CENTER FOR DRUG EVALUATION AND RESEARCH

BLA APPLICATION NUMBER:

125156

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125156
Drug Name:	Lucentis (ranibizumab injection)
Indication(s):	Treatment of patients with neovascular (wet) age-related macular degeneration
Applicant:	Genetech, Inc.
Date(s):	Stamp Date: December 30, 2005 PDUFA due date: June 30, 2006
Review Priority:	Priority
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Keywords: AMD (age-related macular degeneration), BCVA (best corrected visual acuity), sham-control (superiority), active control (non-inferiority).

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This BLA submission (BLA125156) seeks to gain approval for the use of ranibizumab injection in the treatment of patients with neovascular (wet) age-related macular degeneration (AMD).

This submission includes data from two pivotal Phase 3 (FVF2598g and FVF2587g) and one Phase 3b (FVF3192g) clinical trials. These studies demonstrated that both ranibizumab 0.3mg and 0.5mg doses (monthly injection in studies FVF2598g and FVF2587g, or monthly injection for 3 doses followed by quarterly injection in study FVF3192g) were effective in treating subjects with AMD.

Phase 3 study FVF2598g demonstrated that both ranibizumab 0.3mg and 0.5mg doses (monthly injection) yielded statistically significant differences in the proportion of subjects who lost fewer than 15 letters in the best corrected visual acuity (BCVA) score at 12 months compared with the placebo treatment (sham). The efficacy results from this study appeared to be similar between the two ranibizumab dose groups.

Phase 3 study FVF2587g demonstrated that both ranibizumab 0.3mg and 0.5mg doses (monthly injection) yielded statistically significant differences in the proportion of subjects who lost fewer than 15 letters in the BCVA score at 12 months compared with the active control treatment (verteporfin for injection). The efficacy results from this study appeared to be similar between the two ranibizumab dose groups.

Phase 3b study FVF3192g demonstrated that both ranibizumab 0.3mg and 0.5mg doses (monthly injection at Day 0, Month 1, and Month 2, then followed by injection every 3 months) yielded statistically significant differences in the mean change from baseline in the BCVA score at 12 month compared with the placebo treatment (sham). The efficacy results from this study appeared to be similar between the two ranibizumab dose groups.

Each of the three studies was designed to compare each of the two ranibizumab dose groups (0.3mg versus 0.5mg) to the concurrent control group. None of the three studies were designed to compare the efficacy results between the two ranibizumab dose groups. Thus statistically sound comparison of the efficacy results between these two doses could not be made within or across studies. Furthermore, none of the three studies were designed to compare the efficacy results between the two ranibizumab dosing frequencies (monthly injection in both studies FVF2598g and FVF2587g versus monthly injection for 3 doses then followed by quarterly injection in study FVF3192g). Thus statistically sound comparison of the efficacy results between these two dosing frequencies could not be made across studies.

1.2 Brief Overview of Clinical Studies

Study FVF2598g was a Phase 3, randomized, multi-center, double-blind, double-masked, sham-controlled (superiority) study in subjects with angiographically determined, minimally classic or occult subfoveal neovascular AMD. The study subjects received sham, or ranibizumab 0.3mg, or ranibizumab 0.5mg injection monthly for 24 months in a 1:1:1 ratio. There were 238, 238, and 240 randomized subjects in the sham, ranibizumab 0.3mg, and ranibizumab 0.5mg groups, respectively. The primary endpoint was the proportion of subjects losing few than 15 letters in the BCVA score measured at a starting test distance of 4 meters at 12 months. The primary hypothesis was that at least in one of the two ranibizumab dose groups there would be more subjects who lost fewer than 15 letters in the BCVA score at 12 month than those in the sham group.

Study FVF2587g was a Phase 3, randomized, multi-center, double-blind, double-masked, active-controlled (non-inferiority) study in subjects with angiographically determined, predominantly classic subfoveal neovascular AMD. The study subjects received verteporfin, or ranibizumab 0.3mg, or ranibizumab 0.5mg injection monthly for 24 months in a 1:1:1 ratio. There were 143, 140, and 140 randomized subjects in the sham, ranibizumab 0.3mg, and ranibizumab 0.5mg groups, respectively. The study duration was 24 months (but only 1 year data were included in the submission). The primary endpoint was the proportion of subjects who lost few than 15 letters in BCVA score measured at a starting test distance of 4 meters at 12 months. The primary hypothesis was that at least one of the two ranibizumab dose groups would not be non-inferior to the active control group with respect to the efficacy measurement of proportion of subjects who lost fewer than 15 letters in the BCVA score at 12 month. A non-inferiority margin of 7% was used.

Study FVF3192g was a Phase 3b, randomized, multi-center, double-blind, double-masked, sham-controlled (superiority) study in subjects with or without choroidal neovascularization (CNV) secondary to AMD. The study subjects received sham, or ranibizumab 0.3mg, or ranibizumab 0.5mg injection monthly for 3 doses (Day 0, Month 1, Month 2) and followed by doses every 3 months (Months: 5, 8, 11, 14, 20 and 23) in a 1:1:1 ratio. There were 63, 60, and 61 randomized subjects in the sham, ranibizumab 0.3mg, and ranibizumab 0.5mg groups, respectively. The study duration was 24 months (but only 1 year data were included in the submission). The primary endpoint was the change from baseline in BCVA score measured at a starting test distance of 4 meters at 12 months. The primary hypothesis was that at least one of the two ranibizumab doses would result in a better mean change from baseline in the BCVA score at 12 month compared to the sham group.

1.3 Statistical Issues and Findings

In each of the three studies the primary efficacy assessment was based on the best corrected visual acuity (BCVA) score measured at a starting test distance of 4 meters (based on the Early Treatment Diabetic Retinopathy Study visual acuity chart).

Study FVF2598g

This study is a superiority trial. The primary hypothesis tested in this study was that at least in one of the two ranibizumab dose groups there would be more subjects losing fewer than 15 letters in the BCVA score at 12 month than those in the sham group. The primary efficacy analysis was based on the randomized population, with missing data imputed using the last observation carried forward (LOCF) method. The proportions were compared between each of the two ranibizumab dose groups and the sham group, using the Cochran χ^2 test stratified by baseline CNV classification and baseline BCVA score. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for comparison of the two ranibizumab dose groups with the control group in order to maintain an overall Type I error rate of 0.05. The primary efficacy endpoint was also analyzed using the observed data only and using the worst outcome imputation for missing data. The statistical reviewer performed sensitivity analysis by treating missing data as non-response to further exam the robust of the efficacy results.

Study FVF2587g

This study is a non-inferiority trial. The primary hypothesis tested in this study was that at least one of the two ranibizumab dose groups would not be non-inferior to the active control group with respect to the efficacy measurement of proportion of subjects losing fewer than 15 letters in the BCVA score at 12 month. A non-inferiority margin of 7% was used (rationale was provided in applicant's submission). The primary efficacy analysis was based on the randomized population, with missing data imputed using the LOCF method.

For each ranibizumab dose group, non-inferiority to the control group was tested using a one-sided testing procedure (or equivalently, using a one-sided 97.5% CI) and a non-inferiority limit of 7%. A one-sided 97.5% CI for the weighted average of the differences between two proportions over the strata, with baseline visual acuity score as the stratification variable. The Cochran-Mantel-Haenszel weights were used to calculate the weighted average or the overall stratified difference in proportions (see applicant's analysis plan for details). The normal approximation test was performed by applying the procedure proposed by Blackwelder to stratified binomials. The test for proportion difference between each ranibizumab dose group and the control group was performed using the Cochran χ^2 test stratified by baseline BCVA score and baseline CNV classification.

If the non-inferiority test demonstrated that one or both the ranibizumab dose groups were statistically significantly non-inferior to the control group, then the superiority test between each of the ranibizumab groups and the control group would be conducted. The superiority comparison between each ranibizumab dose group and the control group with respect to the

primary efficacy endpoint would be performed using the Cochran χ^2 test stratified by baseline CNV classification and baseline visual acuity score.

To adjust for multiple comparisons of two ranibizumab dose groups with the control group, the Hochberg-Bonferroni multiple comparison procedure was used. A hierarchical procedure was implemented to account for the multiple hypothesis tests of non-inferiority and treatment difference for the comparison of each ranibizumab dose group with the control group.

The primary efficacy endpoint was also analyzed using the observed data only and using the worst outcome imputation for missing data. The statistical reviewer performed sensitivity analysis by treating missing data as non-response to exam further the robust of the efficacy results.

Study FVF3192g

The primary hypothesis tested in this study was that at least one of the two ranibizumab treatment doses would result in a better mean change from baseline in the BCVA score at 12 month compared to the sham group. The primary efficacy analysis was based on the randomized population, with missing data imputed using the LOCF method. The mean change in BCVA score were compared between each ranibizumab group and the control group using an ANOVA model with baseline CNV classification and baseline visual acuity score as covariates. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for comparison of the two ranibizumab groups with the control group in order to maintain an overall Type I error rate of 0.05.

The primary efficacy endpoint was also analyzed using the observed data only and using the worst outcome imputation for missing data. Statistical reviewer also performed sensitivity analysis using test without adjusting baseline CNV classification and baseline visual acuity score for the observed data to exam further the robust of the efficacy results.

Summary

Overall, each of the three studies was designed to compare the two ranibizumab dose groups with the concurrent control group. The applicant's statistical analysis methods were adequate for this purpose.

However, none of the three studies were designed to compare the efficacy results between the two ranibizumab dose groups (0.3mg versus 0.5mg). Thus statistically sound comparison of the efficacy results between these two dose groups could not be made within or across studies.

Furthermore, none of the three studies were designed to compare the efficacy results between the two ranibizumab dosing frequencies (monthly injection in studies FVF2598g and FVF2587g versus monthly injection for 3 doses then followed by quarterly injection in study FVF3192g). Thus statistically sound comparison of the efficacy results between these two dosing frequencies could not be made across studies.

2. INTRODUCTION

Based on the efficacy results presented in the submission, the review team decided at the beginning of the review cycle that statistical review was not necessary. During the labeling meetings, it was decided to do a brief statistical review to address some of the treatment dosing and frequencies.

2.1 Class and Indication

Ranibizumab is a recombinant, humanized monoclonal IgG1 antibody antigen-binding fragment that selectively binds to and neutralized the biological activities of all known isoforms of human vascular endothelial growth factor-A (VEGF), as well as the proteolytic cleavage product $VEGF_{110}$. Ranibizumab is a new molecular entity and has not been marketed in the United States.

In this submission, the proposed indication for ranibizumab [redacted] in patients with Neovascular (wet) age-related macular degeneration.

There are currently two approved drugs for the treatment of age related macular degeneration – Visudyne (verteporfin for injection) and Macugen (pegaptanib sodium injection). Visudyne was approved under NDA 21-119 on April 12, 2000, for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration. Macugen was approved under NDA 21-756 on December 17, 2004, for the treatment of neovascular (wet) age-related macular degeneration.

2.2 History of Drug Development

The initial BB-IND [redacted] for ranibizumab was submitted to the FDA on October 6, 1999. The applicant had a pre-phase 3/End-of-Phase 2 meeting with the FDA on October 31, 2002. Pre-BLA meeting was held on November 9, 2005.

2.3 Data Sources

The applicant's study reports and the data sets for the phase 3 studies and data sets for the phase 3b are available on the EDR at \\2005-11-29 on "cbsap58\M\EDR Submissions\2005 bla'. The applicant didn't provide study report for the phase 3b study yet.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy (Studies FVF2598g, FVF2587g, FVF3192g)

3.1.1 Study Design and Endpoints

Study FVF2598g was a Phase 3, randomized, multi-center, double-blind, double-masked, sham-controlled (superiority) study in subjects with angiographically determined, minimally classic or occult subfoveal neovascular AMD. The study subjects received sham, or ranibizumab 0.3mg, or ranibizumab 0.5mg injection monthly for 24 months in a 1:1:1 ratio. There were 238, 238, and 240 randomized subjects in the sham, ranibizumab 0.3mg, and ranibizumab 0.5mg groups, respectively. The primary endpoint was the proportion of subjects losing few than 15 letters in the BCVA score measured at a starting test distance of 4 meters at 12 months. The primary hypothesis was that at least in one of the two ranibizumab dose groups there would be more subjects who lost fewer than 15 letters in the BCVA score at 12 month than those in the sham group.

Study FVF2587g was a Phase 3, randomized, multi-center, double-blind, double-masked, active-controlled (non-inferiority) study in subjects with angiographically determined, predominantly classic subfoveal neovascular AMD. The study subjects received verteporfin, or ranibizumab 0.3mg, or ranibizumab 0.5mg injection monthly for 24 months in a 1:1:1 ratio. There were 143, 140, and 140 randomized subjects in the sham, ranibizumab 0.3mg, and ranibizumab 0.5mg groups, respectively. The study duration was 24 months (but only 1 year data were included in the submission). The primary endpoint was the proportion of subjects who lost few than 15 letters in BCVA score measured at a starting test distance of 4 meters at 12 months. The primary hypothesis was that at least one of the two ranibizumab dose groups would not be non-inferior to the active control group with respect to the efficacy measurement of proportion of subjects who lost fewer than 15 letters in the BCVA score at 12 month. A non-inferiority margin of 7% was used.

Study FVF3192g was a Phase 3b, randomized, multi-center, double-blind, double-masked, sham-controlled (superiority) study in subjects with or without choroidal neovascularization (CNV) secondary to AMD. The study subjects received sham, or ranibizumab 0.3mg, or ranibizumab 0.5mg injection monthly for 3 doses (Day 0, Month 1, Month 2) and followed by doses every 3 months (Months: 5, 8, 11, 14, 20 and 23) in a 1:1:1 ratio. There were 63, 60, and 61 randomized subjects in the sham, ranibizumab 0.3mg, and ranibizumab 0.5mg groups, respectively. The study duration was 24 months (but only 1 year data were included in the submission). The primary endpoint was the change from baseline in BCVA score measured at a starting test distance of 4 meters at 12 months. The primary hypothesis was that at least one of the two ranibizumab doses would result in a better mean change from baseline in the BCVA score at 12 month compared to the sham group.

The key elements of study design for these three studies are presented in Table 1.

Statistical reviewer's comments: The applicant has defined the primary endpoint using the BCVA score measured at a starting test distance of 2 meters in both studies FVF2598g and FVF2587g. The FDA has requested using the BCVA score measured at a starting test distance of 4 meters in its communications with the applicant dated in 23 April 2003 and 26 January 2004. This distance measure (4 meters) is recommended to minimize the potentially confounding influences of accommodation and patient positioning on the measurement. Thus this review will focus on the study endpoints based on the BCVA score measured at a starting test distance of 4 meters.

Table 1: Study Design and Endpoints

Study (Phase)	Design (Sites)	Population (total no. of subjects enrolled)	Ranibizumab Dose or Control	Treatment Frequency and Duration	Primary Efficacy Endpoint	Some Key Secondary Efficacy Endpoints
FVF2587g (III)	Randomized, double-masked, active treatment-controlled (U.S., Europe, and Australia)	Subjects with predominantly classic subfoveal neovascular AMD (423)	0.3 mg (n = 140), 0.5 mg (n = 140), Verteporfin PDT (+ sham injection) (n = 143)	Intravitreal injection monthly over 2 years, or verteporfin PDT every 3 months as need	Proportion of subjects who lost < 15 letters (approximately 3 lines) in the best corrected visual acuity (BCVA) score at month 12 compared to baseline, based on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart and assessment at 4-meter test distance.	• Proportion of subjects who gained ≥15 letters in the BCVA score at month 12 compared with baseline • Change from baseline in the BCVA score over time up to month 12
FVF2598g (III)	Randomized, double-masked, sham-controlled (U.S.)	Subjects with minimally classic or occult subfoveal neovascular AMD (716)	0.3 mg (n = 238), 0.5 mg (n = 240), sham injection (n = 238)	Intravitreal injection monthly injections over 2 years	Proportion of subjects who lost < 15 letters in the BCVA score at Month 12 compared to baseline, based on the ETDRS visual acuity chart and assessment at 4-meter test distance.	• Proportion of subjects who gained ≥15 letters in the BCVA score at month 12 compared with baseline • Change from baseline in the BCVA score over time up to month 12
FVF3192g (IIIb)	Randomized, double-masked, sham-controlled (U.S.)	Subjects with recurrent subfoveal CNV with or without classic CNV secondary to AMD (184)	0.3 mg 0.5mg sham injection (Target: 61–62 subjects per group)	Intravitreal injection monthly for 3 doses (Day 0, Month 1, and Month 2) followed by doses every 3 months (Months 5, 8, 11, 14, 17, 20, and 23)	Change from baseline in the BCVA score at month 12	• Proportion of subjects who lost < 15 letters in the BCVA score at month 12 compared with baseline. • Proportion of subjects who gained ≥15 letters in the BCVA score at month 12 compared with baseline

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Table 2: Subject Disposition

	Number of Subjects								
	Study FVF2598g			Study FVF2587g			Study FVF3192g		
	Sham Injection N (%)	Ranibizumab		Verteporfin PDT	Ranibizumab			Ranibizumab	
		0.3 mg N (%)	0.5 mg N (%)		0.3 mg N (%)	0.5 mg N (%)	Sham Injection N (%)	0.3 mg N (%)	0.5 mg N (%)
Randomized	238	238	240	143	140	140	63	60	61
Completed Month 12 [a]	212 (89.1%)	226 (95.0%)	226 (94.2%)	127 (88.8%)	128 (91.4%)	131 (93.6%)			
Discontinued Treatment Prematurely	31 (13.0%)	10 (4.2%)	11 (4.6%)	15 (10.5%)	14 (10.0%)	9 (6.4%)	8 (12.7%)	1 (1.7%)	2 (3.3%)
Discontinued Study prematurely	21 (8.8%)	6 (2.5%)	6 (2.5%)	10 (7.0%)	10 (7.1%)	5 (3.6%)	8 (12.7)	1 (1.7)	2 (3.3%)
Safety Evaluable Population received study medication, as treated	236 (99.2%)	238 (100%)	239 (99.6%)	143 (100%)	137 (97.9%)	140 (100%)			
Intent-to-treat Population ≥ 1 on therapy study visit	236 (99.2%)	238 (100%)	239 (99.6%)	143 (100%)	140 (100%)	140 (100%)			
Per Protocol Population (for the analysis of 4 m BCVA at Month 12) No on-therapy study visits or protocol violation	176 (73.9%)	200 (84.0%)	196 (81.7%)	114 (79.7%)	101 (72.1%)	103 (73.6%)			
Excluded from PP Population	62 (26.1%)	38 (11.8%)	44 (18.3%)	62 (26.1%)	38 (11.8%)	44 (18.3%)			
Pharmacokinetic-Evaluable Population	218 (91.6%)	226 (95.0%)	225 (93.8%)	136 (95.1%)	135 (96.4%)	137 (97.9%)			

[a] Defined as having a visual acuity score in the study eye at Month 12. Data from subjects who missed the Month 12 visit but stayed in the study for the second year were not counted.

Note: empty cell means no data were provided in the submision.

Statistical Reviewer's Comments: Overall, both studies had good retention rate through Month 12. The sham injection group had more discontinuations than either ranibizumab treatment group.

Table 3.1: Major Protocol Deviations during the First Treatment Year Randomized Subjects (Study FVF2598g)

Deviation	Sham (N=238)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=240)
Any deviation	55 (23.1%)	57 (23.9%)	62 (25.8%)
Re-randomized	0	0	1 (0.4%)
Dosing error: Overdose	0	1 (0.4%)	1 (0.4%)
Dosing Error: Procedure (injection) accident	0	1 (0.4%)	1 (0.4%)
Dosing Error: Sham injection performed	0	2 (0.8%)	1 (0.4%)
Treatment assignment unmasked [a]	1 (0.4%)	0	4 (1.7%)
Ineligible per protocol off-label PDT use	9 (3.8%)	0	0
Received PDT <21 days after a study drug injection			
Study eye	1 (0.4%)	0	0
Fellow eye	4 (1.7%)	9 (3.8%)	2 (0.8%)
Pre-treatment procedure not followed	5 (2.1%)	1 (0.4%)	4 (1.7%)
Dose-holding criteria not followed	1 (0.4%)	4 (1.7%)	1 (0.4%)
Visual acuity (4 m) not assessed at baseline: study eye	9 (3.8%)	9 (3.8%)	10 (4.2%)
Visual acuity (2 m) assessment incomplete: letters smaller than 20/20 not adequately tested			
Study eye	0	2 (0.8%)	3 (1.3%)
Fellow eye	24 (10.1%)	10 (4.2%)	13 (5.4%)
ETDRS chart with notation for 2-m testing was used	1 (0.4%)	3 (1.3%)	2(0.8%)
ETDRS charts switch usage (left eye chart vs. right eye chart)	0	0	1 (0.4%)
Slit lamp was performed after injection			
On Day 0	1 (0.4%)	2 (0.8%)	1 (0.4%)
At any visit other than Day 0	1 (0.4%)	2 (0.8%)	1 (0.4%)
Required a reader/translator's help for VFQ-25 and other questionnaires	1 (0.4%)	0	1 (0.4%)
Vital signs assessed pre-dose	7 (2.9%)	6 (2.5%)	9 (3.8%)
Inconsistent method for IOP measurement	11 (4.6%)	20 (8.4%)	22 (9.2%)

[a] Only study coordinators were unmasked for one case in the sham-injection group and two cases in the 0.5 mg group. Data Source: Applicant's Table 14.1/5.

Statistical Reviewer's Comments: There was no marked difference in protocol deviations among group groups. The protocol deviations which occurred most frequently were: inconsistent method for IOP measurement, incomplete assessment of 2 m visual acuity in the fellow eye, and failure to assess 4m visual acuity at baseline.

Table 3.2: Major Protocol Deviations during the First Treatment Year Randomized Subjects (Study FVF2587g)

Deviation	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=140)	Ranibizumab 0.5 mg (N=140)
Any deviation	**21 (14.7%)**	**36 (25.7%)**	**26 (18.6%)**
Treatment error: incorrect treatment	2 (1.4%)	7 (5.0%)	2 (1.4%)
Treatment error: received verteporfin PDT + ranibizumab at the same visit	0	2 (1.4%)	2 (1.4%)
Treatment error: incorrect administration	1 (0.7%)	3 (2.1%)	1 (0.7%)
Treatment error: received study drug kit from Study FVF2598G	0	3 (2.1%)	0
Treatment: off-schedule verteporfin/sham PDT	0	1 (0.7%)	1 (0.7%)
Treatment assignment unmasked	2 (1.4%)	1 (0.7%)	4 (2.9%)
Pre- and post-treatment procedure not followed	4 (2.8%)	9 (6.4%)	6 (4.3%)
Treatment holding criteria not followed	2 (1.4%)	1 (0.7%)	2 (1.4%)
Open-label verteporfin PDT in fellow eye <21 days after last ranibizumab/sham injection	5 (3.5%)	7 (5.0%)	3 (2.1%)
Open-label verteporfin PDT in fellow eye <5 days after last ranibizumab/sham injection	1 (0.7%)	2 (1.4%)	1 (0.7%)
Received excluded concomitant treatment in study eye	1 (0.7%)	0	0
Cataract surgery in the study eye within <28 days of a ranibizumab/sham injection	0	4 (2.9%)	1 (0.7%)
Visual acuity (4m) not assessed at Day 0 (study eye)	2 (1.4%)	7 (5.0%)	1 (0.7%)
Visual acuity (2 m) not assessed at Day 0 (study eye)	0	1 (0.7%)	1 (0.7%)
Visual acuity (2m) assessment incomplete; unknown if vision was better than 20/20 (study eye)	0	1 (0.7%)	0
Inconsistent method for measuring IOP	2 (1.4%)	2 (1.4%)	4 (2.9%)
Vital signs assessed predose	5 (3.5%)	3 (2.1%)	5 (3.6%)

Data Source: Applicant's Table 14.1/5.

Statistical Reviewer's Comments: The most protocol deviations occurred in the ranibizumab 0.3 mg group (25.7%) followed by ranibizumab 0.5 mg (18.6%). The three categories of "Treatment errors", "pre- and post-treatment procedure not followed" and "4m visual acuity not assessed at Day 0" represented the majority of the protocol deviations in the ranibizumab 0.3 mg group.

Table 4: Demographic Statistics by Treatment Group
Intent-to-Treat, Randomized Subjects (Study FVF2598g)

	Study FVF2598g			Study FVF2587g			Study FVF3192g		
		Ranibizumab		Verteporfin	Ranibizumab			Ranibizumab	
Demographic	Sham (n = 238)	0.3 mg (n = 238)	0.5 mg (n = 240)	PDT (N=143)	Sham (n = 140)	0.3 mg (n = 140)	Sham (N=63)	0.3 mg (n = 60)	0.5 mg (n = 61)
Age (yr)									
Mean (SD)	77.0 (6.6)	77.4 (7.6)	76.8 (7.6)	77.7 (7.8)	77.4 (7.5)	76.0 (8.6)	77.8 (7.1)	78.7 (6.3)	78.8 (7.9)
Range	56–94	52–95	52–93	53-95	54-97	54-93	59 – 92	60 – 93	54 – 94
Age group (yr)									
50 to < 65	11 (4.6%)	13 (5.5%)	16 (6.7%)	8 (5.6%)	9 (6.4%)	14 (10.0%)	4 (6.3%)	1 (1.7%)	5 (4.1%)
65 to < 75	67 (28.2%)	64 (26.9%)	64 (26.7%)	35 (24.5%)	28 (20.0%)	41 (29.3%)	12 (19.0%)	12 (20.0%)	12 (19.7%)
75 to < 85	132 (55.5%)	130 (54.6%)	124 (51.7%)	74 (51.7%)	84 (60.0%)	64 (45.7%)	36 (57.1%)	37 (61.7%)	31 (50.8%)
≥ 85	28 (11.8%)	31 (13.0%)	36 (15.0%)	26 (18.2%)	19 (13.6%)	21 (15.0%)	11 (17.5%)	10 (16.7%)	14 (23.0%)
Sex									
Male	79 (33.2%)	85 (35.7%)	88 (36.7%)	64 (44.8%)	73 (52.1%)	75 (53.6%)	20 (31.7%)	26 (43.3%)	28 (45.9%)
Female	159 (66.8%)	153 (64.3%)	152 (63.3%)	79 (55.2%)	67 (47.9%)	65 (46.4%)	43 (68.3%)	34 (56.7%)	33 (54.1%)
Race/ethnicity									
White	231 (97.1%)	229 (96.2%)	232 (96.7%)	140 (97.9%)	137 (97.9%)	136 (97.1%)	59 (93.7%)	57 (95.0%)	56 (91.8%)
Asian or Pacific Islander	2 (0.8%)	3 (1.3%)	2 (0.8%)	1 (0.7%)	0	1 (0.7%)	0 (0.0%)	1 (1.7%)	3 (4.9%)
Hispanic	5 (2.1%)	5 (2.1%)	6 (2.5%)	1 (0.7%)	3 (2.1%)	2 (1.4%)	2 (3.2%)	2 (3.3%)	2 (3.3%)
Other	0	1 (0.4%)	0	1 (0.7%)	0	0	2 (3.2%)	0 (0.0%)	0 (0.0%)
Any prior therapy for AMD				64 (44.8%)	63 (45.0%)	58 (41.4%)			
Laser photocoagulation				19 (13.3%)	23 (16.4%)	20 (14.3%)			
Medication /Supplements				52 (36.4%)	49 (35.0%)	46 (32.9%)			

Statistical Reviewer's Comments: The demographics of the subjects are well balanced across treatment groups within each study. The majority of subjects are elderly and white. The study population represents the population affected by this disease. In study FVF2587g approximately 40% of subjects reported prior therapy for AMD in the study eye and approximately 15% reported prior laser photocoagulation in the study eye. No subjects had prior verteporfin PDT therapy because the study excluded it. Baseline ocular characteristics, fluorescein angiography and fundus photography characteristics of the study eye are also balanced across treatment groups within each study (see clinical reviewers' review for details).

3.1.2 Statistical Methodologies

In each of the three studies the primary efficacy assessment was based on the best corrected visual acuity (BCVA) score measured at a starting test distance of 4 meters (based on the Early Treatment Diabetic Retinopathy Study visual acuity chart).

Study FVF2598g

Primary Study Endpoint:

The primary study endpoint was the proportion of subjects who lost fewer than 15 letters (approximately 3 lines) in the BCVA score at Month 12 compared to baseline.

The primary hypothesis tested in this study was that at least in one of the two ranibizumab dose groups there would be more subjects losing fewer than 15 letters in the BCVA score at 12 month than those in the sham group. The primary efficacy analysis was based on the randomized population, with missing data imputed using the last observation carried forward (LOCF) method. The proportions were compared between each of the two ranibizumab dose groups and the sham group using the Cochran χ^2 test stratified by baseline CNV classification (Occult with No Classic CNV, Minimally Classic CNV) and baseline BCVA score ($\leq$54, >55 letters). The Hochberg-Bonferroni multiple comparison procedure was used to adjust for comparison of the two ranibizumab dose groups with the control group in order to maintain an overall Type I error rate of 0.05.

The test was performed at an overall significance level of 0.0497 (after adjusting for the three interim safety reviews by the DMC). If the p-values for both comparisons were $\leq$ 0.0497, both ranibizumab groups were considered statistically significantly different from the sham control group. If the p-value for the comparison of one ranibizumab group with the sham control group was > 0.0497, the other ranibizumab group was considered statistically significantly different from the control group only if the p-value for its comparison with the control group was $\leq$ 0.0497/2 (0.02485).

Sensitivity analyses were performed and included analysis using the observed data only and analysis using the worst outcome imputation for missing data. The statistical reviewer also performed sensitivity analysis by treating missing data as non-response.

Key Secondary Study Endpoints

The key secondary study endpoint was the proportion of subjects who gained at least 15 letters in BCVA score at Month 12 compared to baseline assessment. This endpoint was analyzed in a similar manner as for the primary endpoint.

Another key secondary study endpoint was the change in BCVA score at 12 month from baseline. The mean change in BCVA score were compared between each of the two ranibizumab dose groups and the control group using an ANOVA model with baseline CNV classification and baseline visual acuity score as covariates.

Study FVF2587g

Primary Study Endpoint:

The primary study endpoint was the proportion of subjects who lost fewer than 15 letters in the BCVA score at Month 12 compared to baseline.

The primary hypothesis tested in this study was that at least one of the two ranibizumab dose groups would not be non-inferior to the active control group with respect to the efficacy measurement of proportion of subject losing fewer than 15 letters in the BCVA score at 12 month. A non-inferiority margin of 7% was used. The primary efficacy endpoint was analyzed for the population of randomized subjects, with missing data imputed using the LOCF method.

For each ranibizumab dose group, non-inferiority to the control group was tested using a one-sided testing procedure (or equivalently, using a one-sided CI) and a non-inferiority limit of 7%. A one-sided CI for the weighted average of the differences between two proportions over the strata, with baseline visual acuity score as the stratification variable. The Cochran-Mantel-Haenszel weights were used to calculate the weighted average or the overall stratified difference in proportions (see applicant's analysis plan for details). The normal approximation test was performed by applying the procedure proposed by Blackwelder to stratified binomials. The test for the proportion difference between each of the two ranibizumab dose groups and the control group was performed using the Cochran χ^2 test stratified by baseline BCVA score and baseline CNV classification.

If the non-inferiority test demonstrated that one or both ranibizumab dose groups were statistically significantly non-inferior to the control group, then the superiority test between each of the ranibizumab groups and the control group would be conducted. The superiority comparison between each ranibizumab dose group and the control group with respect to the primary efficacy endpoint would be performed using the Cochran χ^2 test stratified by baseline CNV classification and baseline visual acuity score.

To adjust for multiple comparisons of two ranibizumab dose groups with the control group, the Hochberg-Bonferroni multiple comparison procedure was used. A hierarchical procedure was implemented to account for the multiple hypothesis tests of non-inferiority and treatment difference for the comparison of each ranibizumab dose group with the control group. The targeted level for the overall Type I error, accounting for testing of both dose groups as well as the testing of non-inferiority followed by treatment difference, was $\leq$0.0247 (0.05 minus an adjustment of 0.0003 for three interim safety analyses conducted).

Key Secondary Study Endpoints

The key secondary study endpoint was the proportion of subjects who gained at least 15 letters in BCVA score at Month 12 compared to baseline assessment. This endpoint was analyzed in a similar manner as for the primary endpoint.

Another secondary study endpoint was the change in BCVA score at 12 month from baseline. The mean change in BCVA score were compared between each ranibizumab group and the control group using an ANOVA model.

Study FVF3192g

The primary study endpoint was the mean change in BCVA score at 12 month from baseline.

The primary hypothesis tested in this study was that at least one of the two ranibizumab treatment doses would result in a better mean change from baseline in the BCVA score at 12 month compared to the sham group. The primary efficacy analysis was based on the randomized population, with missing data imputed using the LOCF method. The mean change in BCVA score were compared between each ranibizumab group and the control group using an ANOVA model with baseline CNV classification and baseline visual acuity score as covariates. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for comparison of the two ranibizumab groups with the control group in order to maintain an overall Type I error rate of 0.05.

The primary efficacy endpoint was also analyzed using the observed data only and using the worst outcome imputation for missing data. Statistical reviewer also performed sensitivity analysis using test without adjusting baseline CNV classification and baseline visual acuity score for the observed data to exam further the robust of the efficacy results.

Key Secondary Study Endpoints

The key secondary study endpoint was the proportion of subjects who lost fewer than 15 letters (approximately 3 lines) in the BCVA score at Month 12 compared to baseline.

Another key secondary study endpoint was the proportion of subjects who gained at least 15 letters in BCVA score at Month 12 compared to baseline assessment.

These binary endpoints were analyzed in a similar manner as for those in study FVF2598g.

Summary

Statistical reviewer's comments:

Overall, each of the three studies was designed to compare the ranibizumab treatments with the concurrent control group. The applicant's statistical analysis methods were adequate for this purpose. However, it should be noted that none of the three studies were designed to compare the efficacy results between the two ranibizumab dose groups (0.3mg versus 0.5mg). Thus statistically sound comparison of the efficacy results between these two dose groups could not be

made within or across studies. Furthermore, none of the three studies were designed to compare the efficacy results between the two ranibizumab dosing frequencies (monthly injection in studies FVF2598g and FVF2587g versus monthly injection for 3 doses then followed by quarterly injection in study FVF3192g). Thus statistically sound comparison of the efficacy results between these two dosing frequencies could not be made across studies.

3.1.2 Results and Conclusions

Statistical reviewer's comments:

The key efficacy results for the visual acuity at 12 month at a starting test distance of 4 meters are presented in Table 5 and discussed in the following sections.

The proportions of subject losing fewer than 15 letters

In the control groups the proportions of subject losing fewer than 15 letters are 60% (study FVF2598g), 66% (study FVF2587g), and 49% (study FVF3192g). In the ranibizumab 0.3mg group the proportions of subject losing fewer than 15 letters are 93% (study FVF2598g), 95% (study FVF2587g), and 83% (study FVF3192g). In the ranibizumab 0.5mg group the proportions of subject losing fewer than 15 letters are 91% (study FVF2598g), 98% (study FVF2587g), and 90% (study FVF3192g).

It is noted that in study FVF3192g the proportion of subjects losing fewer than 15 letters is about 10% less than those in study FVF2598g in both the sham group and the ranibizumab 0.3mg group. However, compared to the concurrent control group, the differences in the proportions are about the same as those in study FVF2598g. They are 32% (study FVF2598g), 29% (study FVF2587g), and 34% (study FVF3192g) for the ranibizumab 0.3mg group; 30% (study FVF2598g), 32% (study FVF2587g), and 37% (study FVF3192g) for the ranibizumab 0.5mg group.

In summary, both ranibizumab doses are superior to the concurrent control group. Furthermore, within each trial the proportions in the two ranibizumab groups appear to be similar.
In comparison with the concurrent control group, the proportions in the ranibizumab groups appear to be similar across the three trials.

The proportions of subject gaining at least 15 letters

In the control groups the proportions of subject gaining at least 15 letters are 6% (study FVF2598g), 11% (study FVF2587g), and 10% (study FVF3192g). In the ranibizumab 0.3mg group the proportions of subject gaining at least 15 letters are 18% (study FVF2598g), 28% (study FVF2587g), and 12% (study FVF3192g). In the ranibizumab 0.5mg group the proportions of subject gaining at least 15 letters are 31% (study FVF2598g), 37% (study FVF2587g), and 13% (study FVF3192g).

Compared to the concurrent control group, the differences in the proportions are 12% (study FVF2598g), 17% (study FVF2587g), and 1% (study FVF3192g) for the ranibizumab 0.3mg

group; 25% (study FVF2598g), 26% (study FVF2587g), and 2% (study FVF3192g) for the ranibizumab 0.5mg group.

In study FVF3192g the proportions in both the ranibizumab groups (monthly injections for 3 doses then followed by quarterly injection) appear to be similar as those in the sham control group and lower than those in the ranibizumab groups with monthly injections in the other two studies. However, without a concurrent monthly dosing treatment group in study FVF3192g, one cannot scientifically conclude that these appearing lower response rates were attributed to the less frequently injections after the first three months of the study in comparison with the monthly injections in the other two studies.

In summary, the results show that in study FVF2598g and FVF2587g both ranibizumab dose treatments are superior to the concurrent control group and the proportions in the 0.5mg dose group are higher than those in the 0.3mg dose group. In study FVF3192g, the proportions in both ranibizumab dose groups are similar to those in the sham control group.

Change in BCVA score from baseline

In the control groups the mean change (SD) from baseline in the BCVA score are -11 (17.9) (study FVF2598g), -8.5 (17.8) (study FVF2587g), and -16.3 (22.3) (study FVF3192g). In the ranibizumab 0.3mg group the mean change (SD) from baseline in visual acuity are 5.4 (13.4) (study FVF2598g), 7.2 (15.3) (study FVF2587g), and -1.6 (15.1) (study FVF3192g). In the ranibizumab 0.5mg group the mean change (SD) from baseline in visual acuity are 6.3 (14.1) (study FVF2598g), 11 (15.8) (study FVF2587g), and -0.2 (13.1) (study FVF3192g).

Compared to the control group, the differences in the mean changes are 16.3 (study FVF2598g), 15.9 (study FVF2587g), and 13.8 (study FVF3192g) for the ranibizumab 0.3mg group, 17.1 (study FVF2598g), 19.8 (study FVF2587g), and 14.7 (study FVF3192g) for the ranibizumab 0.5mg group.

In study FVF3192g the proportions in the ranibizumab groups with 3 monthly injections followed by quarterly injection appear to be similar to the sham control group and lower than those observed in the ranibizumab groups with monthly injections in the other two studies. However, without a concurrent monthly dosing treatment group in study FVF3192G, one cannot scientifically conclude that these appearing lower response rates were attributed to the less frequently injections (quarterly) after the first three months in comparison with the monthly injections in the other two studies.

The visual acuity scores at a starting test distance of 4 meters were collected at each study visit in study FVF3192g. Study FVF2598 had 4-meter vision measurement at only two post-baseline time points (Month 12 and Month 24) and had 2-meter vision measurement at each study visit. Study FVF2587g had 4-meter vision measurement at Month 12 available in this submission (The submission had only one year data) and had 2-meter vision measurement at each study visit.

The mean changes in the visual acuity scores over time are plotted in Figure 1. These plots show that the two ranibizumab doses (0.3mg and 0.5mg) had similar effect on the BCVA score.

In the monthly dosing studies VFV2598g and VFV2587g, the gain in the BCVA score was maintained throughout the study period. However, in study FVF3192g (with monthly injection for three doses followed by quarterly dose), the BCVA score trended back toward the baseline in both the ranibizumab treatment groups even though the relative effect of ranibizumab treatments compared with the sham group was maintained and was similar to those observed in the other two studies with monthly injection.

In summary, both ranibizumab doses are superior to the concurrent control group. Furthermore, within each trial the mean changes in BCVA scores in the two ranibizumab groups appear to be similar. In comparison with the concurrent control group, the mean changes in BCVA scores in the ranibizumab groups appear to be similar across the three trials.

Sensitivity Analysis Results

As part of the sensitivity analyses, the applicant also performed the efficacy analyses using the worst outcome imputation for missing data. The results are similar to the ones using the LOCF method. The applicant also provided the efficacy results based on the observed data (see Table 6). The results are consistent with the ones using the LOCF method.

The statistical reviewer also performed additional sensitivity analysis. In this analysis subjects with missing data are treated as failure for the response variables of losing fewer than 15 letters or gaining more than 15 letters. The results are presented in Table 7.

With this missing data imputation, the proportions of subjects losing fewer than 15 letters were about 10% lower compared to the ones using the LOCF method across the treatment groups for studies FVF2598g and FVF2587g. Thus the relative difference in both the ranibizumab groups, compared with the control group, don't differ from the ones using the LOCF method for these two studies. For study FVF3192g, the relative difference in both the ranibizumab groups, compared with the control group, are about 10% higher than the ones using the LOCF method.

Table 5: Visual Acuity in the Study Eye at 12 Months at a Starting Test Distance of 4 Meters (LOCF) (ITT Population)

	Study FVF2598g			Study FVF2587g			Study FVF3192g		
		Ranibizumab		Verteporfin	Ranibizumab			Ranibizumab	
	Sham (N = 238)	0.3 mg (N = 238)	0.5 mg (N = 240)	PDT (N = 143)	0.3 mg (N = 140)	0.5 mg (N = 140)	Sham (N = 63)	0.3 mg (N = 60)	0.5 mg (N = 61)
n	229	229	230	141	133	139	63	60	61
Loss of < 15 letters	138 (60%)	213 (93%)	209 (91%)	93 (66%)	126 (95%)	136 (98%)	31 (49%)	50 (83%)	55 (90%)
Difference[a]		32%	30%		29%	32%		34%	37%
(95%CI)		(25%, 39%)	(23%, 37%)		(20%, 38%)	(24%, 40%)		(19%, 49%)	(23%, 52%)
p-value		< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
Gain of ≥ 15 letters	14 (6%)	42 (18%)	72 (31%)	15 (11%)	37 (28%)	51 (37%)	6 (10%)	7 (12%)	8 (13%)
Difference		12%	25%		17%	26%		1%	2%
(95%CI)		(6%, 18%)	(18%, 31%)		(8%, 26%)	(17%, 36%)		(-10%, 12%)	(-8%, 12%)
p-value		< 0.001	< 0.001		< 0.0001	< 0.001			
Change from baseline									
mean (SD)	-11.0 (17.9)	5.4 (13.4)	6.3 (14.1)	− 8.5 (17.8)	7.2 (15.3)	11.0 (15.8)	-16.3(22.3)	-1.6 (15.1)	-0.2 (13.1)
Difference		16.3	17.1		15.9	19.8		13.8	14.7
(95%CI)		(13.5, 19.2)	(14.2, 20.0)		(11.9, 19.8)	(15.9, 23.7)		(7.0, 20.7)	(8.2, 21.2)
p-value		< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001

Note: The LOCF method was used to impute missing data. Strata were defined using two factors: baseline CNV classification and baseline visual acuity score.

[a] Weighted estimates adjusting for the strata by using the Cochran-Mantel-Haenszel weights.

[b] From Cochran χ_2 tests adjusted for the strata.

Table 6: Visual Acuity in the Study Eye at 12 Months at a Starting Test Distance of 4 Meters (ITT Population, Observed Data)

	Study FVF2598g			Study FVF2587g			Study FVF3192g		
		Ranibizumab		Verteporfin	Ranibizumab			Ranibizumab	
	Sham (N = 238)	0.3 mg (N = 238)	0.5 mg (N = 240)	PDT (N = 143)	0.3 mg (N = 140)	0.5 mg (N = 140)	Sham (N = 63)	0.3 mg (N = 60)	0.5 mg (N = 61)
n	205	216	214	125	119	124	54	59	58
Loss of < 15 letters	117 (57%)	200 (93%)	193 (90%)	77 (62%)	112 (94%)	121 (98%)	26 (48%)	49 (83%)	52 (90%)
Difference[a]		35%	33%		33%	36%		37%	38%
(95%CI)		(28%, 43%)	(25%, 40%)		(24%, 42%)	(27%, 45%)		(21%, 52%)	(22%, 53%)
p-value		< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
Gain of ≥ 15 letters	14 (7%)	42 (19%)	72 (34%)	14 (11%)	37 (31%)	51 (47%)	6 (11%)	7 (12%)	8 (14%)
Difference[a]		13%	26%		20%	30%		-0.0%	2%
(95%CI)		(6%, 19%)	(19%, 33%)		(10%, 30%)	(20%, 40%)		(-12%, 12%)	(-10%, 13%)
p-value		< 0.001	< 0.001		< 0.0001	< 0.001			
Change from baseline									
mean (SD)	-11.9 (17.9)	5.8 (13.7)	6.8 (14.5)	− 9.8 (18.5)	8.0 (16.0)	12.3 (16.2)	-14.8(21.4)	-1.6 (15.2)	-0.1 (13.3)
Difference[b]		17.6	18.5		18.0	22.3		12.7	13.4
(95%CI)		(14.5, 20.7)	(15.4, 21.6)		(13.7, 22.3)	(18.0, 26.5)		(5.7, 19.6)	(6.7, 20.0)
p-value		< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001

Note: Strata were defined using two factors: baseline CNV classification and baseline BCVA score.

[a] Weighted estimates adjusting for the strata by using the Cochran-Mantel-Haenszel weights. P-value was based on Cochran $\chi 2$ tests adjusted for the strata.

[b] From pairwise ANOVA models.

Table 7: Visual Acuity in the Study Eye at 12 Months at a Starting Test Distance of 4 Meters (ITT Population, Not LOCF)

	Study FVF2598g			Study FVF2587g			Study FVF3192g		
		Ranibizumab		Verteporfin	Ranibizumab			Ranibizumab	
	Sham (N = 238)	0.3 mg (N = 238)	0.5 mg (N = 240)	PDT (N = 143)	0.3 mg (N = 140)	0.5 mg (N = 140)	Sham (N = 63)	0.3 mg (N = 60)	0.5 mg (N = 61)
Loss of < 15 letters[a]	117 (49%)	200 (84%)	193 (80%)	77 (54%)	112 (80%)	121 (86%)	26 (41%)	49 (82%)	52 (85%)
Difference (95%CI)[b]		35%	31%		26%	33%		40%	44%
		(27%, 43%)	(23%, 39%)		(16%, 37%)	(23%, 43%)		(25%, 56%)	(29%, 59%)
Gain of ≥ 15 letters[a]	14 (6%)	42 (18%)	72 (30%)	14 (10%)	37 (26%)	51 (36%)	6 (10%)	7 (12%)	8 (13%)
Difference (95%CI)[b]		12%	24%		17%	27%		2%	4%
		(6%, 18%)	(18%, 31%)		(8%, 25%)	(17%, 36%)		(-9%, 13%)	(-8%, 15%)
									14.7 (8.1, 21.3)

[a] Missing data were treated as failure in the binary outcome response variables.
[b] Calculated using normal approximation.

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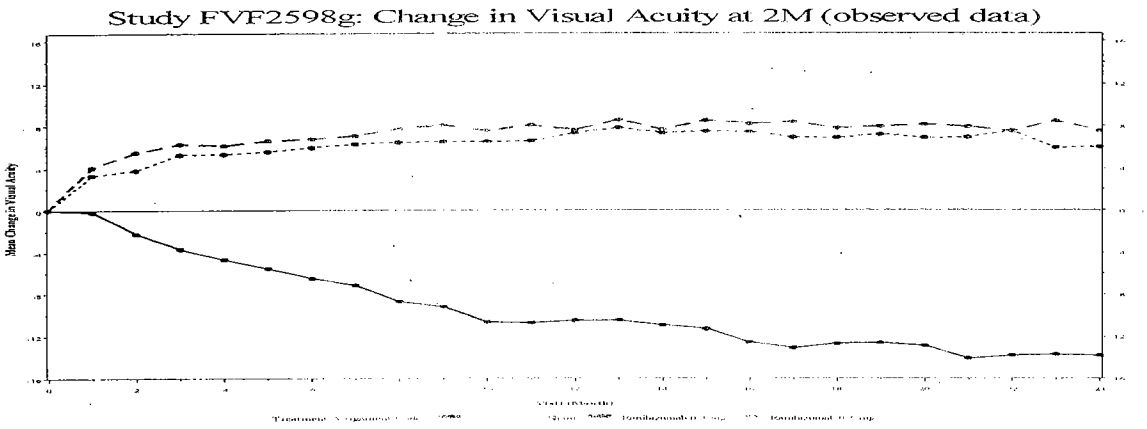
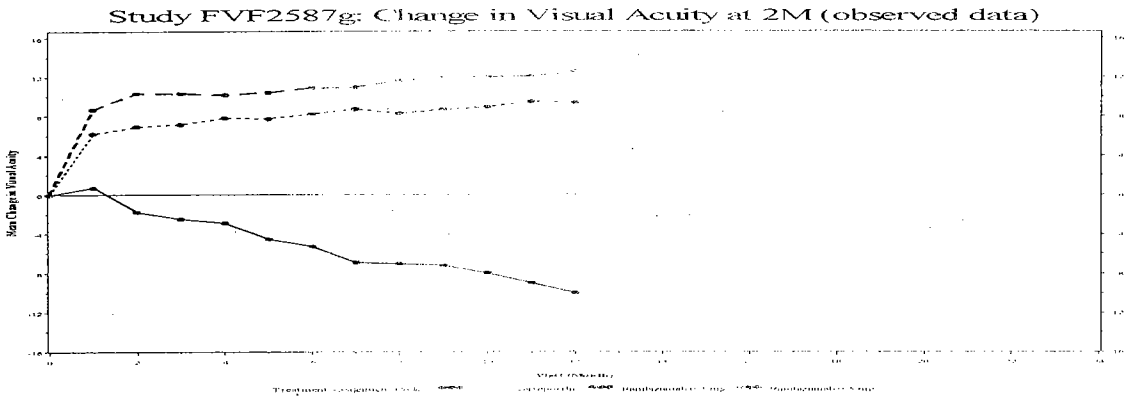
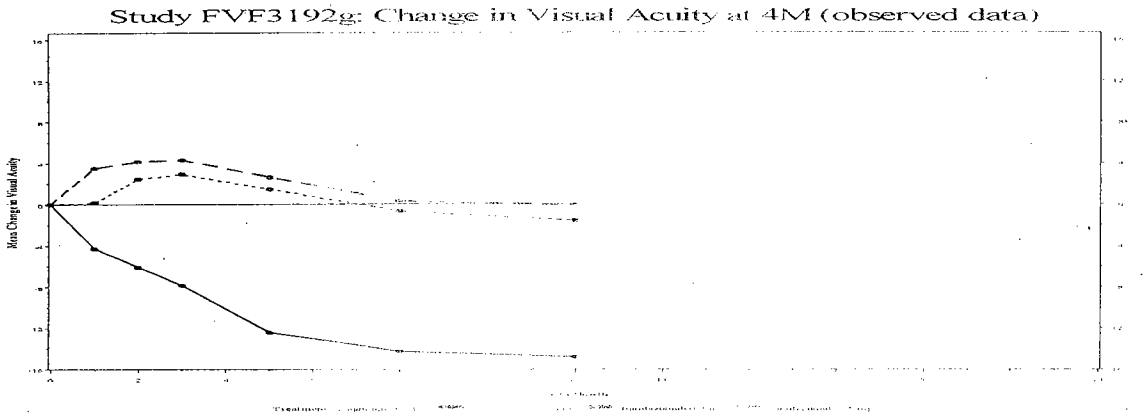
Figure 1







3.2 Evaluation of Safety

See medical reviewers' comments.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

See medical reviewers' comments.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Each of the three studies was designed to compare the ranibizumab treatments with the concurrent control group. The applicant's statistical analysis methods were adequate for this purpose. However, it should be noted that none of the three studies were designed to compare the efficacy results between the two ranibizumab dose groups (0.3mg versus 0.5mg). Thus statistically sound comparison of the efficacy results between these two dose groups could not be made within or across studies. Furthermore, none of the three studies were designed to compare the efficacy results between the two ranibizumab dosing frequencies (monthly injection in studies FVF2598g and FVF2587g versus monthly injection for 3 doses then followed by quarterly injection in study FVF3192g). Thus statistically sound comparison of the efficacy results between these two dosing frequencies could not be made across studies.

5.2 Conclusions and Recommendations

This BLA submission (BLA125156) seeks to gain approval for the use of ranibizumab injection in the treatment of patients with neovascular (wet) age-related macular degeneration (AMD).

[redacted]

This submission includes data from two pivotal Phase 3 (FVF2598g and FVF2587g) and one Phase 3b (FVF3192g) clinical trials. These studies demonstrated that both ranibizumab 0.3mg and 0.5mg doses (monthly injection, or monthly injection for 3 doses followed by quarterly injection) were effective in treating subjects with AMD.

Phase 3 study FVF2598g demonstrated that both ranibizumab 0.3mg and 0.5mg doses (monthly injection) yielded statistically significant differences in the proportion of subjects who lost fewer than 15 letters in the best corrected visual acuity (BCVA) score at 12 months compared with the placebo treatment (sham). The efficacy results from this study appeared to be similar between the two ranibizumab dose groups.

Phase 3 study FVF2587g demonstrated that both ranibizumab 0.3mg and 0.5mg doses (monthly injection) yielded statistically significant differences in the proportion of subjects who lost fewer than 15 letters in the BCVA score at 12 months compared with the active control treatment (verteporfin for injection). The efficacy results from this study appeared to be similar between the two ranibizumab dose groups.

Phase 3b study FVF3192g demonstrated that both ranibizumab 0.3mg and 0.5mg doses (monthly injection at Day 0, Month 1, and Month 2, then followed by injection every 3 months) yielded statistically significant differences in the mean change from baseline in the BCVA score at 12 month compared with the placebo treatment (sham). The efficacy results from this study appeared to be similar between the two ranibizumab dose groups.

Each of the three studies was designed to compare each of the two ranibizumab dose groups (0.3mg versus 0.5mg) to the concurrent control group. None of the three studies were designed to compare the efficacy results between the two ranibizumab dose groups. Thus statistically sound comparison of the efficacy results between these two doses could not be made within or across studies. Furthermore, none of the three studies were designed to compare the efficacy results between the two ranibizumab dosing frequencies (monthly injection in both studies FVF2598g and FVF2587g versus monthly injection for 3 doses then followed by quarterly injection in study FVF3192g). Thus statistically sound comparison of the efficacy results between these two dosing frequencies could not be made across studies.

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