasma concentrations following IVT administration of doses of up to 4 mg/eye (approximately 0.057 mg/kg) were approximately 2 to 3 orders of magnitude lower than free VEGF Trap plasma concentrations observed following IV administration of doses ≥ 1 mg/kg (Figure 6). On average, after a 2 mg/eye IVT injection, the mean C_{max} of free VEGF Trap, 0.019 µg/ml (range 0 to 0.054 µg/ml) occurs by the second day (t_{max}) following dosing. Following C_{max}, free VEGF Trap concentrations decline rapidly, becoming undetectable at approximately 7 to 14 days after dose administration in almost all subjects.

Bound VEGF Trap (i.e., inactive complex) plasma concentrations following IVT administration of doses of up to 2 mg/eye were approximately 20-fold lower than that observed following IV administration of doses of 0.3 to 4 mg/kg (Figure 6).

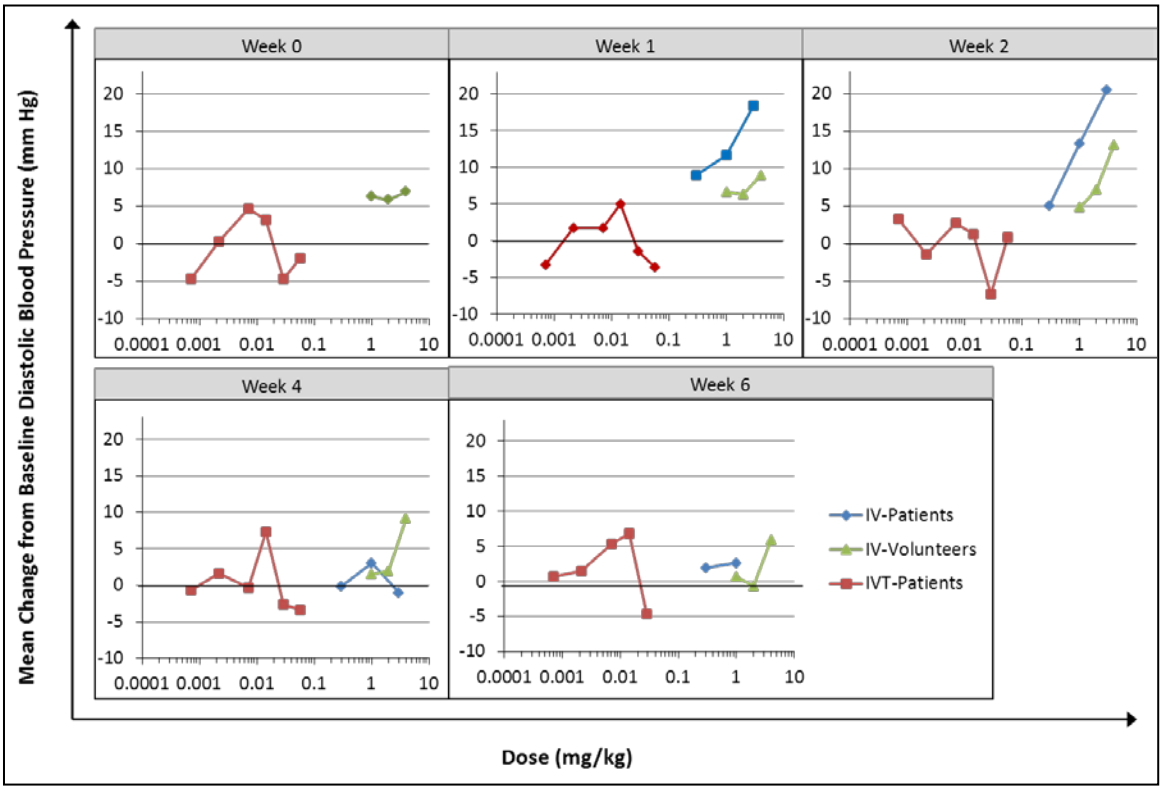
Figure 6: Mean or Median C_{max} of Free and Bound VEGF Trap after IVT, IV, or SC Administration versus Weight-Normalized Dose of VEGF Trap



IVT = Intravitreal; IV = Intravenous; SC = Subcutaneous. The IVT doses were converted to an approximate mg/kg value by assuming a patient weight of 70 kg. The median was used when data were too sparse to calculate means reliably.

On average, C_{max} of free VEGF Trap after IVT administration are approximately 50 to 500 times below the VEGF Trap concentration required to inhibit the biologic activity of systemic VEGF by 50% in animal models. It is estimated that after IVT administration of 2 mg/eye to patients, the mean C_{max} of free VEGF Trap is more than a 100-fold lower than the concentration of VEGF Trap required to half-maximally bind systemic VEGF. Hence, following IVT administration it is unlikely that free VEGF Trap is systemically available at sufficient concentration or duration to produce a pharmacologically meaningful reduction in systemic free VEGF. Therefore, systemic PD effects, such as change in blood pressure, are unlikely with IVT administration (Rudge 2007, Thai 2010), and were not observed in clinical Phase 1 or Phase 2 (Figure 7) or Phase 3 studies (Section 4.8.6.2).

Figure 7: Comparison of Mean Change from Baseline Systolic Blood Pressures Following Administration of VEGF Trap (Phase 1 and Phase 2 Studies)



3.5.4. Rationale for Phase 3 Dosing

Early clinical development demonstrated that IVT doses in the range of 0.5 to 2 mg provided maximal clinical benefit. Greater doses (i.e., 4 mg IVT) did not provide greater effects. The Phase 2 data as well as modeling data suggested that the q8 interval might allow sufficient activity to provide maintenance of visual gains. The Phase 3 program with VEGF Trap-Eye therefore sought to extend the previous dose ranging studies by examining 3 different regimens:

- VEGF Trap-Eye 2 mg every 4 weeks (2Q4)
- VEGF Trap-Eye 0.5 mg every 4 weeks (0.5Q4)
- VEGF Trap-Eye 2 mg every 8 weeks following 3 initial monthly doses (2Q8).

4. PHASE 3 AMD PROGRAM: VIEW 1 AND VIEW 2

The phase 3 AMD program for VEGF Trap-Eye consists of two studies using IVT administration in neovascular AMD. The VIEW 1 study (VGFT-OD-0605) is being conducted by Regeneron Pharmaceuticals, Inc. (Regeneron) at 154 sites in the US and Canada, and the VIEW 2 study (311523) is being conducted by Bayer Healthcare at 185 sites in Asia (Japan, Singapore, South Korea), Australia, Europe (Austria, Belgium, Czech Republic, France, Germany, Hungary, Italy, Latvia, The Netherlands, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, United Kingdom), Latin/South America (Argentina, Brazil, Colombia, Mexico), India, and Israel.

Both phase 3 studies are of 2-year duration and are double-masked, parallel design, non-inferiority studies comprising approximately 1200 subjects in each study, randomized 1:1:1:1 to 3 VEGF Trap-Eye dose regimens or to ranibizumab. The primary endpoint is maintenance of BCVA at week 52 (year 1) in subjects with all subtypes of neovascular AMD. The results from year 1 are summarized here and in the Biologics Licensing Application, based upon prior agreement with FDA.

Enrollment for both studies was completed in September 2009. Results presented here are from the period of 02 August 2007 (first subject's first dose) to 14 September 2010 (last subject's last visit for the primary endpoint) for year 1.

Both studies are continuing for the second year as planned, and masking is maintained for subjects and personnel involved in the studies. Year 2 results (through week 96) will be reported separately for both VIEW 1 and VIEW 2.

4.1. Study Design and Methods

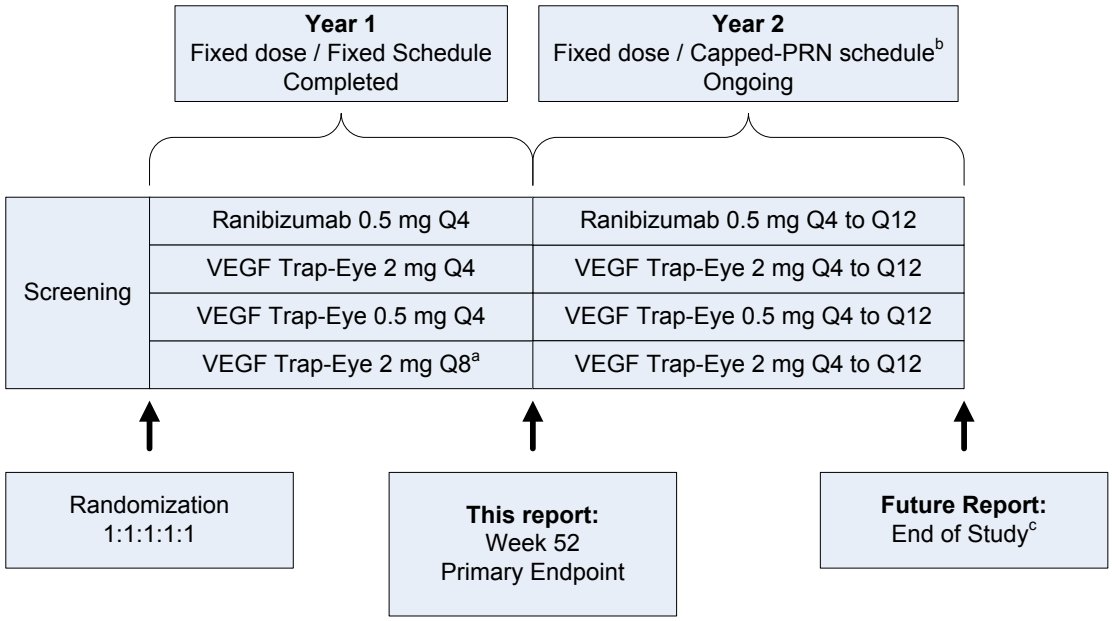
VIEW 1 and VIEW 2 are randomized, double-masked, active-controlled, 2-year, Phase 3 studies of the efficacy, safety, and tolerability of IVT administered VEGF Trap-Eye in subjects with wet AMD. The conduct and analyses of the 2 studies were essentially identical. Figure 8 provides a general overview of the study design. The VIEW 1 study protocol and design (including doses and dose intervals, primary endpoint and analysis, and establishing non-inferiority of VEGF Trap-Eye) were developed in accordance with discussions with the FDA in the context of a Special Protocol Assessment. FDA also agreed that data from year 1 of the VIEW 1 and VIEW 2 studies would be sufficient for filing of a BLA in this indication, wet AMD.

Subjects eligible for the studies were men and women 50 years of age or older with active primary subfoveal CNV lesions secondary to wet AMD. At screening, subjects were to have a BCVA of 20/40 to 20/320 (letter score of 73 to 25) in the study eye, and CNV in the study eye must have been at least 50% of the total lesion size. Both pivotal studies included a maximum 21-day screening period followed by clinic visits every 4 weeks, for a total of 16 visits during the first year or up to Week 52.

Masking of patients and study personnel was maintained by use of sham procedures in the 2Q8 arm and by having distinct masked and unmasked roles at the study site. Site personnel involved with giving patients their treatment and involved in assessing any immediate untoward effects of treatment were unmasked. Patients' eyes were prepped as if they were to receive an injection, including the use of subconjunctival anesthesia where that was the investigator's practice, and the unmasked investigator pressed the blunt end of the syringe against the eye, mimicking an

injection. Masked personnel conducted all patient evaluations, including VA evaluations and collection and interpretation of safety information.

Figure 8: VIEW 1 and VIEW 2 - General Study Design



Q4=every 4 weeks; Q8=every 8 weeks; Q12=every 12 weeks

[a] Subjects in the VEGF Trap-Eye 2Q8 group received 2 mg VEGF Trap-Eye every 4 weeks from Baseline to Week 8 (i.e., three initial monthly doses) and then a sham injection every other visit through Week 48 during the visits when an active injection was not administered.

[b] In Year-2 of the studies, subjects are being assessed against retreatment criteria and are only retreated if one or more of the study retreatment criteria are met, as often as every 4 weeks and no less frequently than every 3 months (i.e., if it has been 12 weeks since the last retreatment, the subject will receive a treatment regardless of whether he/she has met any of the retreatment criteria).

[c] End of study in VIEW 1 is Week 96; End of study in VIEW 2 is Week 96 or Week 100 (if an injection is administered at week 96).

Subjects were evaluated at 4-week intervals for safety and BCVA using the 4-meter ETDRS protocol (ETDRS Group, 1985). 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, on day 1, at all visits in VIEW 2, and at weeks 4, 12, 24, 36, and 52 in VIEW 1. In addition, optional OCT examinations could be performed at weeks 1, 8, 16, 20, 28, 32, 40, 44, and 48 in VIEW 1. Fluorescein angiography examinations were conducted at screening, and at weeks 24 and 52.

Only 1 eye was designated as the study eye whether or not disease involved both eyes. Prior anti-VEGF therapy was not allowed in the study eye. The non-study eye was considered the fellow eye. If a subject's fellow eye required treatment for AMD at study entry, or during the subject's participation in the study, the fellow eye could receive any treatment for wet AMD that was approved in their country. Although the fellow eye could receive treatment, it was not

considered an additional study eye. Subjects who received treatment for the fellow eye could remain in the study. Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g., bevacizumab) was allowed up to 3 months prior to the first dose in the study. Such treatment was not allowed during the study. Ocular (study eye and fellow eye) and non-ocular AEs were collected for year 1 and will continue through year 2.

Year 1 of both studies is complete. Analyses of the year-1 data available as of November 2010 were conducted for inclusion in the BLA for VEGF Trap-Eye and are summarized here for each study separately.

4.2. Pre-Specified Analysis Plan

The VIEW 1 and VIEW 2 studies were designed to determine whether VEGF Trap-Eye at any of three dose regimens was non-inferior to a 0.5 mg dose of ranibizumab given once every 4 weeks with respect to maintenance of vision at 52 weeks (defined as losing fewer than 15 letters compared to baseline), using a conditional sequence of confidence intervals (CIs). If the study met the non-inferiority criteria for the primary endpoints, the secondary endpoints would be used to determine if VEGF Trap-Eye was superior to ranibizumab. The potential utility of criteria-based (PRN) dosing for maintaining vision will be examined during the second year of the study. Subjects enrolled in these studies were to have a diagnosis of visual impairment associated with neovascular AMD.

Assuming that 90% of subjects treated with 0.5 mg ranibizumab maintained vision and also assuming that 90% of subjects treated with VEGF Trap-Eye also maintained vision, and defining the non-inferiority margin to be 10%, 191 subjects per group provided 90% power to demonstrate non-inferiority assuming an alpha level=0.049 (which included an adjustment of 0.001 for the IDMC safety assessments, 0.0001 for each of the 10 assessments, thus preserving an overall alpha of 0.05 for the study) for VIEW 1 and alpha level=0.05 for VIEW 2. Assuming a dropout rate of 30% (a high dropout rate was planned because of the availability of competing, approved therapies), enrollment of 300 subjects per group provided adequate power for these studies to achieve their objectives under the stated assumptions. Although not in the analysis plan for the study, in a separate earlier communication, the FDA further explained that, whereas the 10% confidence interval would be used to assess non-inferiority, a 5% confidence interval would be used to assess clinical equivalence.

4.2.1. Pre-Specified Analysis for Non-Inferiority

A CI approach to hypothesis testing was taken for the non-inferiority analysis for these studies. The statistical objective was to demonstrate that the 95.1% (VIEW 1) or 95% (VIEW 2) CI of the difference between ranibizumab and VEGF Trap-Eye in the proportion of subjects maintaining vision after 52 weeks compared to baseline lied entirely below 10% (the non-inferiority margin).

4.2.2. Primary Endpoints: Testing for Non-Inferiority and Controlling for Multiple Comparisons

Multiplicity for the primary analysis was controlled using a conditional sequence.

The conditional sequence for the primary endpoint was:

1. 2Q4 VEGF Trap-Eye versus 0.5 mg ranibizumab given every 4 weeks (RQ4).

2. 0.5Q4 VEGF Trap-Eye versus RQ4.

3. 2Q8 VEGF Trap-Eye versus RQ4.

At each step in the conditional sequence, VEGF Trap-Eye was considered to be non-inferior to ranibizumab if the CI of the difference was entirely below 10%, where a positive difference was considered to be in favor of ranibizumab. Hypothesis testing would continue through the sequence as long as non-inferiority of VEGF Trap-Eye to ranibizumab was demonstrated at each step in the sequence.

4.2.3. Secondary Endpoints: Testing for Superiority and Controlling for Multiple Comparisons

Only if all three VEGF Trap-Eye groups were shown to be non-inferior to ranibizumab at the primary endpoint would additional comparisons to ranibizumab be made with respect to the secondary endpoints. If non-inferiority was demonstrated in all 3 comparisons described above, hypothesis testing for superiority would continue based on the secondary endpoints. Multiplicity for the secondary analyses was controlled in each study using a conditional sequence as shown in Table 2. For the secondary endpoints, hypothesis testing would continue through the sequence as long as superiority of VEGF Trap-Eye to ranibizumab was demonstrated at each step in the sequence.

Table 2: VIEW 1 and VIEW 2 - Conditional Sequence of Hypothesis Tests for Analyses of Secondary Efficacy Variables

	Visual Acuity Endpoints		Quality-of-Life Endpoint[a]	Morphology Endpoint
Testing order	Change in ETDRS letter score from Baseline to Week 52	Proportion of subjects who gained 15 or more letters at Week 52	Change in total NEI VFQ-25 score from Baseline to Week 52	Change in CNV area from Baseline to Week 52
Entries denote the VEGF Trap-Eye dose group to be tested against RQ4				
1	2Q4			
2		2Q4		
3			2Q4	
4	0.5Q4			
5		0.5Q4		
6			0.5Q4	
7	2Q8			
8		2Q8		
9			2Q8	
10				2Q4
11				0.5Q4
12				2Q8

[a] Quality of life data are not provided in this briefing book

4.2.4. Additional Endpoint: Central Retinal Thickness by OCT

The analysis plan for both studies included an analysis of central retinal thickness (CRT) at week 52. Optical coherence tomography (OCT) data were read and interpreted by independent reading centers for each study. Pre-meetings between the centers sought to harmonize the methodology. However, upon review of the data, it became clear that the centers had taken different approaches. The VIEW 1 readers used primarily a center-point thickness measurement while the VIEW 2 readers used a center subfield approach. Data provided to FDA in the initial BLA reflected these independent approaches. An additional analysis of the VIEW 1 data termed "Total Centerpoint Thickness" was also included in the VIEW 1 CSR. Since the BLA submission, the VIEW 1 images have been re-measured using the same approach as for VIEW 2 (central subfield) to support comparisons between the studies and integration of the data. The main VIEW 1 presentation in this briefing book reflects the center subfield approach. The original VIEW 1 CRT and the total center point thickness OCT data provided in the initial BLA are provided in an Appendix.

4.2.5. Analysis Data Sets

The Full Analysis Set (FAS) included all randomized subjects who received any amount of study medication and had at least one post-baseline BCVA assessment.

The FAS was used for all hypothesis tests of superiority. Analysis of superiority using the PPS was also done for supportive analyses.

The Per Protocol Set (PPS) included all subjects in the FAS who received at least 9 doses of study drug and attended at least 9 scheduled visits during the first year. Sham injections were counted as doses administered for the purpose of defining the PPS. Subjects in the PPS also had not missed two consecutive injections before administration of the 9th injection (per subject) and did not have major protocol violations.

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. However, if a subject met the treatment failure definition and remained in the study, their data at week 52 were used. A subject who had a decrease from baseline in BCVA of at least 15 letters at two consecutive assessments, 4 weeks apart, during the first 52 weeks of the study was considered treatment failure.

A major protocol violation was defined as one that could affect the interpretation of study results. The major protocol violation criteria were decided by the study team, which was masked to subject treatment during the data validity meetings. Final determination of the PPS was made at the masked data review meeting held in accordance with the Internal Conference on Harmonization (ICH) E9 guidance prior to the lock of the Year 1 data. The complete specification was documented separately prior to lock of the Year 1 data.

The PPS was used for primary analysis (statistical evaluation of non-inferiority). For completeness and as a sensitivity analysis, CIs were also constructed using the FAS.

The Safety Analysis Set (SAF) included all subjects who received any amount of study medication.

The SAF was used for safety analyses.

Efficacy analyses were conducted with subjects as randomized. Safety analyses were conducted with subjects as treated.

4.2.6. Subgroups

Subgroups were defined by information recorded on the baseline CRF and listed as follows:

The following subgroups were considered for efficacy and safety analyses:

- Gender
- Age: <65y; ≥ 65y to <75y; ≥75y
- Race: White, Black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, Other
- Ethnicity: Hispanic or Latino (no/yes)
- Renal impairment: i.e. creatinine clearance (CLCR) >80ml/min (normal), >50-80ml/min (mild), >30-50 ml/min (moderate), ≤30ml/min or requiring dialysis (severe). CLCR was calculated using baseline values (creatinine, age, weight, sex) using the Cockcroft-Gault equation:
- Males: CLCR = (140-age)*body weight / (72*creatinine)
- Females: CLCR = (140-age)*body weight*0.85 / (72*creatinine)
- Hepatic impairment

The following subgroups were considered for efficacy analyses only:

- 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 ≤ 10.16 mm^2 (equivalent in disc areas)
- Lesion type: Predominantly classic (if proportion of classic CNV in lesion is 50% or more), minimally classic (if proportion of classic CNV in lesion is greater than 0 and less than 50%), occult (if classic CNV area is 0)

The following subgroups were considered for safety analyses only:

- Medical history of diabetes mellitus (DM)
- Medical history of cataracts
- Medical history of hypertension (HT)
- Medical history of cerebrovascular accident (CVA) / Stroke
- Medical history of myocardial infarction (MI)
- Medical history of proteinuria

4.2.7. Subgroup Analyses

Subgroup analyses based on baseline characteristics were performed at week 52 for the following variables:

- Primary endpoint: proportion of subjects who maintained vision (fewer than 15 letters lost) in both PPS and FAS
- Change from baseline in BCVA in FAS
- Proportion of subjects who gained at least 15 letters of vision in FAS
- Change in total NEI VFQ-25 score from baseline in FAS
- Change in CNV area from baseline in FAS
- Change from baseline in CRT as assessed by OCT in FAS

4.2.8. Missing Data and Sensitivity Analyses

For the primary and secondary endpoints, missing data at week 52 were imputed using the last observation carried forward (LOCF) method. To assess the robustness of the main analysis results, observed case and worst observation carried forward (WOCF) methods were also used for the primary and all secondary endpoints. Additional sensitivity analyses for the primary endpoint included counting all discontinued patients as non-responders and counting all treatment failures as non-responders. An additional sensitivity analysis using the multiple imputation approach for missing data was also performed for the primary endpoint (proportion of subjects who maintained vision) and the secondary endpoint of Change from baseline in BCVA.

4.3. Treatment

In each study, eligible subjects were randomly assigned to 1 of 4 treatment groups (Table 3) and, with respect to the Year 1 analysis, treated at each clinic visit through week 48. Subjects in the 2Q8 group received 2 mg VEGF Trap-Eye every 4 weeks from baseline to week 8 (i.e., 3 initial monthly doses) and then a sham (i.e., pretend) injection every other visit through Week 48.

Table 3: VIEW 1 and VIEW 2 - Summary of Treatment Groups

Treatment Group	Treatment	No. of Subjects Randomized / Treated	
		VIEW 1	VIEW 2
RQ4	0.5 mg ranibizumab every 4 wks	306 / 304	303 / 291
2Q4	2 mg VEGF Trap-Eye every 4 wks	304 / 304	313 / 309
0.5Q4	0.5 mg VEGF Trap-Eye every 4 wks	304 / 304	311 / 297
2Q8[a]	2 mg VEGF Trap-Eye every 8 wks	303 / 303	313 / 307
Total		**1217 / 1215**	**1240 / 1204**

[a] Subjects in the 2Q8 group received 2 mg VEGF Trap-Eye every 4 weeks from baseline to week 8 (,i.e., three initial monthly doses) and then a sham (i.e., pretend) injection every other visit through week 48 during visits when an active injection was not administered.

Following completion of year 1 at week 52, subjects are retreated as often as every 4 weeks and no less frequently than every 3 months (i.e., if it has been 12 weeks since the last retreatment, the

subject will receive a treatment regardless of whether he/she has met any of the retreatment criteria; this is referred to as a "capped PRN" [as needed] dosing schedule). Year 2 is ongoing and will be the subject of a future analysis.

4.4. Patient Disposition

4.4.1. Patient Disposition for VIEW 1

A total of 1217 subjects were randomized in the VIEW 1 study; the numbers of subjects randomized and treated per treatment group are provided in Table 4. A total of 1089 subjects were valid for the PPS and were included in the analysis of the primary efficacy endpoint for non-inferiority; the FAS, used for assessment of all secondary and additional efficacy endpoints, comprised 1210 subjects.

Of the 1217 subjects randomized, 2 did not receive study medication. The majority of subjects (92.9%) completed the first year of the study; only 87 subjects discontinued the study before reaching the year 1 endpoint (Table 4). The percentage of subjects discontinuing the study ranged from 3.6% in the 2Q4 group to 8.9% in the other two VEGF Trap-Eye groups each, and7.2% in the ranibizumab group). In all treatment groups, the most common reason for discontinuation was "withdrawal by subject."

Table 4: VIEW 1 - Disposition of Subjects (Number [%] of Randomized Subjects)

	RQ4	2Q4	0.5Q4	2Q8	VEGF Trap-Eye Combined	Total
Randomized	306 (100)	304 (100)	304 (100)	303 (100)	911 (100)	1217 (100)
Treated	304 (99.3)	304 (100)	304 (100)	303 (100)	911 (100)	1215 (99.8)
Completed Year 1	284 (92.8)	293 (96.4)	277 (91.1)	276 (91.1)	846 (92.9)	1130 (92.9)
Premature discontinuation						
Total	**22 (7.2)**	**11 (3.6)**	**27 (8.9)**	**27 (8.9)**	**65 (7.1)**	**87 (7.1)**
Subject withdrawal	10 (3.3)	5 (1.6)	7 (2.3)	8 (2.6)	20 (2.2)	30 (2.5)
Adverse event	4 (1.3)	3 (1.0)	5 (1.6)	4 (1.3)	12 (1.3)	16 (1.3)
Death[a]	3 (1.0)	1 (0.3)	2 (0.7)	7 (2.3)	10 (1.1)	13 (1.1)
Lost to follow-up	1 (0.3)	2 (0.7)	4 (1.3)	4 (1.3)	10 (1.1)	11 (0.9)
Other	1 (0.3)	0	4 (1.3)	1 (0.3)	5 (0.5)	6 (0.5)
Protocol violation	3 (1.0)	0	3 (1.0)	1 (0.3)	4 (0.4)	7 (0.6)
Treatment failure	0	0	2 (0.7)	2 (0.7)	4 (0.4)	4 (0.3)

RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

[a] An additional four deaths were reported during the study but not captured in the database as a reason for premature discontinuation.

4.4.2. Patient Disposition for VIEW 2

A total of 1240 subjects were randomized in the VIEW 2 study. The numbers of subjects randomized and treated per treatment group are provided in Table 5. A total of 1081 subjects

were valid for the PPS and were included in the analysis of the primary efficacy endpoint; the FAS, used for assessment of all secondary efficacy endpoints, comprised 1202 subjects.

Of the 1240 subjects randomized, 36 did not receive study medication (RQ4, 12 subjects; 2Q4, 4 subjects; 0.5Q4, 14 subjects, and 2Q8, 6 subjects). Of these 36 subjects, 17 withdrew consent prior to receiving the first dose, 1 was lost to follow up, and "other" reasons were given for the remaining 18.

The majority of randomized subjects (89.9%) completed the first year of the study; 125 subjects discontinued the study before reaching the Year-1 endpoint (Table 5). The rate of premature discontinuation was approximately 10% in all treatment groups. In all groups, the most common reason for discontinuation was "withdrawal by subject."

Table 5: VIEW 2 - Disposition of Subjects (Number [%] of Randomized Subjects)

	RQ4	2Q4	0.5Q4	2Q8	VEGF Trap-Eye Combined	Total
Randomized	303 (100)	313 (100)	311 (100)	313 (100)	937 (100)	1240 (100)
Treated	291 (96.0)	309 (98.7)	297 (95.5)	307 (98.1)	913 (97.4)	1204 (97.1)
Completed Year 1	276 (91.1)	281 (89.8)	274 (88.1)	284 (90.7)	839 (89.5)	1115 (89.9)
Premature discontinuation						
Total	**27 (8.9)**	**32 (10.2)**	**37 (11.9)**	**29 (9.3)**	**98 (10.5)**	**125 (10.1)**
Subject withdrawal	11 (3.6)	15 (4.8)	13 (4.2)	11 (3.5)	39 (4.2)	50 (4.0)
Other	7 (2.3)	6 (1.9)	10 (3.2)	5 (1.6)	21 (2.2)	28 (2.3)
Adverse event	2 (0.7)	6 (1.9)	8 (2.6)	9 (2.9)	23 (2.5)	25 (2.0)
Lost to follow-up	4 (1.3)	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.5)	9 (0.7)
Death[a]	1 (0.3)	3 (1.0)	2 (0.6)	1 (0.3)	6 (0.6)	7 (0.6)
Protocol violation	2 (0.7)	1 (0.3)	1 (0.3)	0	2 (0.2)	4 (0.3)
Treatment failure	0	0	1 (0.3)	1 (0.3)	2 (0.2)	2 (0.2)

RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

[a] An additional two deaths were reported during the study but not captured in the database as a reason for premature discontinuation.

4.5. Patient Demographics

4.5.1. Patient Demographics for VIEW 1

The 4 treatment groups were well balanced with regard to baseline demographics. The demographics of the subjects in this study, and in particular the enrollment of few Black patients, were consistent with the known demographics of patients with wet AMD in the US and Canada. Baseline demographics for the FAS are presented in Table 6.

Table 6: VIEW 1 - Baseline Demographics (FAS)

	RQ4 (N=304)	2Q4 (N=304)	0.5Q4 (N=301)	2Q8 (N=301)	VEGF Trap-Eye Combined (N=906)	Total (N=1210)
Sex; n(%)						
Female	172 (56.6)	194 (63.8)	167 (55.5)	178 (59.1)	539 (59.5)	711 (58.8)
Male	132 (43.4)	110 (36.2)	134 (44.5)	123 (40.9)	367 (40.5)	499 (41.2)
Race; n(%)						
White	296 (97.4)	295 (97.0)	291 (96.7)	287 (95.3)	873 (96.4)	1169 (96.6)
Black	1 (0.3)	1 (0.3)	0	1 (0.3)	2 (0.2)	3 (0.2)
Asian	0	3 (1.0)	5 (1.7)	4 (1.3)	12 (1.3)	12 (1.0)
Other	3 (1.0)	0	2 (0.7)	3 (0.7)	5 (0.6)	7 (0.6)
Missing	4 (1.3)	5 (1.6)	3 (1.0)	6 (2.0)	14 (1.5)	18 (1.5)
Age; years						
Mean (SD)	78.2 (7.60)	77.7 (7.93)	78.4 (8.08)	77.9 (8.39)	78.0 (8.13)	78.1 (8.00)
Min[a] -Max	56-99	51-94	50-94	49-94	49-94	49-99

RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

[a] Although the inclusion criterion was ≥ 50 years of age, one subject aged 49 years was included in the study. The subject was close to his 50th birthday and, given that all other causes of CNV were ruled out, the CNV was considered to be age related.

4.5.2. Patient Demographics for VIEW 2

The 4 treatment groups were well balanced with regard to baseline demographics. Baseline demographics for the FAS are presented in Table 7.

Table 7: VIEW 2 - Baseline Demographics (FAS)

	0.5Q4 (N=291)	2Q4 (N=309)	0.5Q4 (N=296)	2Q8 (N=306)	VEGF Trap-Eye Combined (N=911)	Total (N=1202)
Sex						
Female	169 (58.1)	176 (57.0)	147 (49.7)	175 (57.2)	498 (54.7)	667 (55.5)
Male	122 (41.9)	133 (43.0)	149 (50.3)	131 (42.8)	413 (45.3)	535 (44.5)
Race						
White	213 (73.2)	226 (73.1)	219 (74.0)	217 (70.9)	662 (72.7)	875 (72.8)
Black	1 (0.3)	0	1 (0.3)	2 (0.7)	3 (0.3)	4 (0.3)
Asian	60 (20.6)	67 (21.7)	61 (20.6)	69 (22.5)	197 (21.6)	257 (21.4)
Other	0	0	0	0	0	0
Missing	17 (5.8)	16 (5.2)	15 (5.1)	18 (5.9)	49 (5.4)	66 (5.5)
Age (years)						
Mean (SD)	73.0 (9.0)	74.1 (8.5)	74.7 (8.6)	73.8 (8.6)	74.2 (8.6)	73.9 (8.7)
Min-Max	50-92	50-93	51-93	50-93	50-93	50-93

RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

4.6. Disease Characteristics

4.6.1. Disease Characteristics for VIEW 1

The 4 treatment groups were well balanced with regard to disease characteristics and there were no appreciable differences between the baseline disease characteristics of the FAS (Table 8).

Table 8: VIEW 1 - Disease Characteristics (FAS)

	RQ4 (N=304)	2Q4 (N=304)	0.5Q4 (N=301)	2Q8 (N=301)	VEGF Trap-Eye Combined (N=906)	Total (N=1210)
BCVA letter score						
Mean (SD)	54.0 (13.4)	55.2 (13.2)	55.6 (13.1)	55.7 (12.8)	55.5 (13.0)	55.1 (13.1)
Min-Max	10-78	11-81	18-85	15-83	11-85	10-85
CRT; microns						
N	286	286	281	287	854	1140
Mean	315.29	313.60	313.17	324.36	317.08	316.63
(SD)	(108.3)	(103.4)	(106.0)	(111.2)	(106.9)	(107.2)
Min-Max	144-683	151-802	141-739	133-835	133-835	133-835
Total Lesion Size; mm^2						
N	298	302	300	301	903	1201
Mean (SD)	7.0 (5.5)	7.0 (5.4)	7.0 (4.7)	6.9 (5.2)	6.9 (5.1)	7.0 (5.2)
Min-Max	0.1 : 29.0	0.2 : 29.6	0.2 : 24.9	0.0 : 32.6	0.0 : 32.6	0.0 : 32.6
Lesion Type; n(%)						
Occult	115 (37.0)	110 (36.2)	121 (40.2)	118 (39.2)	349 (38.5)	464 (38.3)
Minimally classic	101 (33.2)	105 (34.5)	97 (32.2)	110 (36.5)	312 (34.4)	413 (34.1)
Predominantly classic	82 (27.0)	87 (28.6)	81 (26.9)	71 (23.6)	239 (26.4)	321 (26.5)

RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks;2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

4.6.2. Disease Characteristics for VIEW 2

The 4 treatment groups were well balanced with regard to disease characteristics and there were no appreciable differences between the baseline disease characteristics of the FAS (Table 9).

Table 9: VIEW 2 - Baseline Disease Characteristics (FAS)

	0.5Q4 (N=291)	2Q4 (N=309)	0.5Q4 (N=296)	2Q8 (N=306)	VEGF Trap-Eye Combined (N=911)	Total (N=1202)
BCVA letter score						
Mean (SD)	53.8 (13.5)	52.8 (13.9)	51.6 (14.2)	51.6 (13.9)	52.0 (14.0)	52.4 (13.9)
Min-Max	10-83	10-79	12-79	16-76	10-79	10-83
CRT; microns						
N	290	308	294	302	904	1194
Mean	325.9	334.6	326.5	342.6	334.6	332.5
(SD)	(111.0)	(119.8)	(116.5)	(124.0)	(120.2)	(118.0)
Min-Max	139-810	103-805	107-793	107-868	103-868	103-868
Total Lesion Size; mm^2						
Nn	290	307	296	305	908	1198
Mean (SD)	8.0 (5.7)	8.7 (6.1)	8.2 (5.5)	8.2 (5.9)	8.4 (5.9)	8.3 (5.8)
Min-Max	[0.1; 28.8]	[0.1; 30.0]	[0.1; 26.6]	[0.0; 26.7]	0.0-30.0	[0.0; 30.0]
Lesion Type; n(%)						
Occult	116 (39.9)	123 (39.8)	113 (38.2)	110 (35.9)	346 (38.0)	462 (38.4)
Minimally classic	104 (35.7)	112 (36.2)	103 (34.8)	106 (34.6)	321 (35.2)	425 (35.4)
Predominantly classic	70 (24.1)	72 (23.3)	80 (27.0)	88 (28.8)	340 (26.3)	310 (25.8)
Missing	1 (0.3)	2 (0.6)	0	2 (0.7)	4 (0.4)	5 (0.4)

RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

4.6.3. Treatment Compliance in VIEW 1 and VIEW 2

Treatment compliance was high in both pivotal studies (VIEW 1 and VIEW 2) across all treatment groups (Table 10). In VIEW 1 and VIEW 2, 96.0% and 97.2% of subjects, respectively, in the FASs received the scheduled 3 injections during the first 12 weeks of the studies. Over the first year, approximately 97% of subjects in each study were ≥ 75% compliant. Very few subjects missed a scheduled injection.

Table 10: Treatment Compliance Over the First 12 Weeks and Over 52 Weeks in VIEW 1 and VIEW 2

	RQ4	2Q4	0.5Q4	2Q8
VIEW 1	**N = 304**	**N = 304**	**N = 301**	**N = 301**
Number (%) subjects receiving all 3 injections within the first 12 weeks	289 (95.1)	295 (97.0)	283 (94.0)	289 (96.0)
Number (%) subjects with < 75 % compliance *	2 (0.7)	1 (0.3)	3 (1.0)	8 (2.7)
Number (%) subjects with ≥ 75 % compliance *	302 (99.3)	303 (99.7)	298 (99.0)	293 (97.3)
Mean (SD) compliance	97.0 (6.2)	97.3 (5.5)	97.4 (5.3)	97.0 (8.0)
VIEW 2	**N = 291**	**N = 309**	**N = 296**	**N = 306**
Number (%) subjects receiving all 3 injections within the first 12 weeks	285 (97.9)	301 (97.4)	283 (95.6)	300 (98.0)
Number (%) subjects with < 75 % compliance *	7 (2.4)	15 (4.9)	10 (3.4)	9 (2.9)
Number (%) subjects with ≥ 75 % compliance *	284 (97.6)	294 (95.1)	268 (96.6)	297 (97.1)
Mean (SD) compliance	98.0 (6.0)	97.5 (7.2)	98.1 (6.0)	97.9 (5.8)
Integrated Analysis	**N=595**	**N=613**	**N=597**	**N=607**
Number (%) subjects receiving all 3 injections within the first 12 weeks	574 (96.5)	596 (97.2)	566 (94.8)	589 (97.0)
Number (%) subjects with < 75 % compliance *	9 (1.5)	16 (2.6)	13 (2.2))	17 (2.8)
Number (%) subjects with ≥ 75 % compliance *	586 (98.5)	597 (97.4)	584 (97.8)	590 (97.2)
Mean (SD) compliance	97.0 (7.3)	96.6 (8.5)	97.1 (7.6)	96.8 (8.4)

* Over 52 weeks
RQ4= Ranibizumab 0.5 mg every 4 weeks; 0.5Q4= VEGF Trap-Eye 0.5 mg every 4 weeks; 2Q4= VEGF Trap-Eye 2 mg every 4 weeks; 2Q8= VEGF Trap-Eye 2 mg every 8 weeks after three initial monthly doses
Note: Compliance = (the number of doses administered during period/number of planned doses) x 100%. In the 2Q8 group, planned doses included both active and sham injections.

4.7. Efficacy Results

For Year 1, the primary efficacy variable was the binary response variable of whether or not subjects maintained vision (i.e., lost fewer than 15 letters compared to baseline) and the primary efficacy endpoint was this proportion at week 52. Secondary efficacy variables included changes from baseline to week 52 in (1) BCVA (ETDRS letter score); (2) the proportion of subjects who gained 15 or more letters; (3) total NEI VFQ-25 score; and (4) CNV area as assessed by FA. In addition to the primary and secondary efficacy variables, additional exploratory efficacy variables were also assessed, including CRT by OCT.

4.7.1. Primary Endpoint

As agreed in the Special Protocol Assessment, the primary efficacy analysis for the primary endpoint was conducted with the PPS of subjects, which comprised those subjects in the FAS (i.e., all randomized subjects who received any study drug and had a baseline and at least one post-baseline assessment) who received at least 9 treatments (active or sham) during the first

year, attended at least 9 scheduled visits in the first year, and did not have a major protocol violation. Subjects who met the definition for treatment failure (i.e., experienced a decrease in BCVA from baseline of at least 15 letters at 2 consecutive assessments 4 weeks apart) at any time during the first year were included in the PPS. Results for the primary endpoint variable are shown in Figure 9. Analyses are provided in Table 11 and Table 13 and depicted graphically in Figure 10.

The analysis of the primary efficacy endpoint included a step-wise conditional calculation of the 95.1% (VIEW 1) or 95% (VIEW 2) CI of the difference between the proportion of ranibizumab-treated subjects who maintained vision and the proportion of subjects who maintained vision in each of the VEGF Trap-Eye groups.

Figure 9: VIEW 1 and VIEW 2 Primary Endpoint: Maintenance of Vision at Week 52 (PPS)

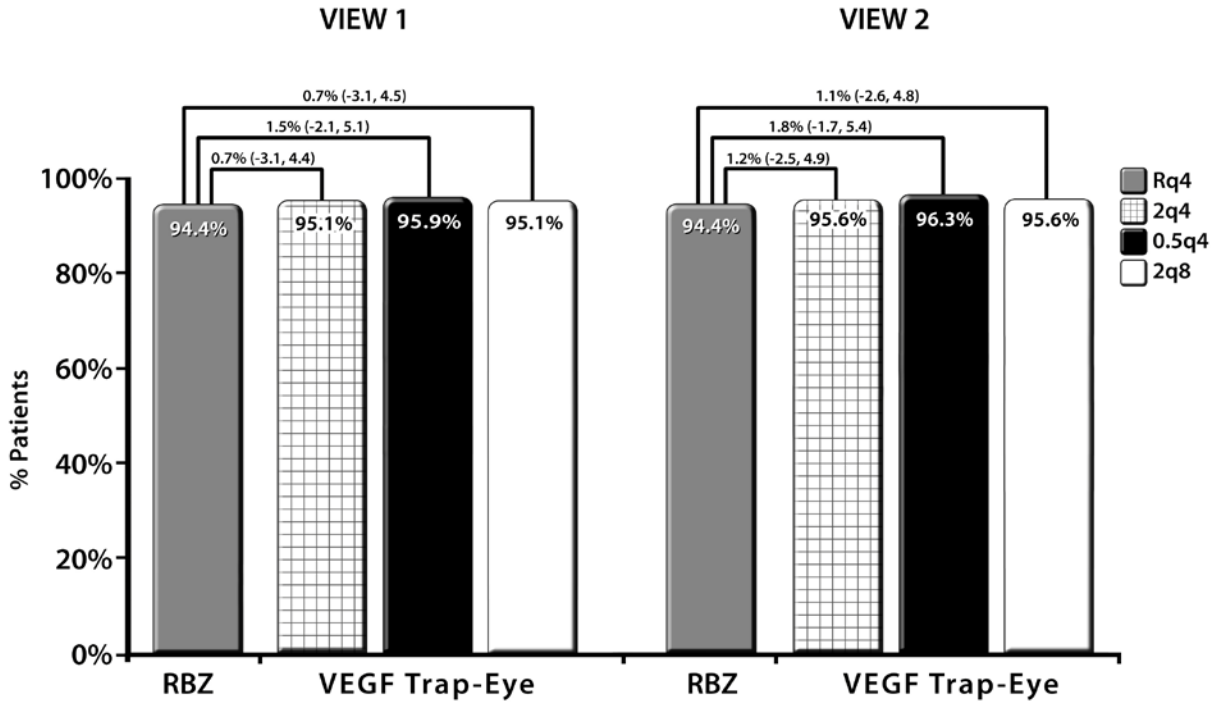
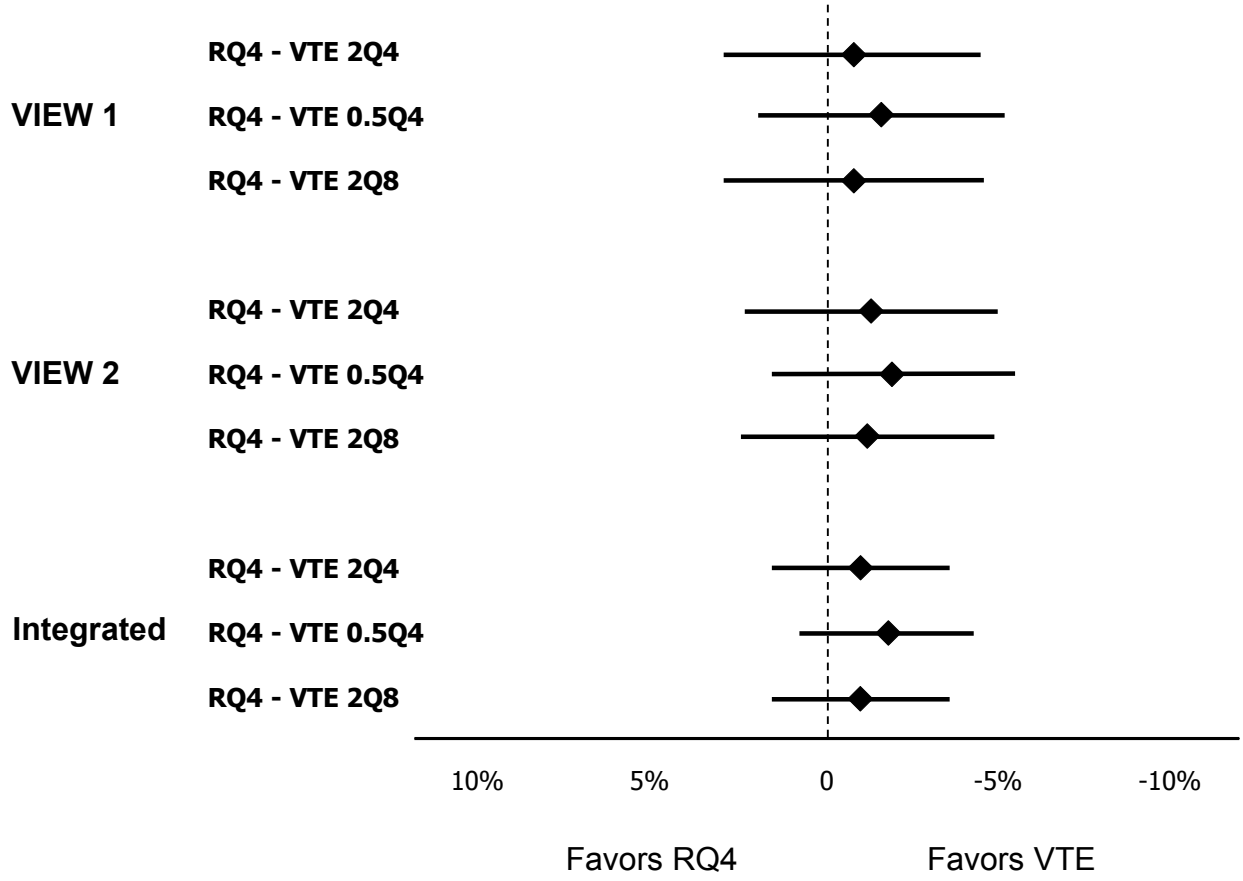


Figure 10: VIEW 1 and VIEW 2 Primary Endpoint: Analysis of Maintenance of Vision at Week 52 (PPS)



Note: The x-axis is reversed such that negative values appear on the right

4.7.1.1. VIEW 1: Proportion of Patients Maintaining Vision at Week 52

In VIEW 1, the proportion of subjects who maintained vision at week 52 was >94% in all treatment groups and all VEGF Trap-Eye treatment groups were numerically similar and proven to be non-inferior to RQ4 in the proportion of subjects maintaining vision at the Year-1 primary endpoint. The specified requirement for non-inferiority was that the upper limit of the 95.1% CI of the difference between RQ4 and VEGF Trap-Eye be entirely below the 10% noninferiority margin and also below 5%; actual upper limits in the per protocol set were 3.1%, 2.1%, and 3.1% for the comparisons of RQ4 to the VEGF Trap-Eye 2Q4, 0.5Q4, and 2Q8 groups, respectively (Table 11). Results in the full analysis set were similar (Table 12).

Table 11: VIEW 1 - Primary Efficacy Analysis of the Proportion of Subjects who Maintained Vision at Week 52 (LOCF, PPS)

Closed test procedure	Treatment Group[a]	Subjects who Maintained Vision at Wk 52; n (%)	Difference % (95.1% CI)[b]	Statistical Interpretation
First hypothesis	2Q4 (N=285) RQ4 (N=269)	271 (95.1) 254 (94.4)	-0.7 (-4.4, 3.1)	Non-inferiority of 2Q4 to RQ4 is statistically proven, test procedure can be continued
Second hypothesis	0.5Q4 (N=270) RQ4 (N=269)	259 (95.9) 254 (94.4)	-1.5 (-5.1, 2.1)	Non-inferiority of 0.5Q4 to RQ4 is statistically proven, test procedure can be continued
Third hypothesis	2Q8 (N=265) RQ4 (N=269)	252 (95.1) 254 (94.4)	-0.7 (-4.5, 3.1)	Non-inferiority of 2Q8 to RQ4 is statistically proven, test procedure can be continued

[a] RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

[b] Difference is ranibizumab minus VEGF Trap-Eye. Negative values favor VEGF Trap-Eye. CI=Confidence interval calculated using normal approximation.

Table 12: VIEW 1 - Sensitivity Efficacy Analysis of the Proportion of Subjects who Maintained Vision at Week 52 (LOCF, FAS)

Closed test procedure	Treatment Group[a]	Subjects who Maintained Vision at Wk 52; n (%)	Difference % (95.1% CI)[b]	Statistical Interpretation
First hypothesis	2Q4 (N=304) RQ4 (N=304)	289 (95.1) 285 (93.8)	-1.3 (-5.0, 2.4)	Non-inferiority of 2Q4 to RQ4 is statistically confirmed
Second hypothesis	0.5Q4 (N=301) RQ4 (N=304)	286 (95.0) 285 (93.8)	-1.3 (-4.9, 2.4)	Non-inferiority of 0.5Q4 to RQ4 is statistically confirmed
Third hypothesis	2Q8 (N=301) RQ4 (N=304)	284 (94.4) 285 (93.8)	-0.6 (-4.4, 3.2)	Non-inferiority of 2Q8 to RQ4 is statistically confirmed

[a] RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

[b] Difference is ranibizumab minus VEGF Trap-Eye. Negative values favor VEGF Trap-Eye. CI=Confidence interval calculated using normal approximation.

4.7.1.2. VIEW 2: Proportion of Patients Maintaining Vision at Week 52

In VIEW 2, the proportion of subjects who maintained vision at week 52 was ≥94% in all treatment groups and all VEGF Trap-Eye treatment groups were numerically similar and proven to be non-inferior to RQ4 in the proportion of subjects maintaining vision at the Year 1 primary endpoint. The specified requirement for non-inferiority was that the upper limit of the 95% CI of the difference between RQ4 and VEGF Trap-Eye be below 10%; actual upper limits in the per protocol set were 2.46%, 1.71%, and 2.55% for the comparisons of RQ4 to the VEGF Trap-Eye 2Q4, 0.5Q4, and 2Q8 groups, respectively (Table 13) and were even below 5%. Results in the full analysis set were similar (Table 14).

Table 13: VIEW-2 - Primary Efficacy Analysis of the Proportion of Subjects who Maintained Vision at Week 52 (LOCF, PPS)

Closed test procedure	Treatment Group[a]	Subjects who Maintained Vision at Wk 52; n (%)	Difference % (95% CI)[b]	Statistical Interpretation
First hypothesis	2Q4 (N=274) RQ4 (N=269)	262 (95.6) 254 (94.4)	-1.20 (-4.9, 2.5)	Non-inferiority of 2Q4 to RQ4 is statistically proven, test procedure can be continued
Second hypothesis	0.5Q4 (N=268) RQ4 (N=269)	258 (96.3) 254 (94.4)	-1.8 (-5.4, 1.7)	Non-inferiority of 0.5Q4 to RQ4 is statistically proven, test procedure can be continued
Third hypothesis	2Q8 (N=270) RQ4 (N=269)	258 (95.6) 254 (94.4)	-1.13 (-4.8, 2.6)	Non-inferiority of 2Q8 to RQ4 is statistically proven, test procedure can be continued

[a] RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4= 2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

[b] Difference is ranibizumab minus VEGF Trap-Eye. Negative values favor VEGF Trap-Eye. CI=Confidence interval calculated using normal approximation.

Table 14: VIEW 2 - Sensitivity Efficacy Analysis of the Proportion of Subjects who Maintained Vision at Week 52 (LOCF, FAS)

Closed test procedure	Treatment Group[a]	Subjects who Maintained Vision at Wk 52; n (%)	Difference % (95.1% CI)[b]	Statistical Interpretation
First hypothesis	2Q4 (N=309) RQ4 (N=291)	292 (94.5) 276 (94.9)	0.4 (-3.3, 3.9)	Non-inferiority of 2Q4 to RQ4 is statistically confirmed
Second hypothesis	0.5Q4 (N=296) RQ4 (N=291)	282 (95.3) 276 (94.9)	-0.4 (-3.9, 3.1)	Non-inferiority of 0.5Q4 to RQ4 is statistically confirmed
Third hypothesis	2Q8 (N=306) RQ4 (N=291)	292 (95.4) 276 (94.9)	-0.6 (-4.0, 2.9)	Non-inferiority of 2Q8 to RQ4 is statistically confirmed

[a] RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

[b] Difference is ranibizumab minus VEGF Trap-Eye. Negative values favor VEGF Trap-Eye. CI=Confidence interval calculated using normal approximation.

4.7.1.3. Sensitivity Analyses of the Primary Endpoint: VIEW 1 and VIEW 2

Sensitivity analyses were performed on the primary endpoint in the PPS and FAS using observed values, the WOCF method, and by multiple imputation. Additional sensitivity analyses imputed "non-responder at week 52" to all drop outs and to subjects considered to be treatment failures at any time point before week 52 regardless of whether they remained in the study. A drop out was defined as any subject who prematurely discontinued the study but did not meet the criteria for treatment failure. Results of the sensitivity analyses were similar to those from the primary analysis of the PPS using the LOCF. In all instances, the upper bound of the 95.1% (VIEW 1) or 95% (VIEW 2) CI was well below the pre-specified 10% margin for noninferiority and all but one were below 5% (all were below 6%).

4.7.1.4. VEGF Trap-Eye 2 mg every 2 months provides efficacy similar to once-a-month dosing of ranibizumab

Of particular interest in both VIEW 1 and VIEW 2 was the finding that dosing with VEGF Trap-Eye 2 mg every 2 months (after three initial monthly loading doses) provided similar efficacy (i.e., was non-inferior) to a once-a-month dosing of ranibizumab. Approximately 95% of subjects treated with VEGF Trap-Eye 2 mg every two months maintained vision at Week 52 compared with approximately 94% in the ranibizumab group (Figure 9) even though subjects in the VEGF Trap-Eye group received fewer injections over the 52 weeks. Mean (± SD) number of active injections in the 2Q8 group was 7.5 (± 1.2) injections in the combined data compared to 12.3 (± 1.9) injections in the RQ4 group (Table 26). Consistent with the every two month dosing regimen (after initial loading) the 2Q8 group had 5 scheduled injections over the last 10 months of each study whereas the Q4 groups had 10 scheduled injections.

4.7.2. Secondary Visual Acuity Efficacy Endpoints

4.7.2.1. Change in BCVA Letter Score

Improvement in BCVA was seen as early as week 1 in all treatment groups in VIEW 1 (Figure 11, Top), VIEW 2 (Figure 11, Middle), and in the integrated analysis (Figure 11, Bottom), with an overall trend of continuing improvement to the week 52 endpoint. Minor differences between treatment groups in VIEW 1 were not reproduced in VIEW 2 (e.g. the treatment groups with the numerically highest and lowest BCVA gains at 52 weeks are reversed in VIEW 1 and VIEW 2), suggesting that the response to the 4 treatments is very similar and that the differences are likely due to random variability and not due to the treatment regimen (i.e., due to experimental/disease variability and/or some unknown baseline differences among these treatment groups). The similarity between the 4 treatment regimens is further emphasized by the integrated data in which any differences among the four treatment regimens are compressed so that all four treatment regimens produce improvements in BCVA at 52 weeks within one letter of each other (8.3 to 9.3 letters). The point that any differences among treatment groups is due to random variability is further reinforced by examining the 2Q4 and 2Q8 curves over the first 12 week period. Patients in these treatment groups received the same 2 mg monthly doses at weeks 0, 4, and 8 and thus any differences in BCVA over the first 12 weeks must be due to experimental/disease variability and/or some unknown baseline differences between these treatment groups; once again, the relative positions of the curves for these two treatment groups are reversed in VIEW 1 and VIEW 2.

Change in BCVA from baseline to week 52 for VIEW 1, VIEW 2, and in the integrated data is analyzed in Table 15, Table 16 and Table 17 and depicted graphically in Figure 12.

Figure 11: Mean Change in BCVA (FAS, LOCF)

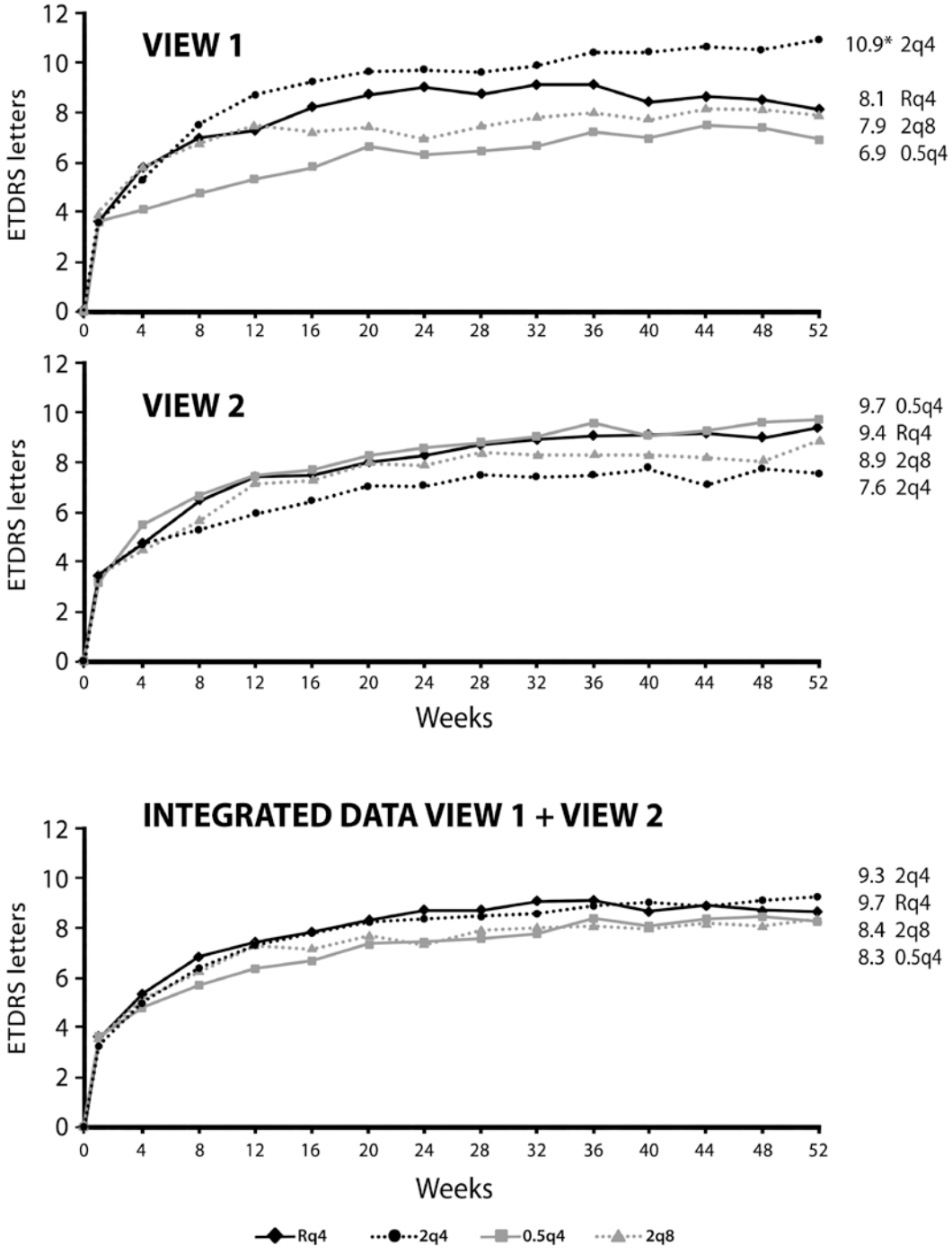
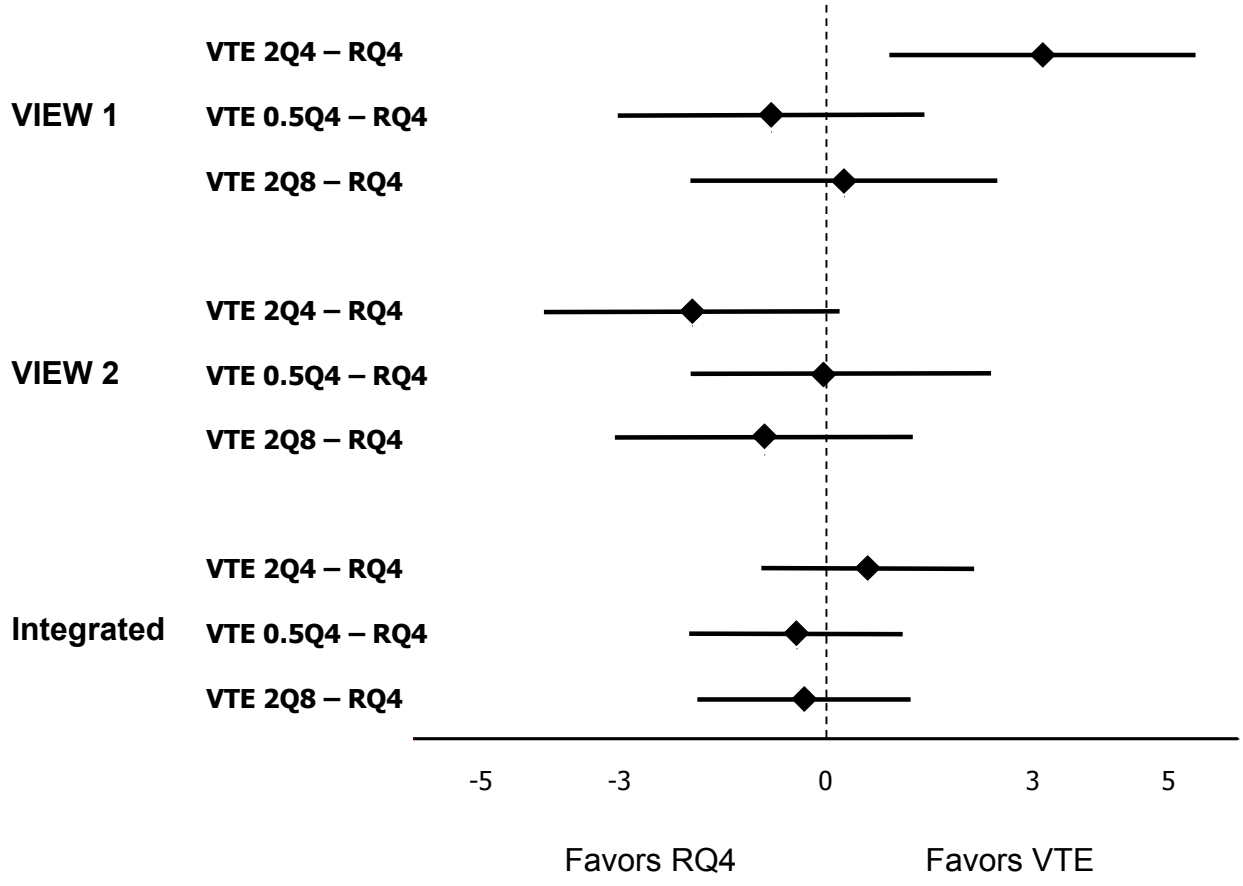


Figure 12: VIEW 1 –Secondary Efficacy Endpoint: Analysis of Change in BCVA at Week 52 (LOCF, FAS)



4.7.2.2. VIEW 1: Change in BCVA Letter Score at Week 52

In VIEW 1, the 2Q4 group experienced the highest mean (±SD) increase in ETDRS letter score (10.9 ± 13.77). Results of the pre-specified sequential testing of the secondary endpoints showed that the 2Q4 group was superior to RQ4 at week 52 for the change in ETDRS letter score (Table 15). The improvements in the 0.5Q4 and 2Q8 groups were similar to RQ4 although the sequential testing was broken before superiority of these groups could be tested. For the 2Q8 dosing regimen, clinical benefit at the end of the year was the same at weeks 48 and 52 (8 and 4 weeks, respectively, after the prior injection).

Table 15: VIEW 1 –Secondary Efficacy Endpoint: Change in BCVA at Week 52 (LOCF, FAS)

	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 304)	2Q4 (N = 304)	0.5Q4 (N = 301)	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)
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)
Week 52 (change from baseline)				
N	304	304	301	301
Mean (SD)	8.1 (15.25)	10.9 (13.77)	6.9 (13.41)	7.9 (15.00)
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

[1] Difference is VEGF Trap-Eye minus ranibizumab. CI calculated using normal approximation.
[2] ANCOVA main effect model with treatment groups as the fixed effect and baseline score as the covariate.

4.7.2.3. VIEW 2: Change in BCVA Letter Score at Week 52

At week 52, all groups had similar gains in ETDRS letter score, approximately 8 to 10 letters. As opposed to in VIEW 1, the 2Q4 group experienced the lowest mean (±SD) increase in ETDRS letter score (7.6 ± 12.6) while the VEGF Trap-Eye 0.5Q4 group had the largest numeric increase (9.7 ± 14.1), with the other two groups in between (RQ4, 9.4 ± 13.5; 2Q8, 8.9 ± 14.4). At Week 52, superiority of VEGF Trap-Eye 2Q4 regimen to ranibizumab was not established (Table 16) and the conditional sequence of hypothesis tests for the secondary efficacy variables in VIEW 2 was stopped. As in VIEW 1, clinical benefit at the end of the year for the 2Q8 regimen was the same at weeks 48 and 52 (8 and 4 weeks, respectively, after the prior injection).

Table 16: VIEW 2 – Secondary Efficacy Endpoint: Change in BCVA at Week 52 (LOCF, FAS)

	RQ4	2Q4	0.5Q4	2Q8
Baseline				
N	291	309	296	306
Mean (SD)	53.8 (13.5)	52.8 (13.9)	51.6 (14.2)	51.6 (13.9)
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)
Week 52 (change from baseline)				
N	291	309	296	306
Mean (SD)	9.4 (13.5)	7.6 (12.6)	9.7 (14.1)	8.9 (14.4)
LS mean difference[a]		-1.95	-0.06	-0.90
95% CI for difference		(-4.10; 0.20)	(-2.24; 2.12)	(-3.06; 1.26)
p-value vs RQ4[b]		0.076	0.956	0.413

[a] Difference is VEGF Trap-Eye minus ranibizumab using LSMeans. Positive values are in favor of VEGF Trap-Eye. CI=confidence interval calculated using normal approximation.
[b] ANCOVA, main effect model with treatment group as the fixed effect and baseline score as the covariate..

4.7.2.4. VIEW 1 and VIEW 2 Combined: Change in BCVA Letter Score at Week 52

In the integrated analysis of the pooled data from the pivotal studies, mean (±SD) change from Baseline at Week 52 (for the FAS) were within one letter for all four treatments, ranging from 8.3 ± 13.8 letters in the lowest-dose VEGF Trap-Eye group (0.5Q4) to 9.3 ± 13.3 letters in the 2Q4 group. Overall, in the integrated analysis of the pooled data from the pivotal studies, there were no apparent differences between ranibizumab and the VEGF Trap-Eye treatment groups in the change from baseline at week 52 (Table 17 and Figure 12). Of particular importance was the observation that at week 52, when the 2Q8 group had been treated less often than the RQ4 group (,i.e., mean [SD] of 12.3 [1.9] active injections of ranibizumab compared with 7.6 [1.1] of VEGF Trap-Eye) over the course of the 52 week study, and with only 5 scheduled injections over the last 10 months for the 2Q8 regimen compared to 10 for ranibizumab), mean changes in ETDRS letter scores were virtually identical (RQ4, 8.7 ± 14.4 letters; 2Q8, 8.4 ± 14.7 letters) in the two groups. As in the individual study analyses, clinical benefit at the end of the year for the 2Q8 regimen was the same at weeks 48 and 52 (8 and 4 weeks, respectively, after the prior injection).

Table 17: Integrated Analysis of the Pooled Data from the Pivotal Studies –Secondary Efficacy Endpoint: Change in BCVA at Week 52 (LOCF, Full Analysis Set)

	RQ4	2Q4	0.5Q4	2Q8
Baseline				
N	595	613	597	607
Mean (SD)	53.9 (13.4)	54.0 (13.6)	53.6 (13.8)	53.6 (13.5)
Week 52				
N	595	613	597	607
Mean (SD)	62.6 (17.2)	63.2 (17.5)	61.9 (17.1)	62.0 (17.3)
Week 52 (change from baseline)				
N	595	613	597	607
Mean (SD)	8.7 (14.4)	9.3 (13.3)	8.3 (13.8)	8.4 (14.7)
LS mean difference[a]		0.60	-0.43	-0.32
95% CI for difference		(-0.94, 2.14)	(-1.99, 1.12)	(-1.87, 1.23)
p-value vs RQ4[b]		0.45	0.59	0.69

[a] Difference is VEGF Trap-Eye minus ranibizumab using LSMeans. Positive values are in favor of VEGF Trap-Eye. CI=confidence interval calculated using normal approximation.
[b] ANCOVA, main effect model with treatment group and study as the fixed effects and baseline score as the covariate.

In both individual studies and the integrated analysis of the pooled data from the pivotal studies, sensitivity analyses using observed values and the WOCF method supported the LOCF analysis with the FAS. Sensitivity analyses in the integrated analysis of the pooled data from the pivotal studies also support the finding that similar efficacy is achieved with less frequent dosing of VEGF Trap-Eye than with the recommended dose of ranibizumab, even when the analysis used the WOCF method.

4.7.2.5. VIEW 1: Secondary Endpoint – Patients who Gained ≥15 Letters

The proportion of subjects who experienced a gain of 15 or more letters at Week 52 was slightly higher in the 2Q4 group compared to the other groups. The difference between this group and ranibizumab was not statistically significant and, therefore, the conditional sequence of testing was broken. Again, there was no relevant difference between the ranibizumab group (30.9%) and 2Q8 (30.6%) indicating that less frequent dosing of VEGF Trap-Eye (i.e., every two months) was as efficacious as ranibizumab 0.5 mg dosed on a monthly basis for this endpoint (Table 18).

Table 18: VIEW 1 - Analysis of the Proportion of Subjects who Gained 15 or More Letters at Week 52 (LOCF; FAS)

Treatment Group[a]	RQ4	2Q4	0.5Q4	2Q8
N	304	304	301	301
Subjects [n (%)] gaining ≥ 15 letters	94 (30.9)	114 (37.5)	75 (24.9)	92 (30.6)
Difference (95.1% CI)[b]	—	6.6 (-1, 14.1)	-6.0 (-13.2, 1.2)	-0.4 (-7.7, 7.0)

[a] RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4= 2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses
[b] Mantel-Haenszel estimate for difference VEGF Trap-Eye minus ranibizumab (positive values are in favor of VEGF Trap-Eye); CI=Confidence interval calculated using normal approximation

4.7.2.6. VIEW 2: Secondary Endpoint – Patients who Gained ≥15 Letters

The proportion of subjects who experienced a gain of 15 or more letters at Week 52 was similar in all treatment groups (RQ2, 34.02%; 2Q4, 29.45%; 0.5Q4, 34.80%; and 2Q8, 31.37%; pairwise comparisons between the different VEGF Trap-Eye groups and the ranibizumab group did not show any relevant treatment differences; in all comparisons, 95% CIs for the difference included zero (Table 19).

Table 19: VIEW 2 - Analysis of the Proportion of Subjects who Gained 15 or More Letters at Week 52 (LOCF; FAS)

Treatment Group[a]	RQ4	2Q4	0.5Q4	2Q8
N	291	309	296	306
Subjects [n (%)] gaining ≥ 15 letters	99 (34.02)	91 (29.45)	103 (34.80)	96 (31.37)
Difference (95% CI)[b]	—	-4.57 (-12.02, 2.88)	0.78 (-6.91, 8.46)	-2.65 (-10.18, 4.88)

[a] RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4= 2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses
[b] Mantel-Haenszel estimate for difference VEGF Trap-Eye minus ranibizumab (positive values are in favor of VEGF Trap-Eye); CI=Confidence interval calculated using normal approximation

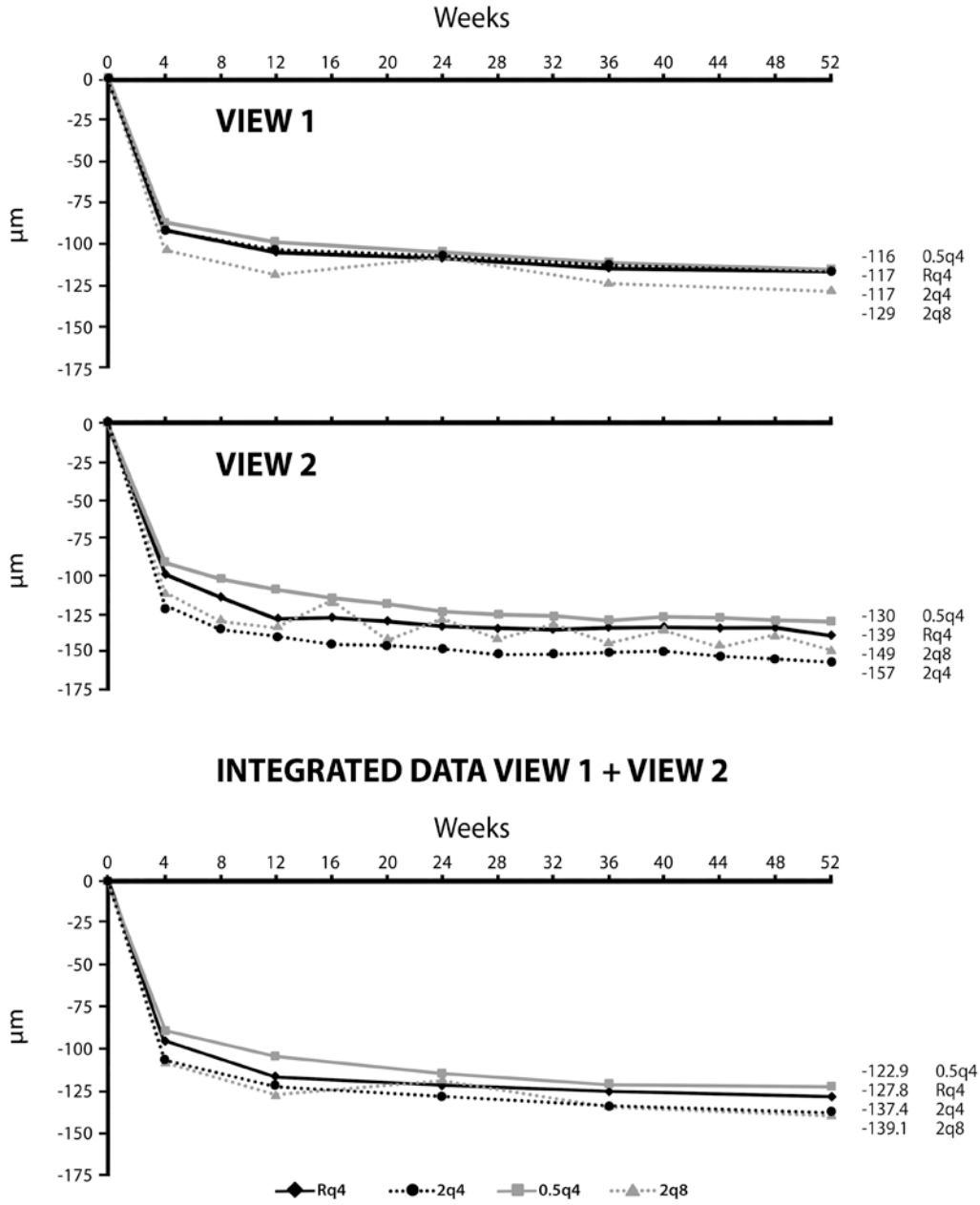
4.7.3. Secondary and Additional Anatomic Efficacy Endpoints

4.7.3.1. Change from Baseline in Central Retinal Thickness (CRT) – VIEW1, VIEW2 and Integrated Analysis

In both VIEW 1 and VIEW 2, a rapid reduction in CRT occurred through week 4 with results that were maintained to week 52 in all treatment groups (Figure 13). This is emphasized by the integrated analysis combining the data from the two studies. All treatment regimens produced similar anatomic improvements in retinal thickness. Particularly because of the precedent of the CATT study which showed that monthly bevacizumab and both PRN ranibizumab and PRN bevacizumab did not reduce retinal thickness to the degree of monthly ranibizumab, it is noteworthy that in both the individual VIEW studies, as well as in the integrated analysis, the 2Q8 longer-interval regimen produced a numerically greater reduction in retinal thickness than

monthly ranibizumab. This demonstrated that the every two month regimen was effective in terms of controlling retinal edema. Interestingly, there was a minor fluctuation in average retinal thickness with this dosing regimen, as seen between the 4-and 8-week time points after an injection; this pattern was evident in VIEW 2 because of the availability of monthly data that was not available for VIEW 1. These minor fluctuations with the 2Q8 regimen steadily diminished to about 8 microns by the latter part of the study; further exploratory analyses (see Section 4.7.3.4 below) show that this minor average fluctuation did not appear to be due to a small subset of patients that were undergoing repeated and much larger fluctuations, and patients with the largest fluctuations did not appear to have worse visual outcomes.

Figure 13: Mean Change from Baseline in Central Retinal Thickness by Treatment Group (LOCF) (Full Analysis Set)



4.7.3.2. VIEW 1: Change from Baseline in Central Retinal Thickness

In VIEW 1, CRT was similar among treatment groups at baseline in the FAS. The magnitude of the change at week 52 was similar in all treatment groups (mean decrease –116.8µm, –116.5µm,

–115.6 µm, and -128.5 µm in the RQ4, 2Q4, 0.5Q4, and 2Q8 groups, respectively), with the 2Q8 group showing the greatest reduction as noted above (Table 20).

Table 20: VIEW 1 - Change from Baseline to Week 52 in Central Retinal Thickness (LOCF) (Full Analysis Set)

	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 304)	2Q4 (N = 304)	0.5Q4 (N = 301)	2Q8 (N = 301)
Baseline				
N	286	286	281	287
Mean (SD) µm	315.3 (108.25)	313.6 (103.40)	313.2(105.96)	324.4 (111.22)
Median	285.5	290.0	291.0	303.0
Min: Max	144:683	151:802	141:739	133:835
Week 52				
N	298	302	292	298
Mean (SD) µm	198.0 (43.96)	197.2 (47.16)	198.3 (44.97)	196.3 (44.01)
Median	193.0	189.0	190.0	191.0
Min: Max	104:418	96:414	108:423	111:537
Week 52 (change from baseline)				
N	281	284	274	286
Mean (SD) µm	–116.8 (108.98)	–116.5 (98.41)	–115.6 (104.08)	–128.5 (108.50)
Median	–91.0	–92.0	–98.0	–107.5
Min: Max	–508:172	–636:51	–534:53.0	–607:131
LS mean difference [1]		-1.21	0.32	-3.04
95.1% C.I. for difference		(-8.39, 5.96)	(-6.92, 7.56)	(-10.21, 4.13)
P-value vs. RQ4 [2]		0.7389	0.9306	0.4037

[1] Difference is VEGF Trap-Eye minus ranibizumab. CI calculated using normal approximation.
[2] ANCOVA, main effect model.
Note: LOCF: The missing values were replaced by the last observed post baseline values prior to the missing value.

4.7.3.3. VIEW 2: Change from Baseline in Central Retinal Thickness

In VIEW 2, mean CRT at Baseline was similar among the treatment groups (Table 21). At week 52, a mean reduction by >40% was seen in all groups (FAS, LOCF). The absolute decrease in CRT was numerically most pronounced in the 2Q4 (-156.8 µm; mean) and 2Q8 groups group (-149.2 µm; mean). Irrespective of the treatment group, the variability of the changes was large as indicated by the broad SD to the means. The point estimate for the difference between the 2Q4 group and the RQ4 group was -10.7 µm (95% CI: -22.2 to -0.13 µm), i.e., nominally in favor of the VEGF Trap-Eye treatment. As noted above and to be discussed in more detail in the next section, the 2Q8 group had a pattern of minor fluctuations in average retinal thickness, as seen between the 4- and 8-week timepoints after an injection. These minor fluctuations steadily diminished to about 8 microns by the latter part of the study; further exploratory analyses (see 6.7.3.3 below) show that these minor average fluctuation did not appear to be due to a small subset of patients that were undergoing repeated and much larger fluctuations, and patients with the largest fluctuations did not appear to have worse visual outcomes.

Table 21: VIEW 2 - Change from Baseline to Week 52 in Central Retinal Thickness [µm] – LOCF (Full Analysis Set)

Time	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 291)	2Q4 (N = 309)	0.5Q4 (N = 296)	2Q8 (N = 306)
Baseline				
N	290	308	294	302
Mean (SD)	325.9 (110.9)	334.6 (119.8)	326.5 (116.5)	342.6 (124.0)
Median	309.5	309.0	313.5	327.5
Min: Max	[139; 810]	[103; 805]	[107; 793]	[107; 868]
Week 52				
N	291	308	295	306
Mean (SD)	187.1 (60.1)	178.0 (66.3)	196.5 (72.1)	193.7 (71.7)
Median	175.0	169.0	183.0	179.0
Min: Max	[86; 481]	[81; 848]	[90; 708]	[86; 695]
Week 52 (change from Baseline)				
N	290	307	293	302
Mean (SD)	-138.5 (122.2)	-156.8 (122.8)	-129.8 (114.8)	-149.2 (119.7)
Median	-119.5	-141.0	-118.0	-133.5
Min: Max	[-628; 263]	[-657; 309]	[-637; 251]	[-645; 206]
Difference in LSmeans [1]		-10.68	9.26	3.60
95% CI for the difference		(-21.22; -0.13)	(-1.40; 19.92)	(-6.99; 14.20)
P-value		0.047	0.089	0.505

Note: Pairwise comparisons are for descriptive purposes only.
[1] ANCOVA, main effect model. Difference is VEGF Trap-Eye minus ranibizumab; C.I. = confidence interval was calculated using a normal approximation.

4.7.3.4. VIEW 2: Additional exploration of the CRT data

Although each treatment arm in the VIEW studies displayed a prompt and robust decrease in retinal thickness, and although the 2Q8 arm produced a numerically greater reduction in retinal thickness than monthly ranibizumab in both studies, this dosing regimen had a minor fluctuation in average retinal thickness, as seen between the 4-and 8-week time points after an injection; this pattern was evident in VIEW 2 because of the availability of monthly data that were not available for VIEW 1. Careful analysis of these fluctuations reveals that the mean initial increase in retinal thickness is only 17 microns in the interval between the week 12 and week 16, visits, decreasing steadily to about 8 microns by the end of the first year (Figure 13). In clinical practice, inter-dose change in CRT is sometimes used to assess whether a patient should receive additional anti-VEGF treatment. It was therefore of interest to determine if a patient's change in inter-visit CRT is predictive of their VA outcome. On average, these minor CRT fluctuations seen in the 2Q8 group did not appear to have a deleterious effect on VA outcome in the overall group, as visual outcome for the 2Q8 groups was quite similar to that of the other regimens, including ranibizumab dosed monthly (8.7 letters versus 8.4 letters in the integrated BCVA analysis).

A further concern raised by these minor fluctuations is whether they might reflect a small subset of patients for whom the Q8 dosing interval was too long, and that this small subset had very large and repeated OCT fluctuations that would be correlated with worse visual outcome which were not reflected in the overall group. To explore this concern we performed a post hoc analysis not previously submitted to FDA (Figure 14). In this analysis, we asked how often, in

each of the dose groups, patients had inter-visit increases of greater than 50 microns in CRT on OCT. This analysis showed that all treatment groups had such changes (Figure 14). Furthermore, in Figure 15, the visual acuity outcomes at week 52 for each patient were plotted against the number of times each individual patient had an increase of > 50 microns of CRT. As can be seen in the figure, these inter-visit OCT changes of >50 microns did not correlate with worse visual outcome at 52 weeks, even for patients who had several of them. Thus, the 2Q8 group does not seem to have a substantial subset of patients who undergo repeated large increases in OCT as compared to the other treatment groups, and there does not appear to be an association with worse visual outcome for patients who have such increases, regardless of their treatment regimen. Similar results were obtained in analyses of inter-visit increases of greater than 25 microns or 100 microns.

Figure 14: VIEW 2: Distribution of Episodes of OCT Increase of >50 Microns

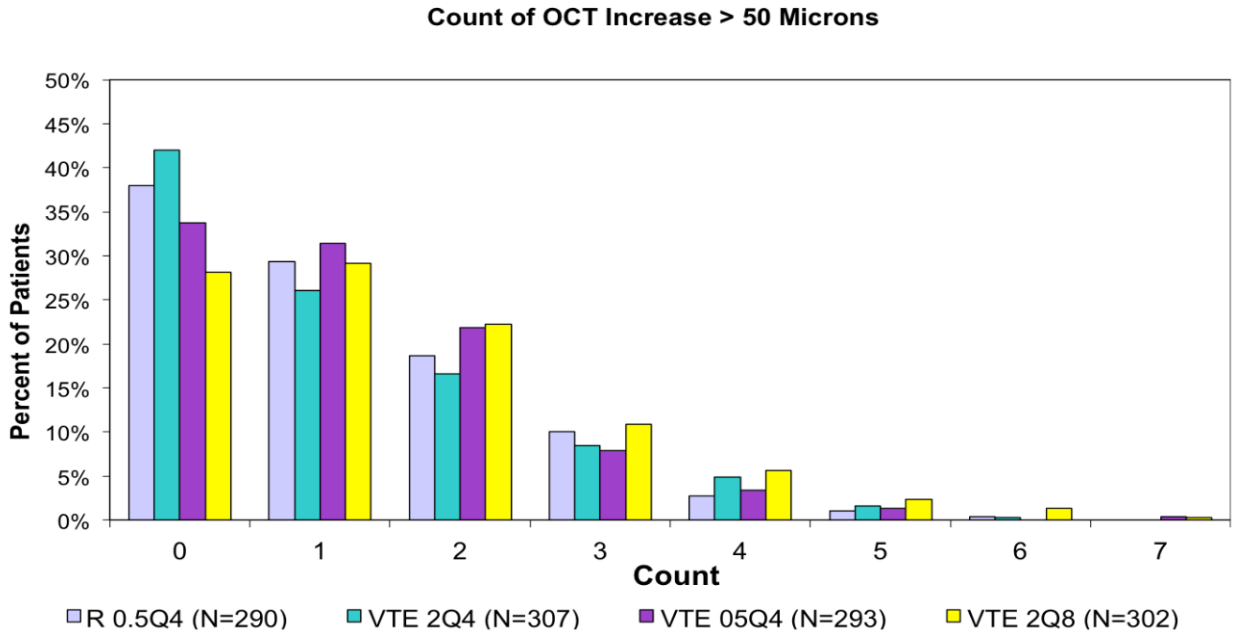
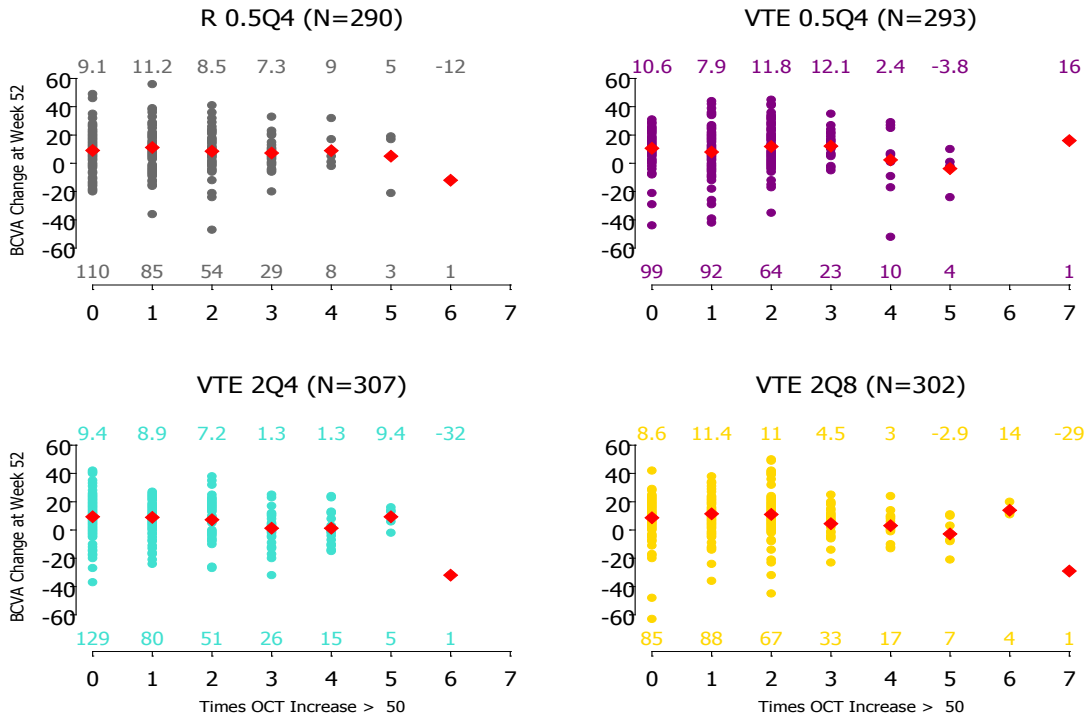


Figure 15: VIEW 2: BCVA Change at Week 52 vs. Count of OCT Increase from Previous Timepoint of > 50 Microns



4.7.3.5. Change in Choroidal Neovascularization Area from Baseline

In both studies, CNV area decreased in all treatment groups. Minor differences between treatment groups in one study were not reproduced in the second study, consistent with the notion that all treatments had similar effects and that any differences were due to random variability.

4.7.3.6. VIEW 1: Change in Choroidal Neovascularization Area from Baseline

The mean CNV area was comparable among treatment groups at baseline. At week 52, mean CNV area decreased in all treatment groups. These decreases were similar between the 2Q4 group and the RQ4 group (–4.6 mm^2 versus -4.2 mm^2). Changes in the 0.5Q4 and 2Q8 groups were slightly lower and similar to each other (-3.5 and -3.4 mm^2, respectively) with a difference noted between the RQ4 and the 2Q8 groups in favor of RQ4 (difference = 0.86 mm^2, 95.1% CI = 0.15 - 1.58) (Table 22).

Table 22: VIEW 1: Change from Baseline to Week 52 in CNV Area (mm^2) (LOCF) (Full Analysis Set)

	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 304)	2Q4 (N = 304)	0.5Q4 (N = 301)	2Q8 (N = 301)
Baseline				
N	298	302	300	300
Mean (SD)	6.5 (5.25)	6.6 (5.05)	6.5 (4.45)	6.6 (5.14)
Median	5.2	5.6	5.9	5.4
Min: Max	0.1:29.0	0.2:29.6	0.0:24.9	0.0:32.6
Week 52				
N	292	298	288	286
Mean (SD)	2.2 (4.06)	1.9 (4.21)	3.0 (4.82)	3.1 (5.13)
Median	0.0	0.0	0.0	0.0
Min: Max	0.0:19.6	0.0:22.7	0.0:22.2	0.0:32.6
Week 52 (change from baseline)				
N	288	296	287	286
Mean (SD)	–4.2 (5.59)	–4.6 (5.47)	–3.5 (5.27)	–3.4 (6.02)
Median	–3.3	–3.7	–2.7	–2.3
Min: Max	–29.0:10.7	–29.6:11.9	–24.9:18.6	–32.6:26.4
LS mean difference [1]		–0.33	0.71	0.86
95.1% CI for difference		(–1.04 , 0.38)	(–0.01 , 1.42)	(0.15 , 1.58)
p-value vs. RQ4 [2]		0.3575	0.0507	0.0173

[1] Difference is VEGF Trap-Eye minus ranibizumab. CI calculated using normal approximation.

[2] ANCOVA, main effect model.

Note: LOCF: The missing values were replaced by the last observed post baseline values prior to the missing value.

4.7.3.7. VIEW 2: Change in Choroidal Neovascularization Area from Baseline

Mean CNV area at Baseline ranged between 7.58 mm^2 (RQ4 group) and 8.24 mm^2 (2Q4 group). At Week 52, mean CNV area had decreased to < 3.5 mm^2 in all groups. In this study, the 2Q4 (-5.95 mm^2) and the 2Q8 (-5.160) groups had the largest mean decreases, while the RQ4 group (-4.16) had the lowest mean decrease. Using the LS means from the exploratory ANCOVA (main effect model), the difference between these two groups (i.e., 2Q4 and RQ4) was -1.18 mm^2 (95% CI: -1.98 to -0.38 mm^2). The pairwise comparisons between the RQ4 and the 0.5Q4 and the 2Q8 groups, respectively, did not indicate any relevant differences.

A summary of the changes from Baseline to Week 52 and the results of the pairwise comparisons between the different VEGF Trap-Eye groups and the RQ4 group are shown in Table 23.

Table 23: VIEW 2: Change from Baseline to Week 52 in CNV Area [mm2] – LOCF (Full Analysis Set)

Time	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 291)	2Q4 (N = 309)	0.5Q4 (N = 296)	2Q8 (N = 306)
Baseline				
N	291	308	296	305
Mean (SD)	7.584 (5.342)	8.243 (5.770)	7.692 (5.264)	7.750 (5.515)
Median	6.410	6.670	6.825	6.360
Min: Max	[0.09; 28.79]	[0.12; 26.86]	[0.07; 26.57]	[0.00 24.85]
Week 52				
N	278	295	287	290
Mean (SD)	3.198 (4.977)	2.339 (5.035)	3.497 (5.903)	2.597 (4.860)
Median	0.000	0.000	0.000	0.000
Min: Max	[0.00; 25.89]	[0.00; 32.23]	[0.00; 36.93]	[0.00 23.71]
Week 52 (change from Baseline)				
N	278	294	287	289
Mean (SD)	-4.160 (5.900)	-5.950 (6.116)	-4.236 (6.129)	-5.160 (5.866)
Median	-3.455	-4.610	-3.750	-4.110
Min: Max	[-27.79; 16.38]	[-26.86; 10.99]	[-23.72; 18.68]	[-24.48; 14.43]
Difference in LSmeans [1]		-1.180	0.170	-0.733
95% CI for the difference		(-1.979; -0.382)	(-0.632; 0.972)	(-1.534; 0.068)
P-value		0.004	0.678	0.073

Note: Pairwise comparisons are for descriptive purposes only.
[1] ANCOVA, main effect model. Difference is VEGF Trap-Eye minus ranibizumab; C.I. = confidence interval was calculated using a normal approximation.

4.7.4. Secondary Quality of Life Endpoint

In both studies, quality of life as measured using the NEI-VFQ-25 improved in all treatment groups. Minor differences between treatment groups in one study were not reproduced in the second study, consistent with the notion that all treatments had similar effects and that any differences were due to random variability. Of note, improvement in quality of life in the 2Q8 arm may be underestimated from what might be obtained in clinical practice because, in these studies, patients in the 2Q8 treatment arm had to come to the clinic monthly and undergo sham procedures. Neither of these measures, instituted in these studies to mask patients and assessors to treatment, would be necessary with the anticipated clinical use of VEGF Trap-Eye.

4.7.4.1. VIEW 1: Change in NEI-VFQ -25 Scores at Week 52

Mean changes in total NEI-VFQ-25 scores at Week 52 are summarized in Table 24. A clinically relevant improvement in mean NEI VFQ-25 scores was seen in all treatment groups at Week 52. Mean (±SD) improvements ranged from 4.5 (±11.87) in the 0.5Q4 group to 6.7 (±13.50) in the 2Q4 group; mean improvement in the ranibizumab and 2Q8 groups were virtually identical (4.9 ± 14.01 and 5.1 ± 14.74, respectively).

Table 24: VIEW 1 - Change from Baseline to Week 52 in Total NEI VFQ-25 Score (LOCF; FAS)

	RQ4	2Q4	0.5Q4	2Q8
Baseline				
n	303	300	297	293
Mean (SD)	71.8 (17.16)	70.4 (16.60)	71.1 (17.77)	69.6 (16.83)
Week 52				
n	300	302	292	299
Mean (SD)	76.8 (16.09)	77.0 (16.92)	75.4 (17.37)	74.6 (17.68)
Week 52 (change from baseline)				
n	300	298	289	292
Mean (SD)	4.9 (14.01)	6.7 (13.50)	4.5 (11.87)	5.1 (14.74)
Point estimate for the contrast[a]		1.28	-0.67	-0.60
95.1% CI for difference		(-0.73 , 3.28)	(-2.69 , 1.35)	(-2.61, 1.42)
p-value vs RQ4[b]		0.2090	0.5128	0.5579

[a] Difference is VEGF Trap-Eye minus ranibizumab using LSMeans. Positive values are in favor of VEGF Trap-Eye. CI=confidence interval calculated using normal approximation.
[b] ANCOVA, main effect model using LSMeans.

4.7.4.2. VIEW 2: Change in NEI-VFQ -25 Scores at Week 52

Mean changes in total NEI VFQ-25 scores are summarized in Table 25. A clinically relevant improvement in mean NEI VFQ-25 scores was seen in all treatment groups at Week 52. Mean (±SD) improvements ranged from 4.5 (±15.0) in the 2Q4 group to 6.3 (±14.8) in the RQ4 group. Comparisons did not indicate a relevant difference between the RQ4 and the 0.5Q4 and 2Q8 groups (ie, 95% CI of the differences contained zero) and, although a difference between RQ4 and 2Q4 is suggested by the data (95% CI of -4.90 to -0.68), both groups experienced a clinically significant improvement in total NEI VFQ-25 scores.

Table 25: VIEW 2 - Change from Baseline to Week 52 in Total NEI VFQ-25 Score (LOCF; FAS)

	RQ4	2Q4	0.5Q4	2Q8
Baseline				
n	291	309	295	306
Mean (SD)	72.9 (19.1)	70.3 (19.4)	74.0 (18.2)	71.3 (19.1)
Week 52				
n	287	304	291	299
Mean (SD)	79.5 (16.7)	74.6 (19.2)	79.1 (16.8)	76.4 (19.3)
Week 52 (change from baseline)				
n	287	304	290	299
Mean (SD)	6.3 (14.8)	4.5 (15.0)	5.1 (13.7)	4.9 (14.7)
Point estimate for the contrast[a]		-2.79	-0.93	-1.95
95% CI for difference		(-4.90; -0.68)	(-3.07; 1.20)	(-4.07; 0.17)
p-value vs RQ4[b]		0.010	0.392	0.072

[a] Difference is VEGF Trap-Eye minus ranibizumab using LSMeans. Positive values are in favor of VEGF Trap-Eye. CI=confidence interval calculated using normal approximation.
[b] ANCOVA, main effect model using LSMeans.

4.7.5. Subgroup Analysis of Efficacy

Subgroup analyses were performed for the VIEW 1 and VIEW 2 studies and as part of the integrated analysis of the pooled data from the pivotal studies. Subgroup analyses by age, sex, race, ethnicity, renal function, history of hepatic impairment, baseline visual acuity, and baseline lesion size and type were to be performed contingent upon the availability of adequate sample size, for the following 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), change from baseline in total NEI VFQ-25 score at week 52 (FAS), change from baseline in CNV area at week 52 (FAS), and change from baseline in CRT at week 52 (FAS).

In the individual pivotal studies, some subgroups comprised too few subjects (i.e., less than 10% of all subjects) to allow for a meaningful comparison. With the combination of subjects from both studies, most subgroups in the integrated analysis of the pooled data from the pivotal studies comprised an adequate number of subjects for assessment. In the integrated analysis, however, the Black subgroup of race and positive history of hepatic impairment still comprised too few subjects for an adequate comparison. Nonetheless, there were no notable differences in these subgroups. For analysis of renal impairment in the integrated analysis of the pooled data from the pivotal studies, the moderate renal impairment and severe renal impairment subgroups were combined into one subgroup.

Few differences were noted between treatments within the individual studies (not shown) and the integrated analysis of the pooled data from the VIEW 1 and VIEW 2 studies (Figure 16, Figure 17, and Figure 18). More common were apparent differences between subgroups for a given parameter (e.g., younger subjects performing subjectively different from older subjects regardless of treatment group). No formal testing of the differences between subgroups was performed. Overall, all efficacy results in all evaluable subgroups in each pivotal study and in the integrated analysis were consistent with the results in the overall populations.

In addition to analysis by subgroup, in VIEW 2, centers were pooled, prior to unmasking of the data, into 8 "geographic" regions, so that the ratio of the largest to the smallest region did not exceed 2 (i.e., pooling of centers was based more on the number of randomized subjects than geography). Adjustment for region did not alter the VIEW 2 efficacy results.

Figure 16: Subgroup Analysis – VEGF Trap-Eye 2Q4: Primary Endpoint (% Maintenance of Vision) (Integrated Data, PPS, LOCF)

Subgroup	n (%)	% (95% CI)
Gender		
Male	214 (96.4)	-2.4 (-6.3, 1.6)
Female	319 (94.7)	0.1 (-3.3, 3.6)
Age		
<65	63 (100.0)	-3.8 (-9.1, 1.4)
≥65-<75	158 (96.3)	-4.0 (-9.1, 1.1)
≥75	312 (94.0)	0.9 (-2.7, 4.4)
Race		
White	449 (94.7)	0.0 (-2.9, 2.9)
Asian	63 (98.4)	-1.8 (-7.5, 3.9)
Base Visual Acuity		
<35	53 (100.0)	-3.2 (-9.5, 3.1)
≥35-<50	112 (95.7)	-1.5 (-7.7, 4.7)
≥50	368 (94.6)	-0.8 (-4.1, 2.5)
Area of CNV		
≤4DA (10.16 mm2)	399 (96.1)	-1.8 (-4.7, 1.1)
>4DA (10.16 mm2)	131 (92.9)	1.6 (-4.2, 7.5)
CNV Type		
Occult, no classic	206 (97.2)	-2.0 (-5.7, 1.7)
Minimally classic	183 (92.4)	2.7 (-2.1, 7.5)
Predominantly classic	140 (96.6)	-3.8 (-9.0, 1.4)

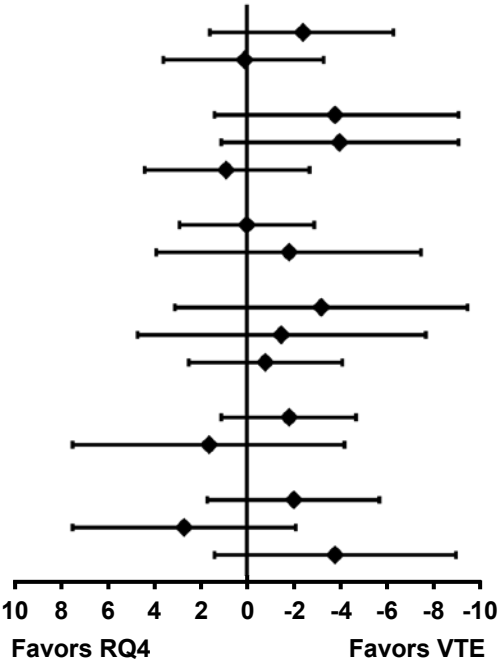


Figure 17: Subgroup Analysis – VEGF Trap-Eye 0.5Q4: Primary Endpoint (% Maintenance of Vision) (Integrated Data, PPS, LOCF)

Subgroup	n (%)	% (95% CI)
Gender		
Male	246 (95.7)	-1.7 (-5.6, 2.3)
Female	271 (96.4)	-1.6 (-4.9, 1.7)
Age		
<65	58 (98.3)	-1.2 (-6.1, 3.7)
≥65-<75	135 (97.1)	-4.8 (-9.8, 0.3)
≥75	324 (95.3)	-0.5 (-3.8, 2.9)
Race		
White	443 (96.1)	-1.4 (-4.1, 1.4)
Asian	57 (98.3)	-1.6 (-7.6, 4.4)
Base Visual Acuity		
<35	59 (96.7)	1.6 (-4.7, 8.0)
≥35-<50	101 (97.1)	-2.9 (-8.9, 3.0)
≥50	357 (95.7)	-1.9 (-5.1, 1.3)
Area of CNV		
≤4DA (10.16 mm2)	398 (96.8)	-2.5 (-5.3, 0.3)
>4DA (10.16 mm2)	119 (93.7)	0.8 (-5.0, 6.7)
CNV Type		
Occult, no classic	204 (98.1)	-2.9 (-6.3, 0.6)
Minimally classic	172 (94.0)	1.2 (-3.4, 5.8)
Predominantly classic	141 (95.9)	-3.1 (-8.5, 2.3)

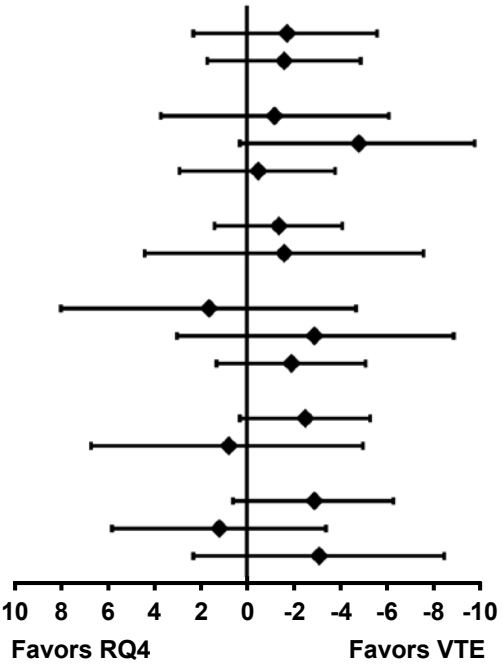
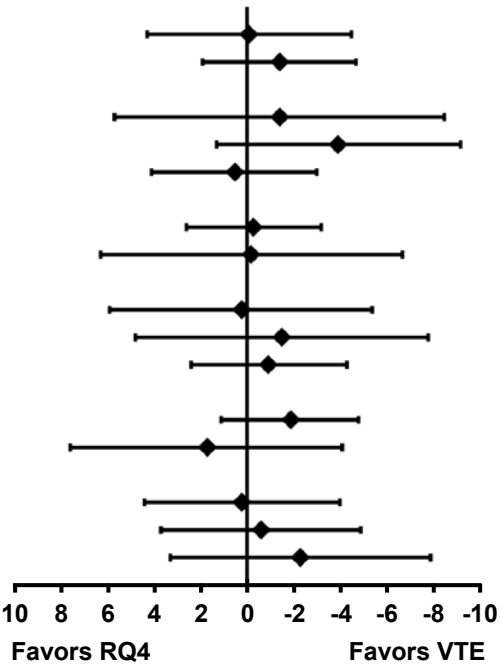


Figure 18: Subgroup Analysis – VEGF Trap-Eye 2Q8: Primary Endpoint (% Maintenance of Vision) (Integrated Data, PPS, LOCF)

Subgroup	n (%)	% (95% CI)
Gender		
Male	207 (94.1)	-0.1 (-4.5, 4.3)
Female	303 (96.2)	-1.4 (-4.7, 1.9)
Age		
<65	64 (98.5)	-1.4 (-8.5, 5.7)
≥65-<75	132 (96.4)	-3.9 (-9.2, 1.3)
≥75	314 (94.3)	0.5 (-3.0, 4.1)
Race		
White	422 (95.0)	-0.3 (-3.2, 2.6)
Asian	64 (97.0)	-0.2 (-6.7, 6.3)
Base Visual Acuity		
<35	58 (98.3)	0.2 (-5.4, 5.9)
≥35-<50	110 (95.7)	-1.5 (-7.8, 4.8)
≥50	342 (94.7)	-0.9 (-4.3, 2.4)
Area of CNV		
≤4DA (10.16 mm2)	380 (96.2)	-1.9 (-4.8, 1.1)
>4DA (10.16 mm2)	129 (92.8)	1.7 (-4.1, 7.6)
CNV Type		
Occult, no classic	191 (95.0)	0.2 (-4.0, 4.4)
Minimally classic	179 (95.7)	-0.6 (-4.9, 3.7)
Predominantly classic	138 (95.2)	-2.3 (-7.9, 3.3)



4.7.6. Efficacy Conclusions

Administration of 2 mg VEGF Trap-Eye every two months produced essentially the same efficacy results as monthly dosing of 2 mg or 0.5 mg VEGF Trap-Eye or monthly dosing of 0.5 mg ranibizumab, the current standard of care for subjects with wet AMD.

Both pivotal studies and the integrated analysis of the pooled data from the pivotal studies fully met the stated primary endpoint. The proportions of subjects who maintained vision in the different VEGF Trap-Eye groups each exceeded 95% and were numerically similar and clearly non-inferior to the proportion in the ranibizumab group, even in the VEGF Trap-Eye group with dosing every two months. Although the statistical analysis plans stated a pre-specified non-inferiority margin of 10%, non-inferiority was clearly established at a substantially smaller margin. The non-inferiority of the different VEGF Trap-Eye dosing regimens was confirmed in all sensitivity analyses, even those using the WOCF method. Thus, with respect to efficacy, both drugs, VEGF Trap-Eye and ranibizumab, can be considered clinically equivalent.

At the 1-year endpoint in both pivotal studies as well as in the integrated analysis combining the two studies, VEGF Trap-Eye dosed every two months, following three initial monthly loading doses, demonstrated strikingly similar improvements in all visual acuity endpoints compared to the ranibizumab group dosed monthly; in the integrated analysis combining the results from VIEW1 and VIEW 2, the gain in letters for these two groups was remarkably similar and within half a letter, corresponding to 8.4 letters for the 2Q8 regimen as compared to 8.7 letters for monthly ranibizumab.

Improvements in visual acuity coincided with rapid, consistent, and robust responses in morphologic endpoints (as assessed by FA and OCT) in all dosing groups. It is important to note that the 2Q8 regimen produced numerically greater decreases in CRT (determined by OCT), as compared to monthly ranibizumab, in both VIEW 1 and VIEW 2, since longer-interval or as-needed dosing of ranibizumab compared to monthly ranibizumab does not seem to provide similar anatomical benefit, as most recently confirmed in the CATT study; some believe that CRT by OCT is a useful biomarker of sufficient and ongoing VEGF blockade.

In general, the results of the subgroup analyses were consistent with those seen with the overall population and no clinically relevant or consistent differences between treatment groups were observed.

Thus, the key finding is that with 2 mg VEGF Trap-Eye dosed every two months, patients with wet AMD can undergo less frequent intravitreal injections without sacrificing efficacy as assessed by visual acuity or anatomic disease control as determined using morphological endpoints. Moreover, monthly monitoring of patients, a requirement with monthly anti-VEGF therapy and as-needed dosing schemes, appears generally unnecessary with this regimen. According to the protocols for the two pivotal studies (VIEW 1 and VIEW 2), subjects in the 2Q8 groups did not undergo any treatment modifications based on the interim (sham) visits nor were they permitted to be re-dosed at these visits, but these subjects still experienced similar benefits to those in the RQ4 group, confirming the lack of utility or need for these interim visits.

4.8. Safety Results

Safety data were consistent across the VIEW 1 and VIEW 2 studies. Therefore, the data from these studies were combined to provide greater precision and the integrated results are presented in this document.

4.8.1. Patient Exposure

During the first year of treatment, planned exposure to VEGF Trap-Eye in the study eye was 2 mg administered monthly (13 IVT injections, 26 mg/yr) or every 2 months (8 IVT injections, 16 mg/yr), or 0.5 mg administered monthly (13 IVT injections, 6.5 mg/yr), and planned exposure to ranibizumab was 0.5 mg administered monthly (13 IVT injections, 6.5 mg/yr). The mean number of injections administered was similar among the monthly dosing regimens (12.3 in the RQ4, 12.3 in the 2Q4, and 12.2 in the 0.5Q4 groups) and just over half of that in the 2Q8 treatment group (7.5) (Table 26). The total mean exposure was 6.08 mg (RQ4), 24.62 mg (2Q4), 6.08 mg (0.5Q4), and 14.93 mg (2Q8) (Table 26), over a mean duration of 347 to 353 days (Table 27).

Table 26: Exposure in the First Year (Number of Active Injections) (Safety Analysis Set)

	R 0.5 mg Q4 N=595 (100%)	VTE 2.0 mg Q4 N=613 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q8 N=610 (100%)	VTE total N=1824 (100%)
Number of active injections					
Sum	7301	7570	7323	4586	19479
Mean (SD)	12.3 (1.9)	12.3 (1.8)	12.2 (2.2)	7.5 (1.2)	10.7 (2.9)
Median	13.0	13.0	13.0	8.0	12.0
Min: Max	1: 13	1: 13	1: 13	1: 9	1: 13
Total amount (mg)					
Mean (SD)	6.08 (1.01)	24.62 (3.56)	6.08 (1.10)	14.93 (2.79)	15.27 (8.03)
Median	6.50	26.00	6.50	16.00	16.00
Min: Max	0.5: 8.0	2.0: 28.0	0.5: 8.0	0.0: 34.0	0.0: 34.0

VTE=VEGF Trap-Eye

Table 27: Treatment Duration (Number of Days) (Safety Analysis Set)

	R 0.5 mg Q4 N=595 (100%)	VTE 2.0 mg Q4 N=613 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q8 N=610 (100%)	VTE total N=1824 (100%)
Treatment Duration (DAYS) [1]					
N	595	613	601	610	1824
Mean (SD)	351.6 (51.9)	353.2 (47.3)	348.6 (59.7)	347.4 (60.1)	349.8 (56.0)
Median	364.0	364.0	364.0	364.0	364.0
Min: Max	28: 378	28: 400	28: 385	28: 385	28: 400

VTE=VEGF Trap-Eye

[1] Treatment duration (days) is calculated as last dose date – first dose date + 28

4.8.2. Safety Summary

4.8.2.1. Safety Summary: VIEW 1

An overview of the overall AE experience in the first year of study is provided in Table 28. Almost all subjects (92% to 95% of subjects in each treatment group) experienced at least 1 TEAE during the first year of the study and no dose-response was observed. Overall, the incidences of TEAEs, ocular TEAEs in the study eye, and non-ocular TEAEs were similar among treatment groups. The incidence of severe ocular and non-ocular TEAEs was numerically lower with VEGF Trap-Eye than in the ranibizumab group. The incidences TEAEs that led subjects to discontinue study drug, SAEs, and death were low in all treatment groups. Deaths occurred in all treatment groups: RQ4 (5 subjects), 2Q4 (1 subject), 0.5Q4 (1 subject), and 2Q8 (7 subjects). In addition, 3 deaths occurred during year 1 that were not captured in the clinical dataset: 1 death in the 2Q4 group was reported 54 days after the last dose, and 1 death in each of the 0.5Q4 and 2Q8 groups were recorded on the end-of-study CRF page, and not on the AE CRF page.

Table 28: VIEW 1: Overall Summary of Treatment-Emergent Adverse Events (TEAEs) (Safety Analysis Set)

	R 0.5 mg Q4 N=304 (100%)	VTE 2.0 mg Q4 N=304 (100%)	VTE 0.5 mg Q4 N=304 (100%)	VTE 2.0 mg Q8 N=303 (100%)	TOTAL VTE N=911 (100%)
Any TEAE[a]	290 (95.4%)	281 (92.4%)	280 (92.1%)	289 (95.4%)	850 (93.3%)
Any non-ocular TEAE	234 (77.0%)	220 (72.4%)	231 (76.0%)	223 (73.6%)	674 (74.0%)
Any severe non-ocular TEAE	35 (11.5%)	21 (6.9%)	34 (11.2%)	28 (9.2%)	83 (9.1%)
Any ocular TEAE (study eye)	246 (80.9%)	228 (75.0%)	226 (74.3%)	238 (78.5%)	692 (76.0%)
Any severe ocular TEAE (study eye)	13 (4.3%)	11 (3.6%)	8 (2.6%)	4 (1.3%)	23 (2.5%)
Any death[b]	5 (1.6%)	1 (0.3%)	1 (0.3%)	7 (2.3%)	9 (1.0%)
Any TE SAE[c]	68 (22.4%)	46 (15.1%)	56 (18.4%)	56 (18.5%)	158 (17.3%)
Any non-ocular TE SAE	57 (18.8%)	40 (13.1%)	50 (16.5%)	51 (16.8%)	141 (15.4%)
Any ocular TE SAE (Study Eye)	10 (3.3%)	7 (2.3%)	6 (2.0%)	3 (1.0%)	16 (1.8%)
Any TEAE causing disc. of study drug	5 (1.6%)	3 (1.0%)	5 (1.6%)	3 (1.0%)	11 (1.2%)

VTE=VEGF Trap-Eye

[a] Includes patients with TEAEs in the fellow eye

[b] Does not include 1 death in the 2Q4 group reported 54 days after the last dose, and 1 death in each of the 0.5Q4 and 2Q8 groups recorded on the end-of-study CRF page, and not on the AE CRF page

[c] Includes patients with TE SAEs in the fellow eye

4.8.2.2. Safety Summary: VIEW 2

An overview of the overall AE experience in the first year of study is provided in Table 29. Almost all subjects (85% to 90% of subjects in each treatment group) experienced at least 1 TEAE during the first year of the study and no dose-response was observed. Overall, the incidences of TEAEs, ocular TEAEs in the study eye, and non-ocular TEAEs were similar among treatment groups. The incidence of severe ocular and non-ocular TEAEs, which in VIEW 1 had been numerically lower in the VEGF Trap-Eye group, was in VIEW 2 numerically lower in the ranibizumab group than in the VEGF Trap-Eye groups. The incidences of TEAEs

that led subjects to discontinue study drug, SAEs, and death were low in all treatment groups. Deaths occurred in all treatment groups: RQ4 (2 subjects), 2Q4 (3 subjects), 0.5Q4 (2 subjects), and 2Q8 (2 subjects).

Table 29: VIEW 2: Overall Summary of Treatment-Emergent Adverse Events (TEAEs) (Safety Analysis Set)

	R 0.5 mg Q4 N=291 (100%)	VTE 2.0 mg Q4 N=309 (100%)	VTE 0.5 mg Q4 N=297 (100%)	VTE 2.0 mg Q8 N=307 (100%)	TOTAL VTE N=913 (100%)
Any TEAE[a]	248 (85.2)	274 (88.7)	255 (85.9%)	276 (89,9%)	805 (88.2%)
Any non-ocular TEAE	181 (62.2%)	231 (74.8%)	206 (69.4%)	213 (69.4%)	650 (71.2%)
Any severe non-ocular TEAE	15 (5.2%)	19 (6.1%)	25 (8.4%)	27 (8.8%)	71 (7.8%)
Any ocular TEAE (study eye)	187 (64.3%)	191 (61.8%)	182 (61.3%)	198 (64.5%)	571 (62.5%)
Any severe ocular TEAE (study eye)	6 (2.1%)	10 (3.2%)	19 (6.4%)	13 (4.2%)	42 (4.6%)
Any death[b]	2 (0.7%)	3 (1.0%)	2 (0.7%)	2 (0.7%)	7 (0.8%)
Any TE SAE[c]	35 (12.0%)	49 (15.9%)	41 (13.8%)	48 (15.6%)	138 (15.1%)
Any non-ocular TE SAE	26 (8.9%)	36 (11.7%)	37 (12.5%)	38 (12.4%)	111 (12.2%)
Any ocular TE SAE (Study Eye)	9 (3.1%)	6 (1.9%)	5 (1.7%)	9 (2.9%)	20 (2.2%)
Any TEAE causing disc. of study drug	4 (1.4%)	12 (3.9%)	14 (4.7%)	10 (3.3%)	36 (3.9%)

VTE=VEGF Trap-Eye

[a] Includes patients with TEAEs in the fellow eye

[b] Includes 2 deaths not considered "treatment-emergent" because the underlying fatal AEs started more than 30 days after the last administration of study drug.

[c] Includes patients with TE SAEs in the fellow eye

4.8.2.3. Safety Summary: Integrated data

An overview of the overall AE experience in the first year of study is provided in Table 30. Pooling of the data from the two studies is supported by the nearly identical size and design of the two studies and because both utilized the same 1:1:1:1 randomization scheme. The integrated data are consistent with those of the individual studies. The small numeric imbalances that in one study favored ranibizumab and in the other favored VEGF Trap-Eye are no longer apparent in the more robust integrated data set, consistent with their being chance observations. Because the integrated data provide additional precision over the data from the individual studies, the integrated safety data are presented in subsequent sections of this briefing book.

Table 30: Overall Summary of Treatment-Emergent Adverse Events (TEAEs) (Integrated Data) (Safety Analysis Set)

	R 0.5 mg Q4 N=595 (100%)	VTE 2.0 mg Q4 N=613 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q8 N=610 (100%)	VTE total N=1824 (100%)	TOTAL N=2419 (100%)
Number (%) of subjects with:						
Any TEAE	538 (90.4%)	555 (90.5%)	535 (89.0%)	565 (92.6%)	1655 (90.7%)	2193 (90.7%)
Any non-ocular TEAE	415 (69.7%)	451 (73.6%)	437 (72.7%)	436 (71.5%)	1324 (72.6%)	1739 (71.9%)
Any severe non-ocular TEAE	50 (8.4%)	40 (6.5%)	59 (9.8%)	55 (9.0%)	154 (8.4%)	204 (8.4%)
Any ocular TEAE (study eye)	433 (72.8%)	419 (68.4%)	408 (67.9%)	436 (71.5%)	1263 (69.2%)	1696 (70.1%)
Any severe ocular TEAE (study eye)	19 (3.2%)	21 (3.4%)	27 (4.5%)	17 (2.8%)	65 (3.6%)	84 (3.5%)
Any TEAE leading to death [1,2]	7 (1.2%)	2 (0.3%)	3 (0.5%)	8 (1.3%)	13 (0.7%)	20 (0.8%)
Any TE SAE	103 (17.3%)	95 (15.5%)	97 (16.1%)	104 (17.0%)	296 (16.2%)	399 (16.5%)
Any non-ocular TE SAE	83 (13.9%)	76 (12.4%)	87 (14.5%)	89 (14.6%)	252 (13.8%)	335 (13.8%)
Any ocular TE SAE (Study Eye)	19 (3.2%)	13 (2.1%)	11 (1.8%)	12 (2.0%)	36 (2.0%)	55 (2.3%)
Any TEAE causing disc. of study drug	9 (1.5%)	15 (2.4%)	19 (3.2%)	13 (2.1%)	47 (2.6%)	56 (2.3%)

Note: This Table is summarizing all subjects with treatment emergent adverse events starting post first injection
VTE = VEGF Trap-Eye

[1] SAEs resulting in death or AEs with fatal outcome.

[2] This Table only includes deaths associated with fatal SAEs that began within 30 days of the last administration of study drug. A total of 26 subjects died in the 2 studies combined: 7, 5, 4, and 10 in the RQ4, 2Q4, 0.5Q4, and 2Q8 groups, respectively.

4.8.3. Ocular Safety

4.8.3.1. Ocular Treatment Emergent Adverse Events in the Study Eye

Ocular TEAEs in the study eye were reported by 70.1% of subjects in VIEW 1 and VIEW 2. The frequency of ocular TEAEs was similar across treatment groups: (72.8% [RQ4], 68.4% [2Q4], 67.9% [0.5Q4], and 71.5% [2Q8]).

The most common adverse events (>5%) reported in patients receiving VEGF Trap-Eye and not related to the underlying disease process were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. In addition, macular degeneration, retinal hemorrhage, and visual acuity reduced were reported as adverse events in >5% of patients.

All TEAEs were reported with similar frequency across the treatment groups and were generally consistent with disease progression, or with the expected adverse consequences of the injection procedure (Table 31).

It should be emphasized that, to maintain masking of patients and assessors, patients in the 2Q8 treatment group received the same number of ocular interventions as patients in the Q4 groups. That is, at sham injection visits, patients' eyes were prepped for an intraocular injection, including the use of subconjunctival anesthesia where that was the investigator's practice, and the blunt end of the syringe was pressed against the eye to mimic an injection. Ocular AEs typical of those associated with an injection procedure, such as conjunctival hemorrhage and eye

pain, were also reported after these sham injections. Therefore, in the context of this clinical study, a difference in the incidence of ocular TEAEs between the 2Q8 and the Q4 doses would not be expected.

Table 31: Ocular Treatment-Emergent Adverse Events in the Study Eye (in ≥ 5% of Subjects in Any Treatment Group) (by SOC and PT) (Integrated Data) (Safety Analysis Set)

Primary system organ class Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595 (100%)	VTE 2.0 mg Q4 N=613 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q8 N=610 (100%)	VTE total N=1824 (100%)	TOTAL N=2419 (100%)
Number of subjects with at least 1 ocular TEAE	433 (72.8%)	419 (68.4%)	408 (67.9%)	436 (71.5%)	1263 (69.2%)	1696 (70.1%)
Eye disorders						
Conjunctival hemorrhage	167 (28.1%)	133 (21.7%)	157 (26.1%)	161 (26.4%)	451 (24.7%)	618 (25.5%)
Eye pain	53 (8.9%)	66 (10.8%)	49 (8.2%)	43 (7.0%)	158 (8.7%)	211 (8.7%)
Macular degeneration	39 (6.6%)	43 (7.0%)	40 (6.7%)	40 (6.6%)	123 (6.7%)	162 (6.7%)
Retinal hemorrhage	48 (8.1%)	36 (5.9%)	47 (7.8%)	50 (8.2%)	133 (7.3%)	181 (7.5%)
Visual acuity reduced	40 (6.7%)	50 (8.2%)	57 (9.5%)	53 (8.7%)	160 (8.8%)	200 (8.3%)
Vitreous detachment	33 (5.5%)	44 (7.2%)	32 (5.3%)	34 (5.6%)	110 (6.0%)	143 (5.9%)
Vitreous floaters	44 (7.4%)	48 (7.8%)	30 (5.0%)	30 (4.9%)	108 (5.9%)	152 (6.3%)
Investigations						
Intraocular pressure increased	41 (6.9%)	38 (6.2%)	27 (4.5%)	30 (4.9%)	95 (5.2%)	136 (5.6%)

VTE = VEGF Trap-Eye

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

All events reported by at least 5% of subjects are displayed.

4.8.3.2. Serious Treatment Emergent Adverse Events in the Study Eye

The frequency of ocular SAEs in the study eye was low and similar across treatment groups (2.4%, 59 subjects) (Table 32). Most SAEs in the study eye were attributable to the injection procedure or progression of disease. The most commonly occurring ocular SAEs in the study eye were reduced VA (0.6% [15 subjects]), retinal hemorrhage (0.4% [10 subjects]), and endophthalmitis (0.2% [6 subjects]).

Table 32: Ocular Serious Treatment-Emergent Adverse Events in the Study Eye (by SOC and PT) (Integrated Data) (Safety Analysis Set)

Primary SOC Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595	VTE 2.0 mg Q4 N=613	VTE 0.5 mg Q4 N=601	VTE 2.0 mg Q8 N=610	VTE total N=1824	TOTAL N=2419
Number of subjects with at least 1 ocular serious TEAE	20 (3.4%)	14 (2.3%)	12 (2.0%)	13 (2.1%)	39 (2.1%)	59 (2.4%)
Eye disorders	17 (2.9%)	11 (1.8%)	11 (1.8%)	12 (2.0%)	34 (1.9%)	51 (2.1%)
Angle closure glaucoma	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Cataract	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)	4 (0.2%)
Cataract cortical	1 (0.2%)	0	0	0	0	1 (<0.1%)
Cataract nuclear	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Choroidal detachment	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Hyphaema	1 (0.2%)	0	0	0	0	1 (<0.1%)
Keratits	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Macular cyst	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Macular degeneration	0	1 (0.2%)	0	1 (0.2%)	2 (0.1%)	2 (<0.1%)
Macular hole	0	0	2 (0.3%)	0	2 (0.1%)	2 (<0.1%)
Posterior capsule opacification	2 (0.3%)	0	0	0	0	2 (<0.1%)
Retinal degeneration	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	2 (<0.1%)
Retinal detachment	2 (0.3%)	0	2 (0.3%)	0	2 (0.1%)	4 (0.2%)
Retinal hemorrhage	3 (0.5%)	2 (0.3%)	2 (0.3%)	3 (0.5%)	7 (0.4%)	10 (0.4%)
Retinal edema	1 (0.2%)	0	1 (0.2%)	0	1 (<0.1%)	2 (<0.1%)
Retinal pigment epithelial tear	1 (0.2%)	0	1 (0.2%)	2 (0.3%)	3 (0.2%)	4 (0.2%)
Retinal pigment epitheliopathy	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Retinal tear	1 (0.2%)	0	1 (0.2%)	0	1 (<0.1%)	2 (<0.1%)
Visual acuity reduced	5 (0.8%)	2 (0.3%)	3 (0.5%)	5 (0.8%)	10 (0.5%)	15 (0.6%)
Vitreous hemorrhage	1 (0.2%)	0	0	0	0	1 (<0.1%)
Infections and infestations	3 (0.5%)	3 (0.5%)	0	0	3 (0.2%)	6 (0.2%)
Endophthalmitis	3 (0.5%)	3 (0.5%)	0	0	3 (0.2%)	6 (0.2%)
Injury, poisoning and proced. complicat.	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	2 (<0.1%)
Incorrect dose administered	1 (0.2%)	0	0	0	0	1 (<0.1%)
Macular scar	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Investigations	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	2 (0.1%)	3 (0.1%)
Intraocular pressure increased	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	2 (0.1%)	3 (0.1%)

VTE = VEGF Trap-Eye
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

4.8.3.3. Injection-Related Serious Treatment Emergent Adverse Events in the Study Eye

Sixteen of the ocular SAEs reported in the study eye of patients in VIEW 1 and VIEW 2 were considered to be related to the injection procedure; 8 in the ranibizumab treatment group and 8 in the VEGF Trap-Eye groups. In the SOC of eye disorders, SAEs considered to be related to the injection procedure included cataract, cataract cortical, hyphaema, keratitis, macular hole, and retinal hemorrhage. In the SOC of infections and infestations, only endophthalmitis was reported. In addition, 1 incorrect dose of study drug and 2 IOP increased (1 of which was in the subject who received the incorrect dose) were recorded. These injection-related SAEs occurred in fewer than 1 in 1000 injections with either VEGF Trap-Eye or ranibizumab (Table 33).

Table 33: Number of Ocular Injection-Related Treatment Emergent Serious Adverse Events of the Study Eye per Subject (by SOC and PT) (Integrated Data) (Safety Analysis Set)

Primary system organ class Preferred term MedDRA Version 13.1	R 0.5 mg Q4 (N=595) n (n/N) [1]	VTE 2.0 mg Q4 (N=613) n (n/N) [1]	VTE 0.5 mg Q4 (N=601) n (n/N) [1]	VTE 2.0 mg Q8 (N=610) n (n/N) [1]	VTE total (N=1824) n (n/N) [1]	TOTAL (N=2419) n (n/N) [1]
Total number of injections (not including sham)	N1=7301	N1=7570	N1=7323	N1=4586	N1=19479	N1=26780
Total number of events (rate per 100 subjects)	8 (1.3)	6 (1.0)	1 (0.2)	1 (0.2)	8 (0.4)	16 (0.7)
Total number of events (rate per 1000 injections)	8 (1.1)	6 (0. 8)	1 (0.1)	1 (0.2)	8 (0.4)	16 (0.6)
EYE DISORDERS	3	3	1	0	4	7
CATARACT	1	1	0	0	1	2
CATARACT CORTICAL	1	0	0	0	0	1
HYPHAEMA	1	0	0	0	0	1
KERATITIS	0	1	0	0	1	1
MACULAR HOLE	0	0	1	0	1	1
RETINAL HAEMORRHAGE	0	1	0	0	1	1
INFECTIONS AND INFESTATIONS	3	3	0	0	3	6
ENDOPHTHALMITIS	3	3	0	0	3	6
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	0	0	0	0	1
INCORRECT DOSE ADMINISTERED	1	0	0	0	0	1
INVESTIGATIONS	1	0	0	1	1	2
INTRAOCULAR PRESSURE INCREASED	1	0	0	1	1	2

VTE = VEGF Trap-Eye

[1] N = Total number of subjects or total number of injections, not including sham

4.8.3.4. Prespecified Serious Treatment Emergent Adverse Events of Interest in the Study Eye

Analysis of TEAEs of interest was pre-specified in the analysis plan. Serious ocular TEAEs of interest are shown in Table 34. A total of 29 subjects (1.2%) had at least 1 serious ocular TEAE of interest with a similar percentage of subjects in each treatment group experiencing these events (0.8% to 1.5%). The most common were any intraocular inflammatory response (20 subjects, 0.8%); and any clinically significant decrease in BCVA (13 subjects, 0.5%).

Table 34: Ocular Treatment-Emergent Serious Adverse Events of Interest of the Study Eye (by SOC and PT) (Integrated Data) (Safety Analysis Set)

Primary system organ class Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595	VTE 2.0 mg Q4 N=613	VTE 0.5 mg Q4 N=601	VTE 2.0 mg Q8 N=610	VTE total N=1824	TOTAL N=2419
Number of subjects with at least 1 ocular treatment-emergent serious AEI of study eye	9 (1.5%)	7 (1.1%)	5 (0.8%)	8 (1.3%)	20 (1.1%)	29 (1.2%)
Visual acuity reduced	3 (0.5%)	2 (0.3%)	3 (0.5%)	5 (0.8%)	10 (0.5%)	13 (0.5%)
Endophthalmitis	3 (0.5%)	3 (0.5%)	0	0	3 (0.2%)	6 (0.2%)
Retinal pigment epithelial tear	1 (0.2%)	0	1 (0.2%)	2 (0.3%)	3 (0.2%)	4 (0.2%)
Intraocular pressure increased	1 (0.2%)	0	0	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Hyphemia	1 (0.2%)	0	0	0	0	1 (<0.1%)
Keratitis	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Macular hole	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Retinal hemorrhage	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)

VTE = VEGF Trap-Eye

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

4.8.4. Non-Ocular Safety

4.8.4.1. Serious Treatment Emergent Adverse Events

In the VIEW 1 and VIEW 2 studies, 14.4% (349) subjects had at least 1 non-ocular SAE: 14.6% (RQ4), 13.1% (2Q4), 14.8% (0.5Q4), and 15.2% (2Q8) (Table 35).

Most non-ocular SAEs were reported in the following SOCs:

- Cardiac disorders were reported in 79 (3.3%) subjects. The most commonly occurring cardiac TEAEs were myocardial infarction (18 subjects, 0.7%), atrial fibrillation (17 subjects, 0.7%), coronary artery disease (9 subjects, 0.4%), and cardiac failure, congestive (8 subjects, 0.3%); all cardiac SAEs occurred with similar frequency across the treatment groups.
- Infections and infestations were reported in 64 (2.6%) subjects in total. The most commonly occurring TEAE in this SOC was pneumonia (in 22 subjects, 0.9%). All other TEAEs in this SOC occurred in < 1% of subjects overall.
- Neoplasms benign, malignant and unspecified (including polyps) were reported in 63 (2.6%) subjects in total. The most commonly occurring TEAEs in this SOC were squamous cell carcinoma of skin (9 subjects, 0.4%), and breast cancer (7 subjects, 0.3%).
- Nervous system disorders were reported in 41 (1.7%) subjects in total. The most commonly occurring nervous system TEAEs were transient ischemic attack (TIA) (10 subjects, 0.4%), and CVA (8 subjects, 0.3%). The incidence of nervous system

disorders was lowest in the ranibizumab treatment group; no subject in the RQ4 group had a TIA.

All non-ocular SAEs occurred with similar frequency across the treatment groups (Table 35).

Table 35: Non-Ocular Serious Treatment-Emergent Adverse Events (by SOC) (Integrated Data) (Safety Analysis Set)

Primary system organ class MedDRA Version 13.1	R 0.5 mg Q4 N=595	VTE 2.0 mg Q4 N=613	VTE 0.5 mg Q4 N=601	VTE 2.0 mg Q8 N=610	VTE total N=1824	TOTAL N=2419
Number of subjects with at least 1 non-ocular serious TEAE	87 (14.6%)	80 (13.1%)	89 (14.8%)	93 (15.2%)	262 (14.4%)	349 (14.4%)
Blood system and lymphatic disorders	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	4 (0.2%)	4 (0.2%)
Cardiac disorders	20 (3.4%)	17 (2.8%)	19 (3.2%)	23 (3.8%)	59 (3.2%)	79 (3.3%)
Congenital, familial, and genetic disorders	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Ear and labyrinth disorders	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (0.2%)	4 (0.2%)	5 (0.2%)
Gastrointestinal disorders	5 (0.8%)	8 (1.3%)	10 (1.7%)	9 (1.5%)	27 (1.5%)	32 (1.3%)
General disorders and administration site conditions	4 (0.7%)	7 (1.1%)	3 (0.5%)	3 (0.5%)	13 (0.7%)	17 (0.7%)
Hepatobiliary disorders	4 (0.7%)	5 (0.8%)	1 (0.2%)	1 (0.2%)	7 (0.4%)	11 (0.5%)
Infections and infestations	21 (3.5%)	11 (1.8%)	11 (1.8%)	21 (3.4%)	43 (2.4%)	64 (2.6%)
Injury, poisoning, and procedural complications	7 (1.2%)	8 (1.3%)	12 (2.0%)	15 (2.5%)	35 (1.9%)	42 (1.7%)
Investigations	0	3 (0.5%)	0	1 (0.2%)	4 (0.2%)	4 (0.2%)
Metabolism and nutritional disorders	4 (0.7%)	4 (0.7%)	3 (0.5%)	3 (0.5%)	10 (0.5%)	14 (0.6%)
Musculoskeletal and connective tissue disorders	7 (1.2%)	4 (0.7%)	1 (0.2%)	5 (0.8%)	10 (0.5%)	17 (0.7%)
Neoplasms benign malignant and unspecified (incl. cysts and polyps)	14 (2.4%)	13 (2.1%)	19 (3.2%)	17 (2.8%)	49 (2.7%)	63 (2.6%)
Nervous system disorders	3 (0.5%)	14 (2.3%)	15 (2.5%)	9 (1.5%)	38 (2.1%)	41 (1.7%)
Psychiatric disorders	2 (0.3%)	0	0	3 (0.5%)	3 (0.2%)	5 (0.2%)
Renal and urinary disorders S	1 (0.2%)	1 (0.2%)	2 (0.3%)	3 (0.5%)	6 (0.3%)	7 (0.3%)
Reproductive system and breast disorders	0	2 (0.3%)	0	1 (0.2%)	3 (0.2%)	3 (0.1%)
Respiratory, thoracic and mediastinal disorders	6 (1.0%)	8 (1.3%)	4 (0.7%)	7 (1.1%)	19 (1.0%)	25 (1.0%)
Skin and subcutaneous tissue disorders	2 (0.3%)	1 (0.2%)	2 (0.3%)	1 (0.2%)	4 (0.2%)	6 (0.2%)
Surgical and medical procedures	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)	5 (0.2%)
Vascular disorders	8 (1.3%)	4 (0.7%)	5 (0.8%)	7 (1.1%)	16 (0.9%)	24 (1.0%)

VTE = VEGF Trap-Eye
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

4.8.4.2. Treatment-Emergent Serious Adverse Events of Interest

Analysis of non-ocular TEAEs of interest was pre-specified in the analysis plan. These TEAEs of interest were identified based on known unfavorable effects associated with systemic administration of VEGF inhibitors or on pre-clinical study results with VEGF Trap (see Section 3.3). In total there were 65 subjects with at least one serious non-ocular TEAE of Interest, nearly all of which were reports of hypertension or arterial thromboembolic events.

4.8.4.2.1. Hypertension: Serious Adverse Events of Interest

Serious adverse events of interest consistent with hypertension occurred in a combined total of 8 (0.3%) subjects in the VIEW 1 and VIEW 2 studies. The most common events were hypertension and hypertensive crisis (Table 36).

Table 36: Serious Adverse Events of Interest (Integrated Data) (Hypertension)

Primary system organ class Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595	VTE 2.0 mg Q4 N=613	VTE 0.5 mg Q4 N=601	VTE 2.0 mg Q8 N=610	VTE total N=1824	TOTAL N=2419
Hypertension	2 (0.3%)	1 (0.2%)	2 (0.3%)	3 (0.5%)	6 (0.3%)	8 (0.3%)
Blood pressure increased	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Hypertension	2 (0.3%)	0	2 (0.3%)	0	2 (0.1%)	4 (0.2%)
Hypertensive crisis	0	1 (0.2%)	0	1 (0.2%)	2 (0.1%)	2 (<0.1%)
Hypertensive encephalopathy	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)

VTE = VEGF Trap-Eye

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

4.8.4.2.2. Arterial Thromboembolic Events

The analysis plan prespecified an analysis of a wide range of terms consistent with potential arterial thromboembolic events. A second analysis was then performed post-hoc using a masked adjudication process and the standardized definitions from the Anti-Platelet Trialists' Collaboration (APTC) (Antiplatelet Trialists' Collaboration 1994; Antiplatelet Trialists' Collaboration 2002).

4.8.4.2.2.1. Pre-specified Potential Arterial Thromboembolic Events of Interest

A pre-specified grouping of serious adverse events of interest consistent with potential arterial thromboembolic events (potential ATEs) occurred in a combined total of 54 (2.2%) subjects in the VIEW 1 and VIEW 2 studies, with a range of 1.3% of subjects in the ranibizumab group to 3.2% in the 0.5Q4 VEGF Trap-Eye group (Table 37). Although this was a prespecified grouping of events, it is a mixture of both so-called "soft" events (such as transient ischemic attacks, or TIAs) together with "hard" endpoint events (i.e., myocardial infarction, stroke, and vascular death). In addition, these potential ATE events did not exhibit an obvious dose response among the VEGF Trap-EYE dosing regimens (with the lowest rate in the highest dose 2Q4 group, and the highest rate in the lowest dose 0.5Q4 group), and the lower rate within the ranibizumab group could largely be attributable to a lower rate of so-called soft-events such as TIAs. This is in contrast to the rates of "hard" endpoint events that have historically been reported for ranibizumab in this elderly population, including within its product labeling. Moreover, in this analysis, these potential ATE events were tabulated as reported by the treating ophthalmologist, and were not independently evaluated or adjudicated. Nevertheless, concerns about the numeric differences between the VEGF Trap-Eye groups and the ranibizumab group compelled us to do a more rigorous follow-up analysis. To further address these concerns, we adopted the approach described in the ranibizumab product labeling and assessed these events based on the endpoint defined by the Anti-Platelet Trialists' Collaboration (Section 4.8.4.2.2.2). A masked expert adjudication committee ensured that these events were properly assessed and categorized.

Table 37: Serious Adverse Events of Interest (Integrated Data) (Potential Arterial Thromboembolic Events)

Primary system organ class Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595	VTE 2.0 mg Q4 N=613	VTE 0.5 mg Q4 N=601	VTE 2.0 mg Q8 N=610	VTE total N=1824	TOTAL N=2419
Grouping of potential arterial thomboembolic events	8 (1.3%)	13 (2.1%)	19 (3.2%)	14 (2.3%)	46 (2.5%)	54 (2.2%)
Acute coronary syndrome	0	3 (0.5%)	2 (0.3%)	1 (0.2%)	6 (0.3%)	6 (0.2%)
Acute myocardial infarction	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)	4 (0.2%)
Carotid artery stenosis	0	2 (0.3%)	0	0	2 (0.1%)	2 (<0.1%)
Cerebral artery thrombosis	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Cerebral hemorrhage	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Cerebral infarction	0	0	2 (0.3%)	0	2 (0.1%)	2 (<0.1%)
Cerebrovascular accident	1 (0.2%)	1 (0.2%)	1 (0.2%)	5 (0.8%)	7 (0.4%)	8 (0.3%)
Coronary artery occlusion	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	2 (<0.1%)
Ischaemic cerebral infarction	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Lacunar infarction	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Myocardial infarction	5 (0.8%)	1 (0.2%)	6 (1.0%)	5 (0.8%)	12 (0.7%)	17 (0.7%)
Subarachnoid hemorrhage	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)	2 (<0.1%)
Transient ischaemic attack	0	4 (0.7%)	5 (0.8%)	1 (0.2%)	10 (0.5%)	10 (0.4%)

VTE = VEGF Trap-Eye

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

4.8.4.2.2.2. Additional Adverse Events of Interest: Arterial Thromboembolic Events Based on Anti-Platelet Trialists' Collaboration (APTC) Endpoint

A second analysis of ATEs was performed by a masked expert adjudication committee according to criteria formerly applied and published by the APTC (Antiplatelet Trialists' Collaboration 1994; Antiplatelet Trialists' Collaboration 2002). The APTC defined an ATE event as a nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, or death owing to vascular or unknown causes. These are the most clinically important arterial thromboembolic events because they represent irreversible morbidity and/or mortality.

The expert panel consisted of the clinical leaders of the cardiovascular departments of Regeneron and Bayer-Schering Pharma, the sponsor of the VIEW 2 study. These individuals had not been unmasked to the study data. They reviewed the list of prespecified MedRA terms previously alluded to that had been used to identify the potential arterial thromboembolic events described in Table 37 and added additional terms to this list to broaden the scope of their inquiry. Then they were provided the MedWatch forms and the case report forms for all patients with events coded to the indicated MedRA terms and also for all patients who died. If the adjudicators could not conclude whether an event was an APTC event, they consulted the external cardiologists from the independent data monitoring committees that had been monitoring data from the ongoing studies, with the VIEW 1 cardiologist providing input on cases from VIEW 2 and vice versa.

There were no notable differences in the rates of treatment-emergent APTC events observed during year 1 between the VEGF Trap-Eye and RQ4 groups. The overall rate of these events was 1.8% (32 out of 1824) in the combined group of subjects treated with VEGF Trap-Eye compared with 1.5% (9 out of 595) in subjects treated with ranibizumab. Amongst the VEGF Trap-Eye, there was no suggestion of a dose response, as the highest dose group, 2Q4, had a rate of 1.0% and the lowest dose group, 05.Q4, had a rate of 2.0%). These rates of APTC events with VEGF Trap-Eye are similar to reported rates of APTC events in the ranibizumab phase 3 trials (ANCHOR [Brown 2006] and MARINA [Rosenfeld 2006]) and in the US product circular for ranibizumab (Table 38).

Table 38: APTC Events in VIEW 1 and VIEW 2 (Integrated Data) (Safety Analysis Set)

		VTE			
APTC Cardiovascular event PT MedDRA Version 13.0	***R 0.5Q4 (N=595)***	***2Q4 (N=613)***	***0.5Q4 (N=601)***	***2Q8 (N=610)***	***Combined (N=1824)***
Any APTC event	9 (1.5%)	6 (1.0%)	12 (2.0%)	14 (2.3%)	32 (1.8%)
Non-fatal myocardial infarction	6 (1.0%)	3 (0.5%)	6 (1.0%)	6 (1.0%)	15 (0.8%)
Acute Coronary Syndrome	0	3 (0.5%)	0	1 (0.2%)	4 (0.2%)
Acute Myocardial Infarction	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)
Coronary Artery Disease	1 (0.2%)	0	1 (0.2%)	0	1 (<0.1%)
Myocardial Infarction	5 (0.8%)	0	4 (0.7%)	4 (0.7%)	8 (0.4%)
Non-fatal stroke	1 (0.2%)	2 (0.3%)	3 (0.5%)	3 (0.5%)	8 (0.4%)
Carotid Artery Stenosis	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)
Cerebrovascular Accident	1 (0.2%)	0	1 (0.2%)	3 (0.5%)	4 (0.2%)
Hemiplegia	0	0	1 (0.2%)	0	1 (<0.1%)
Lacunar Infarction	0	1 (0.2%)	0	0	1 (<0.1%)
Vascular Death	2 (0.3%)	1 (0.2%)	3 (0.5%)	5 (0.8%)	9 (0.5%)
Acute Myocardial Infarction	1 (0.2%)	0	0	0	0
Arteriosclerosis	0	0	0	1 (0.2%)	1 (<0.1%)
Cerebral Haemorrhage	0	0	1 (0.2%)	0	1 (<0.1%)
Cerebrovascular Accident	0	1 (0.2%)	0	1 (0.2%)	2 (0.1%)
Myocardial Infarction	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	2 (0.1%)
Shock Haemorrhagic	0	0	0	1 (0.2%)	1 (<0.1%)
Vascular Death	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)

VTE = VEGF Trap-Eye

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

4.8.4.3. ENT Substudy

A subset of 160 subjects in VIEW 2 was additionally examined by an ENT specialist, including nasal endoscopy (ENT sub-study). The aim of this prespecified sub-study was to determine any clinical correlates to toxicologic findings of respiratory epithelial changes (see Section 3.3).

A targeted, standardized medical history was taken concerning chronic airway diseases and endoscopy of the nasal airways was performed by an ENT specialist prior to study treatment at visit 2 (baseline).

At week 12 and week 52, the participants were reevaluated by an ENT specialist. The ENT specialist queried about nose bleeds and new nasal symptoms since the last ENT visit, and nasal endoscopy was performed. Results of these periodic interviews and tests were reported as AEs when they showed worsening or new findings.

No ENT-specific serious TEAEs were reported. ENT-specific non-serious TEAEs occurred in 39 of the 160 subjects (24.4%) in the ENT sub-study. The incidence of any ENT-specific TEAEs by treatment groups was 37.8% (RQ4), 16.7% (2Q4), 24.3% (0.5Q4), and 20.5% (2Q8). The incidence in the VEGF Trap-Eye combined group was 20.3%. Although the rate of ENT-specific TEAEs was substantially higher in the ranibizumab group, it seems unlikely that this would reflect a true difference, as this numerical difference was largely driven by a higher occurrence of infections that are not likely related to the treatment. Overall, other than for infections, the incidence and pattern of nasomucosal conditions was similar among the treatment groups (see Table 39) and typical of their incidence in the population, suggesting that there are no unique nasomucosal risks associated with VEGF Trap-Eye treatment in comparison to ranibizumab during the first year.

Table 39: Number of Subjects (%) with ENT-Specific TEAEs (Subjects Valid for ENT Sub-Study; N=160)

System organ class MedDRA preferred term	Ranibizumab 0.5Q4 (N = 37) n (%)	VEGF Trap-Eye 2Q4 (N = 42) n (%)	VEGF Trap-Eye 0.5Q4 (N = 37) n (%)	VEGF Trap-Eye 2Q8 (N = 44) n (%)	VEGF Trap-Eye Combined (N = 123) n (%)
Any ENT-specific TEAE	14 (37.8)	7 (16.7)	9 (24.3)	9 (20.5)	25 (20.3)
Respiratory, thoracic and mediastinal disorders	**6 (16.2)**	**6 (14.3)**	**6 (16.2)**	**6 (13.6)**	**18 (14.6)**
Nasal septum deviation	4 (10.8)	2 (4.8)	0 (0.0)	3 (6.8)	5 (4.1)
Nasal mucosal disorder	1 (2.7)	1 (2.4)	2 (5.4)	1 (2.3)	4 (3.3)
Rhinorrhoea	0 (0.0)	1 (2.4)	2 (5.4)	1 (2.3)	4 (3.3)
Epistaxis	1 (2.7)	1 (2.4)	1 (2.7)	1 (2.3)	3 (2.4)
Nasal polyps	1 (2.7)	1 (2.4)	1 (2.7)	0 (0.0)	2 (1.6)
Nasal turbinate hypertrophy	0 (0.0)	0 (0.0)	1 (2.7)	1 (2.3)	2 (1.6)
Nasal dryness	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.8)
Nasal mucosal discolouration	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	1 (0.8)
Nasal oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.8)
Paranasal cyst	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	1 (0.8)
Rhinitis hypertrophic	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	**9 (24.3)**	**3 (7.1)**	**6 (16.2)**	**4 (9.1)**	**13 (10.6)**
Nasopharyngitis	5 (13.5)	2 (4.8)	4 (10.8)	2 (4.5)	8 (6.5)
Upper respiratory tract infection	1 (2.7)	1 (2.4)	1 (2.7)	2 (4.5)	4 (3.3)
Rhinitis	2 (5.4)	0 (0.0)	1 (2.7)	0 (0.0)	1 (0.8)
Viral rhinitis	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	1 (0.8)
Acute tonsillitis	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: System organ classes (SOCs) as well as preferred terms within each SOC are sorted in descending order by frequency in the VEGF Trap-Eye combined group.

4.8.5. Deaths/Overall Mortality in VIEW 1 and VIEW 2

A total of 26 patients in the VIEW 1 and VIEW 2 studies died during year 1 (7 subjects in the RQ4 group, 5 subjects in the 2Q4 group, 4 subjects in the 0.5Q4 group, and 10 subjects in the 2Q8 group) (cut-off date of 10 November 2010), see Table 40. None of the deaths was considered related to study drug.

Table 40: Adverse Events with Death Reported as an Outcome (by SOC and PT), (Integrated Data) (Safety Analysis Set)

Primary SOC Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595	VTE 2.0 mg Q4 N=613	VTE 0.5 mg Q4 N=601	VTE 2.0 mg Q8 N=610	VTE total N=1824	TOTAL N=2419
Number of subjects who died	7 (1.2%)	4 (0.7%)	3 (0.5%)	9 (1.5%)	16 (0.9%)	23* (1.0%)
Cardiac disorders	3 (0.5%)	2 (0.3%)	1 (0.2%)	3 (0.5%)	6 (0.3%)	9 (0.4%)
Acute myocardial infarction	1 (0.2%)	0	0	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Cardiac arrest	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Cardiac failure congestive	1 (0.2%)	0	0	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Cardiopulmonary failure	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Myocardial infarction	1 (0.2%)	1 (0.2%)	1 (0.2%)	0	2 (0.1%)	3 (0.1%)
General disorders and administration site conditions	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)	2 (<0.1%)
Death	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Pyrexia	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Neoplasms benign malignant and unspecified (incl. cysts and polyps)	3 (0.5%)	0	0	2 (0.3%)	2 (0.1%)	5 (0.2%)
Hepatic neoplasm malignant	1 (0.2%)	0	0	0	0	1 (<0.1%)
Leukemia	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Lung cancer metastatic	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Lung neoplasm malignant	1 (0.2%)	0	0	0	0	1 (<0.1%)
Esophageal carcinoma	1 (0.2%)	0	0	0	0	1 (<0.1%)
Nervous system disorders	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)	3 (0.1%)
Cerebral hemorrhage	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Cerebrovascular accident	0	1 (0.2%)	0	1 (0.2%)	2 (0.1%)	2 (<0.1%)
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	2 (0.1%)	3 (0.1%)
Chronic obstructive pulmonary disease	0	1 (0.2%)	0	1 (0.2%)	2 (0.1%)	2 (<0.1%)
Pneumonia aspiration	1 (0.2%)	0	0	0	0	1 (<0.1%)
Vascular disorders	0	0	0	2 (0.3%)	2 (0.1%)	2 (<0.1%)
Arteriosclerosis	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Shock hemorrhagic	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)

VTE = VEGF Trap-Eye

Note: *Total number of deaths was actually 26, however, 1 subject in VIEW 1 (314002 in the VTE 2.0 mg Q4) died and was reported in the safety data base but was not captured in EDC by data base lock

Note: Two deaths in VIEW 1 (subjects 502003 and 505004 in the VTE 0.5 mg Q4, VTE 2.0 mg Q8 groups) were reported in the disposition dataset, but there were no corresponding entries of AE with fatal outcome reported for these subjects.

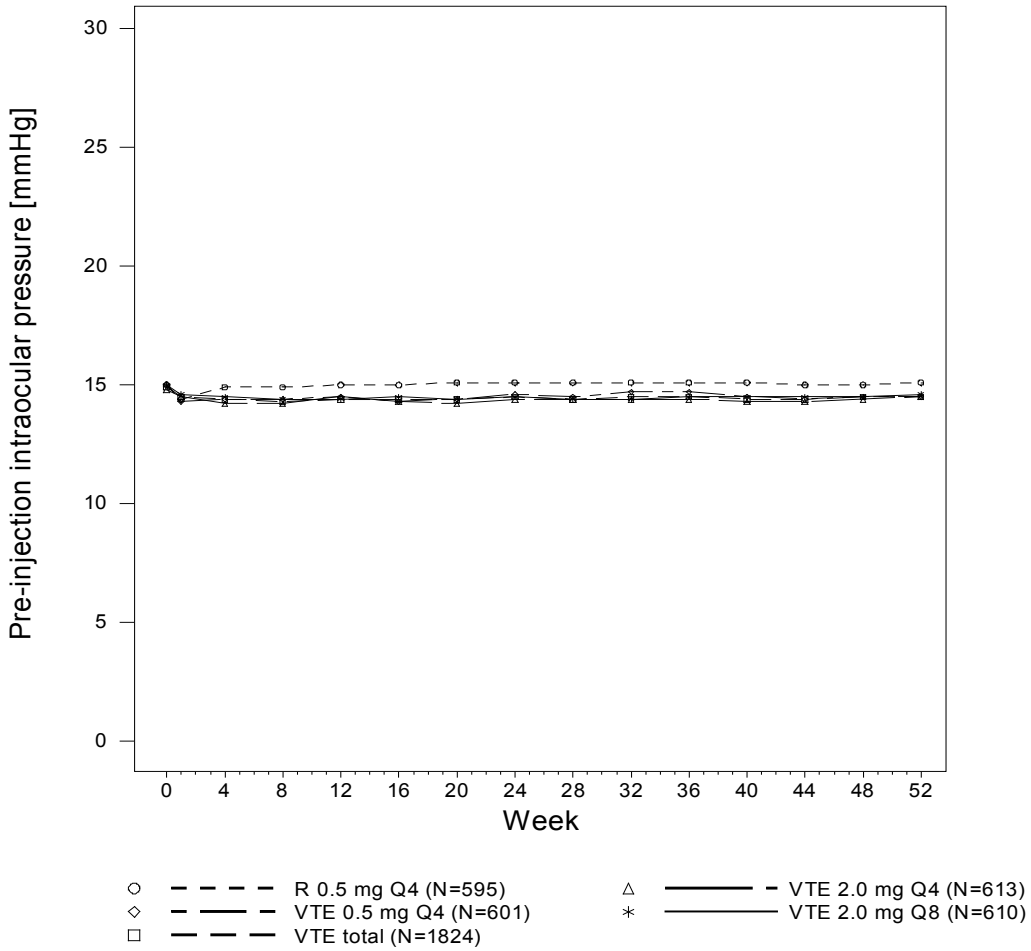
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

4.8.6. Other Safety Measurements

4.8.6.1. Changes in Intraocular Pressure Over Time in VIEW 1 and VIEW 2

There were mild fluctuations in mean pre-injection IOP from baseline to week 52 in all treatment groups in subjects in the VIEW 1 and VIEW 2 studies. Overall, small decreases in mean pre-injection IOP over time were seen in each treatment group from baseline to week 52 in the study eye, with the exception of the RQ4 group, which showed minor increases or no change in mean pre-injection IOP from week 12 to week 52 (Figure 19).

Figure 19: Mean Pre-Injection Intraocular Pressure (mm Hg) in the Study Eye over Time by Treatment Group (Integrated Data) (Safety Analysis Set)



4.8.6.2. Changes in Blood Pressure Over Time in VIEW 1 and VIEW 2

The mean and median values for treatment group systolic pressure (Figure 20) and diastolic pressure (Figure 21) varied relative to baseline with no apparent trend over time in subjects in the VIEW 1 and VIEW 2 studies.

Figure 20: Mean Systolic Blood Pressure (mmHg) over Time by Treatment Group (Integrated Data) (Safety Analysis Set)

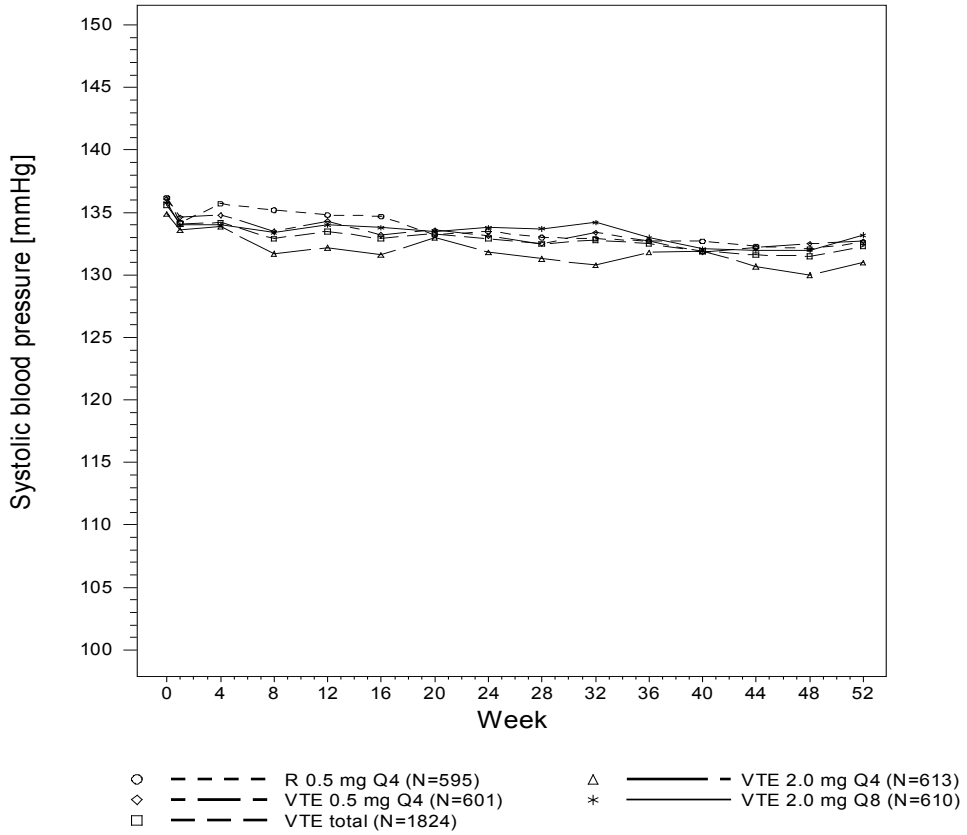
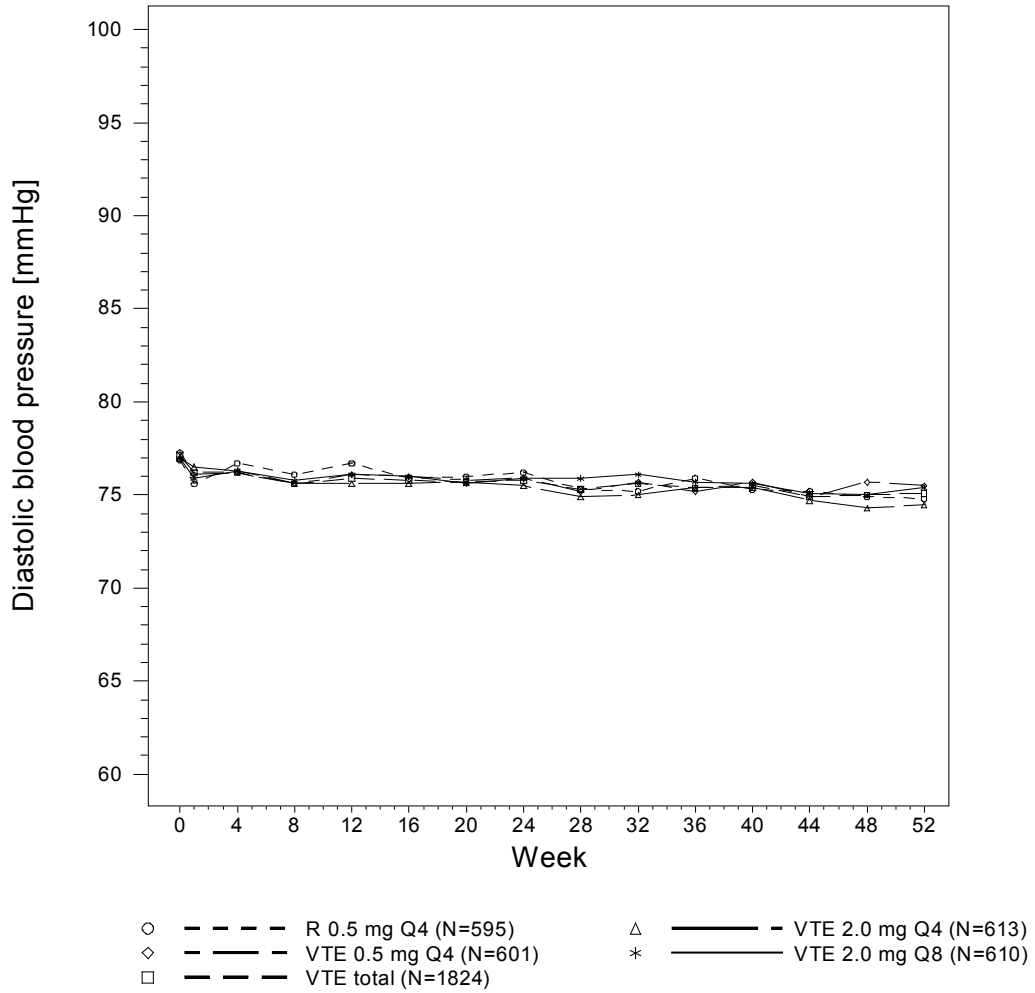


Figure 21: Mean Diastolic Blood Pressure (mmHg) over Time by Treatment Group (Integrated Data) (Safety Analysis Set)



4.8.7. Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with VEGF Trap-Eye. Immunogenicity was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VEGF Trap-Eye in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

In the phase 3 studies, the pre-treatment incidence of immunoreactivity to VEGF Trap-Eye was 1% to 3% across treatment groups. After dosing with VEGF Trap-Eye for 52 weeks, antibodies to VEGF Trap-Eye were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without anti-drug reactivity.

4.8.8. Safety Conclusions

Overall, VEGF Trap-Eye has a favorable safety profile. The safety of VEGF Trap-Eye was studied in 1824 patients with wet AMD, including 1223 patients treated with the 2 mg dose for up to 12 months, in 2 double-masked, active-controlled clinical studies (VIEW 1 and VIEW 2). These data show that VEGF Trap-Eye was well tolerated and without notable differences in ocular or non-ocular TEAEs compared to ranibizumab 0.5Q4. The most common (>5%) adverse experiences reported in patients receiving VEGF Trap-Eye and not related to the underlying disease process were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased IOP. Serious adverse reactions related to the injection procedure occurred in <0.1% of IVT injections with either VEGF Trap-Eye or ranibizumab and included endophthalmitis, traumatic cataract, and transient increased IOP. The incidence of SAEs, fatal events, and withdrawals due to AEs was balanced between treatment groups, as was the incidence of adjudicated APTC events. There was no dose-response across VEGF Trap-Eye groups with regards to APTC events or serious AEs potentially related to systemic VEGF inhibition and the frequencies of these were low across treatment groups and, in the VEGF Trap-Eye groups, consistent with those previously reported for ranibizumab. Finally, review of AEs consistent with nasal erosions, including those from the ENT substudy of VIEW 2, did not identify an increased risk with VEGF Trap-Eye therapy.

5. BENEFIT RISK ASSESSMENT

The Benefit/Risk of VEGF Trap-Eye is favorable for the treatment of wet AMD and the 2Q8 regimen, in particular, represents an improvement over regimens that require either monthly dosing or monthly monitoring.

Wet AMD is a blinding disease that affects 1 and a half million patients in the United States alone. Until recently there was little that could be done to stop the progression of this disease, but now, with anti-VEGF therapy, such as ranibizumab, even moderate vision loss can be avoided in most patients, and about a third experience significant vision gains. However, to achieve the maximum benefit, monthly visits, and possibly monthly injections are necessary. This presents a significant burden on patients, their caregivers, and the health care system.

Benefit

VEGF Trap-Eye is a new anti-VEGF therapy that has the potential of changing this paradigm. As a fully human, soluble decoy receptor, VEGF Trap-Eye binds all isoforms of VEGF as well as PlGF with high affinity. There is low systemic exposure after intravitreal injection with VEGF Trap-Eye, reducing the potential risk of systemic adverse events or immunogenic reactions. But most importantly, the data demonstrate that VEGF Trap-Eye has an extended dosing interval compared to monthly ranibizumab and an extended monitoring interval compared to PRN ranibizumab, with a safety profile that is similar to ranibizumab.

The Phase 3 program of VEGF Trap-Eye included two pivotal studies, each comparing three different dosing regimens of VEGF Trap-Eye (0.5 Q4; 2Q4; 2Q8) versus the active comparator ranibizumab at the dose of 0.5 mg administered every 4 weeks. The VEGF Trap-Eye regimens included 2 different doses (0.5 mg and 2 mg) and two different intervals (monthly and every two months). The primary endpoint was analyzed to assess noninferiority to ranibizumab while the

secondary endpoints were analyzed to assess superiority. Multiplicity was rigorously controlled using a step-wise analysis approach. The comparator treatment regimen, ranibizumab 0.5 mg monthly, is known from published, controlled studies to provide best efficacy of ranibizumab, the current standard of care, and was therefore suitable as an active comparator for a non-inferiority design.

The primary endpoints in Phase 3 provided robust evidence of noninferiority to ranibizumab in maintaining visual acuity, with the confidence intervals of the difference between ranibizumab and VEGF Trap-Eye arms well below the 10% boundary established in the analysis plan and even below 5%. Although superiority to ranibizumab was not established in both studies, the secondary and additional efficacy endpoints further support the conclusion that all VEGF Trap-Eye regimens studies provide gains in visual acuity, improvement in anatomic endpoints, and improvement in function that is highly similar to ranibizumab 0.5 mg monthly.

Efficacy results in all evaluable subgroups (e.g., age, gender, race, baseline visual acuity, lesion type, and lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

Confidence in the results of the VEGF Trap-Eye Phase 3 studies is supported by constancy of results for ranibizumab, compared with its performance in the two studies upon which its approval was based (ANCHOR [Brown 2006] and MARINA [Rosenfeld 2006]).

In the VIEW studies, patients in the 2Q8 group had clinical benefit that was non-inferior to and clinically similar to monthly ranibizumab. In the setting of these clinical studies, the 2Q8 patients were seen monthly to preserve masking and, at non-injection visits, underwent a sham injection procedure. Although the personnel involved in the sham procedure were unmasked to the patients' treatment group, efficacy and safety evaluations were conducted by study personnel who were masked to the patients' treatment group. Overall, it is highly unlikely that these sham procedures would have contributed to or confounded the evaluation of efficacy observed in the 2Q8 treatment group and, with respect to safety, may have added to the safety burden beyond what would be anticipated in clinical practice where patients would not undergo sham procedures. In addition, although data were collected from examinations performed at the non-dosing visits in the 2Q8 group, they could not be used for clinical decision making (other than withdrawal of patients from the study) and were only collected for analytic purposes. Thus, the results demonstrate that a regimen of 2 mg of VEGF Trap-Eye administered every 2 months provides efficacy benefits equivalent to monthly ranibizumab without the need for between-visit monitoring.

There are major potential benefits of a regular 2 mg VEGF Trap-Eye every-two-month dosing regimen that can produce efficacy equivalent to the current gold standard of treatment (i.e., monthly ranibizumab) both in terms of visual acuity measures as well as anatomic markers of disease control, but with substantially fewer injections and without the need for interim monitoring visits. Thus, compared to current monthly therapies, this regimen has the potential to reduce the overall incidence of injection-related SAEs. These SAEs, including endophthalmitis, retinal detachments, traumatic cataract, and increased IOP, all represent important risks for these patients and has motivated the desire for regimens that reduce the number of injections while maintaining efficacy. Second is the potential to reduce the burden on patients, caregivers, and the health care system that is associated with having to visit their retinal physician every month (for either injections or monthly monitoring exams). This burden is more than just an

inconvenience. These elderly patients frequently require the assistance of a family member to come to the ophthalmologist. And this family member is frequently somebody with a full-time job who needs to miss a day of work to help the patient. Thus there are hidden economic costs associated with monthly monitoring. It is estimated that there are over 220,000 Medicare patients with wet-AMD (Brechner 2011). In the first year of treatment with ranibizumab or bevacizumab dosed either monthly or with a PRN regimen that requires monthly monitoring like the regimen studied in the CATT trial, these patients would require 12 visits to the ophthalmologist. With VEGF Trap-Eye 2Q8, they would require just 7 visits in the first year of treatment (and after loading, just 5 visits over the last 10 months of the first year of treatment). The difference, in just the Medicare population, translates to a reduction of over 1 million office visits. Last, in contrast to "as needed" PRN regimens which require complex treatment decisions during monthly monitoring visits based on incompletely understood anatomical correlates of disease activity, the regular every two month regimen does not depend on making such treatment decisions.

Risk

Overall, VEGF Trap-Eye has a favorable safety profile. The Phase 3 safety data base for VEGF Trap-Eye provides a broad and robust basis for the assessment of the drug's safety and tolerability profile, covering a total of 1824 subjects exposed to VEGF Trap-Eye, including 621 subjects on the proposed posology of 2Q8 over one year. The experience includes a total of 19,479 injections of VEGF Trap-Eye in the Phase 3 studies. In addition, 157 patients were treated for up to 44 months in a long-term extension of the Phase 1 and Phase 2 studies. The safety profile in this long-term extension was consistent with that seen in the phase 3 studies.

The safety data from the clinical program conducted with VEGF Trap-Eye show that VEGF Trap-Eye was well tolerated and without notable differences in ocular or non-ocular TEAEs compared to ranibizumab 0.5Q4. The most common (>5%) adverse experiences reported in patients receiving VEGF Trap-Eye and not related to the underlying disease process were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased IOP. Serious adverse reactions related to the injection procedure occurred in <0.1% of IVT injections with either VEGF Trap-Eye or ranibizumab and included endophthalmitis, traumatic cataract, and transient increased IOP. The incidence of SAEs, fatal events, and withdrawals due to AEs was balanced between treatment groups, as was the incidence of adjudicated APTC events. APTC events (non-fatal myocardial infarctions, non-fatal strokes, and fatal vascular events) are the most clinically important arterial thromboembolic events because they represent irreversible morbidity or mortality. There was no dose-response across VEGF Trap-Eye groups with regards to APTC events or serious AEs potentially related to systemic VEGF inhibition and the frequencies of these were low across treatment groups and, in the VEGF Trap-Eye groups, consistent with those previously reported for ranibizumab.

Benefit-risk balance

All regimens of VEGF Trap-Eye demonstrated non-inferiority to ranibizumab in rigorously designed Phase 3 studies. The data support that all 3 regimens provide essentially the same efficacy as ranibizumab. In clinical studies, VEGF Trap-Eye had an excellent safety profile similar to that of ranibizumab. Therefore, it is reasonable to conclude that the benefit of VEGF Trap-Eye outweighs the potential risks.

The VEGF Trap regimen utilizing regular every two month dosing (after loading) without need for intervening monitoring visits has additional potential benefits. These include (i) substantially decreasing the numbers of required injections, (ii) thus decreasing the overall rate of adverse events related to the injection procedure, (iii) and also not requiring interim monitoring visits (as well as the need to make difficult treatment decisions during monitoring visits based on incompletely understood anatomical correlates of disease activity), (iv) thus decreasing the treatment burden on patients, their caregivers and physicians, and the overall healthcare system. These additional potential benefits do not have associated additional risks. Visual acuity, anatomic endpoints, and functional endpoints at 52 weeks are not compromised by a fixed 2Q8 regimen and there is little reason to believe that interim monitoring visits would meaningfully improve patient safety.

In summary, dosing of VEGF Trap-Eye has a clearly positive benefit / risk balance in patients with wet AMD and the regimen of VEGF Trap-Eye every two months (after loading) provides additional potential benefit over current therapies.

Conclusion

Based on the current evidence and taking into account the severity and the burden of untreated wet AMD, it can be concluded that the benefits, in particular the possibility of prolonging the dosing and monitoring intervals to every second month with VEGF Trap-Eye therapy, clearly outweigh potential risks arising from its use. The uncompromised, robust and durable efficacy of VEGF Trap-Eye administered every two months further underlines the utility of this treatment. For those instances where it may be clinically warranted, VEGF Trap-Eye may be dosed as frequently as once per month.

Therefore, VEGF Trap-Eye treatment should be initiated with one injection per month for three consecutive months, followed by one injection every 2 months.

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7. APPENDICES

Central retinal thickness was similar among treatment groups at baseline in the FAS. A rapid reduction in CRT occurred through week 4 with results that were maintained to week 52 in all treatment groups (Figure 22). The magnitude of the change at week 52 was similar in all treatment groups (mean decrease –129.0 µm, –121.3 µm, –122.6 µm, and -130.3 µm in the R0.5Q4, 2Q4, 0.5Q4, and 2Q8 groups, respectively) (Table 41).

Table 41: VIEW 1 – Change from Baseline to Week 52 in Central Retinal Thickness (LOCF) (Full Analysis Set) (Original BLA Analysis)

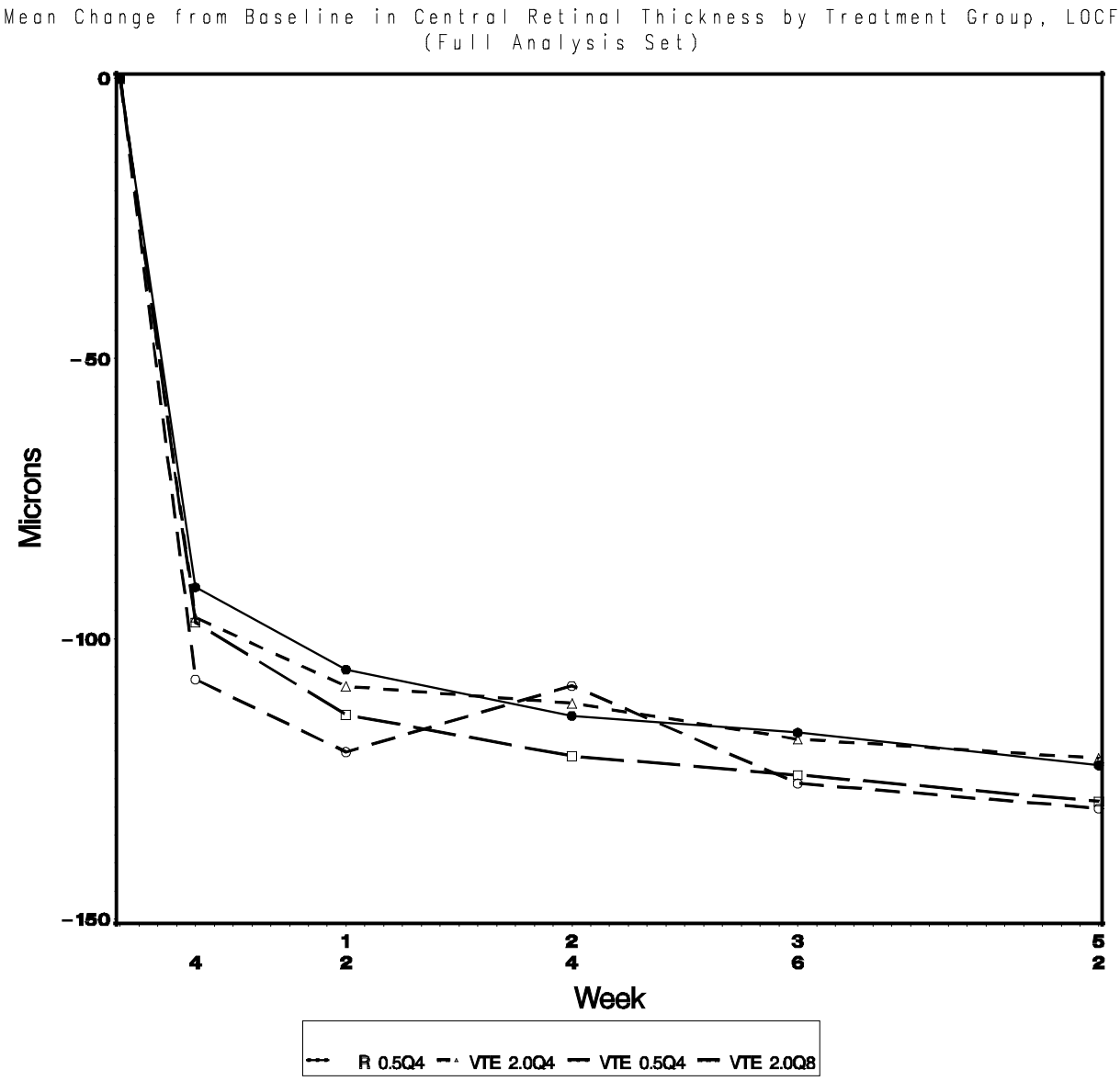
	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 304)	2Q4 (N = 304)	0.5Q4 (N = 301)	2Q8 (N = 301)
Baseline				
n	304	303	300	301
Mean (SD) µm	266.8 (126.73)	261.8 (122.42)	266.7 (139.15)	269.0 (133.34)
Median	233.5	236.0	234.0	238.0
Min: Max	51.0:822.0	65.0:714.0	66.0:1257.0	60.0:845.0
Week 52				
n	302	304	300	301
Mean (SD)	138.7 (54.87)	140.5 (65.81)	144.7 (65.11)	138.7 (55.37)
Median	132.0	134.0	135.0	132.0
Min: Max	22.0:418.0	22.0:638.0	11.0:660.0	8.0:506.0
Week 52 (change from baseline)				
n	302	303	299	301
Mean (SD) µm	–129.0 (129.85)	–121.3 (120.81)	–122.6 (147.25)	–130.3 (141.21)
Median	–98.5	–94.0	–93.0	–103.0
Min: Max	–694.0:201.0	–557.0:264.0	–1092:384.0	–713.0:230.0
Point estimate for the contrast[1]		2.20	6.06	-0.05
95.1% C.I. for difference		(–7.40 , 11.79)	(–3.57, 15.68)	(–9.66 , 9.56)
P-value[2] vs. RQ4		0.6517	0.2153	0.9916

[1] Difference is VEGF Trap-Eye minus ranibizumab. C.I. = confidence interval calculated using normal approximation.

[2] ANCOVA, main effect model.

Note: Last observation carried forward: The missing values were replaced by the last observed post baseline values prior to the missing value.

Figure 22: VIEW 1 – Change from Baseline in Central Retinal Thickness by Treatment Group (LOCF) (Full Analysis Set) (Original BLA Analysis)



Using an alternate method of OCT measurement, including elements of CNV and pigment epithelial detachment, (in addition to the measures of the thickness of the retina at the center of the fovea and subretinal fluid used to calculate the central retinal thickness described above), a total center point thickness score was generated. All four treatment groups were balanced at baseline in the FAS. A rapid reduction in this parameter occurred through week 4 with results that were maintained to week 52 in all treatment groups (Figure 23). The magnitude of the change at week 52 was similar in all treatment groups (mean decrease -230.1 µm, -227.6 µm, -217.5 µm, and -227.2µm in the R0.5Q4, 2Q4, 0.5Q4, and 2Q8 groups, respectively (Table 42).

Table 42: VIEW 1 – Change from Baseline to Week 52 in Total Centerpoint Thickness (LOCF) (Full Analysis Set) (Original BLA Analysis)

	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 304)	2Q4 (N = 304)	0.5Q4 (N = 301)	2Q8 (N = 301)
Baseline				
n	304	303	300	301
Mean (SD) µm	492.5 (182.53)	476.4 (162.67)	482.2 (182.19)	496.4 (180.68)
Median	440.0	442.0	447.0	458.0
Min: Max	178.0 : 1096.0	169.0 :1126.0	139.0 : 1307.0	141.0 : 1093.0
Week 52				
n	302	304	300	301
Mean (SD)	263.8 (116.30)	248.8 (103.23)	265.6 (119.91)	269.3 (131.83)
Median	229.0	224.0	240.0	235.0
Min: Max	73.0 : 792.0	73.0 : 871.0	62.0: 953.0	90.0 : 1089.0
Week 52 (change from baseline)				
n	302	303	299	301
Mean (SD) µm	–230.1 (167.11)	–227.6 (146.90)	–217.5 (179.61)	–227.2 (174.34)
Median	–187.0	–206.0	–191.0	–198.0
Min: Max	–929.0 : 240.0	–866.0 : 94.0	–1025 : 454.0	–840.0 : 541.0
Point estimate for the contrast[1]		–10.19	4.95	4.76
95.1% C.I. for difference		(–27.48 , 7.09)	(–12.39, 22.28)	(–12.54 , 22.06)
P-value[2] vs. RQ4		0.2454	0.5739	0.5878

Total centerpoint thickness includes elements of pigment epithelial detachment (PED) and choroid neovascularization (CNV), in addition to the thickness of retina at the fovea and subretinal fluid

[1] Difference is VEGF Trap-Eye minus ranibizumab. C.I. = confidence interval calculated using normal approximation.

[2] ANCOVA, main effect model.

Note: Last observation carried forward: The missing values were replaced by the last observed post baseline values prior to the missing value.

Figure 23: VIEW 1 – Change from Baseline in Total Centerpoint Thickness by Treatment Group (LOCF) (Full Analysis Set) (Original BLA Analysis)