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Title: Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration

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Table of Contents

Table of Contents 2

List of Tables 4

List of Figures 4

1. Introduction 5
    - 1.1 Primary Study Objectives and Design 5
    - 1.2 Sample Size 6
    - 1.3 Database Lock and Procedures of Maintaining Masking 7
2. Analysis Populations and Data Conventions 7
    - 2.1 Analysis Populations 7
    - 2.2 Handling Mis-randomization and Mis-stratification 8
    - 2.3 Analysis Visit Windows 8
    - 2.4 Data Conventions 9
3. Disposition and Exit Status 10
    - 3.1 Disposition and Exit Status 10
    - 3.2 Significant Protocol Deviations 11
4. Demographics and Other Baseline Characteristics 11
    - 4.1 Demographics 11
    - 4.2 Baseline Characteristics 11
    - 4.3 Prior Medications/Procedures 11
    - 4.4 Concomitant Medications/Procedures 12
    - 4.5 Medical History 13
5. Efficacy Analyses 13
    - 5.1 Collection of Primary Efficacy Measurement and Derivation of Primary Efficacy Variable 14
    - 5.2 Primary Efficacy Analyses 14
        - 5.2.1 Statistical Hypothesis 14
        - 5.2.2 Primary Analyses of Primary Efficacy Variable 15
        - [redacted]
    - 5.3 Secondary Efficacy Analyses 18
        - 5.3.1 BCVA Mean Change from Baseline 18

5.3.2 SD-OCT CRT Mean Change from Baseline 19
5.3.3 BCVA Improvement of ≥ 15 Letters from Baseline 20
[redacted]
6.1 Study Treatment – Exposure and Administration 23
6.1.1 Exposure to Study Treatments 23
6.2 Adverse Events 24
6.2.1 TEAEs of Special Interest 25
[redacted]
8. Subgroup Analyses 35
9. Interim Analyses 35
[redacted]
11. Deviations from Protocol 38
12. References 38
13. Amendment(s) 38

13.1 Amendment 1 38
14. Appendix A 38

List of Tables

Table 1 Definitions for Analysis Visit Windows........ 9

[redacted]

List of Figures

[redacted] [redacted]

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1. Introduction

This document describes the planned analysis that will be used for Study 150998-006 clinical study report. This randomized, parallel-group study is designed to assess the safety and efficacy of abicipar pegol (hereafter referred to as abicipar) compared with ranibizumab in treatment-naïve patients with neovascular age-related macular degeneration (nAMD).

There will be two database locks. The first database lock (referred to as primary DBL) will occur when all patients have completed the Week 52 visit, or exited earlier. The study will be unmasked to a restricted group for primary analyses.

The second database lock (referred to as final DBL) will occur when all patients have completed the study entirely (Week 104 visit) or exited early from the study.

The analysis plan will support both primary and final DBL, but some analyses will be reduced for the final DBL. For example, demographic, baseline disease characteristics, and medical history will not be re-produced at the final DBL.

1.1 Primary Study Objectives and Design

The study objectives are to assess the safety and efficacy of abicipar compared with ranibizumab in treatment-naïve patients with nAMD.

The clinical hypotheses are:

- Multiple intravitreal injections of 2 mg abicipar have an acceptable safety profile in treatment-naïve patients with nAMD
- The efficacy of at least 1 of the 2 abicipar regimens is non-inferior to that of monthly ranibizumab intravitreal injections as assessed by the proportion of patients with stable vision at Week 52

This is a multicenter, double-masked, randomized, 104-week, parallel-group, active-controlled study to evaluate the safety and efficacy of abicipar in treatment-naïve patients with nAMD. Approximately 900 patients will be randomized by region with a 1:1:1 allocation ratio to receive one of the following three treatments:

- Treatment group 2Q8: 2 mg abicipar administered at baseline (Day 1) and Weeks 4 and 8, followed by doses at 8-week intervals through Week 96

- Treatment group 2Q12: 2 mg abicipar administered at baseline (Day 1), and Weeks 4 and 12, followed by doses at 12-week intervals through Week 96

- Treatment group rQ4: 0.5 mg ranibizumab administered every 4 weeks from baseline (Day 1) through Week 96

Regions are defined primarily based on geographical locations (eg, North America, EAME [Europe, Africa, and Middle East], Asia Pacific, and Latin America). For randomization purposes, some regions are combined and the following 3 regions are used: North America, Asia, and the rest of the world. The defined 3 regions for randomization will be used for statistical analysis. Within each region, randomization to treatment groups will be stratified by baseline value for best-corrected visual acuity (BCVA ≤ 55 versus > 55 ETDRS letters), central retinal thickness (CRT ≤ 400 versus > 400 microns), and lesion type of choroidal neovascularization (predominantly classic versus minimally classic or occult) in the study eye.

The study design including treatment and visit schedules is shown in Figure 1 below.

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1.2 Sample Size

For the primary efficacy endpoint of stable vision (ie, patients who lose fewer than 15 letters in BCVA from baseline) at Week 52, a sample size of 240 patients in each treatment group will provide approximately 95% power with a 2-sided alpha level of 0.05 to demonstrate non-inferiority of an abicipar group versus ranibizumab with a non-inferiority margin of 10%. This calculation is based on the assumption of a 90% response rate for both groups.

With an anticipated dropout rate of approximately 20% over the 52-week period, a total of 900 patients will be enrolled so that approximately 720 patients (240 per group) will complete 52 weeks as required for the primary endpoint evaluation.

1.3 Database Lock and Procedures of Maintaining Masking

The study will be unmasked to a restricted group for the primary analysis following the Week 52 database lock. Access to randomization codes and unmasked information will be strictly limited to team members who will be working on data analysis, study report completion, and submission-related documents. To maintain the integrity of the ongoing study, Allergan personnel who become unmasked after the Week 52 database lock will not participate in any masked activities during the remaining part of the study until after the final database lock at study completion. In particular, the unmasked study statistician(s) and programmer(s) will no longer be involved in any ongoing study conduct or data review activities. Other statisticians and programmers, who are still masked to study treatment, will assume these responsibilities until study completion.

2. Analysis Populations and Data Conventions

2.1 Analysis Populations

The following 3 populations will be used for statistical analysis: intent-to-treat (ITT), per-protocol (PP), and safety.

The ITT population includes all randomized patients. The ITT population will be used for all efficacy analyses.

The PP population includes all randomized and treated patients who do not have protocol deviations that impact the primary efficacy variable. The PP population will be used for analyses of the primary and secondary efficacy variables. Primary considerations for PP definition include treatment compliance that would represent the intended regimen adequately.

Specifically, the PP population will include patients who

1. Received at least 9 study treatments (including sham) and attended at least 9 scheduled monthly visits during the first year (before the Week 52 visit), and;
2. Had not missed 3 or more consecutive study treatments (including sham) before the 9th study treatment, and;

3. Did not have any major protocol deviations that impacted efficacy outcomes prior to the Week 52 visit

The PP population will also include patients who discontinued from the study as a result of treatment failure without a major deviation prior to Week 52 that impacted efficacy outcomes (even if they met criteria #1 or #2 above). Patients who escaped to standard of care by meeting the protocol criteria before Week 52 and study exit are considered as treatment failures. Final determination of the PP population will be made based on masked review of the data. Detailed specification will be documented separately prior to the primary database lock.

The safety population includes all treated patients and will be used for all safety analyses.

Analyses for ITT and PP populations will be based on randomized treatment group, whereas analyses for safety populations will be as treated, ie, based on the actual treatment that the patient received.

2.2 Handling Mis-randomization and Mis-stratification

In the event of mis-stratification that resulted in randomization under the wrong stratum, all PP analyses will be based on the actual stratum to which the patient belongs. ITT analysis that uses the randomization stratification factor(s) will be based on the stratum as randomized for the primary efficacy analysis and the actual stratum to which the patient belongs for other analyses such as model-based approaches.

2.3 Analysis Visit Windows

Analysis visit windows are defined according to study days, which are defined in Table 1.

Visit windows defined in Table 1 will be applied to all by-visit analyses of efficacy and safety variables. Out-of-window visits (including the exit visit) and unscheduled visits will be reassigned to the visit that the actual study days fall within.

In cases where multiple visits occurred within a single visit window, which resulted in multiple data points for the same window, the last visit with non-missing data will be used for analysis.

Table 1 Definitions for Analysis Visit Windows

Visit	Target Day of Visit	Analysis Visit Window (Study Days)
Baseline (Day 1)	1	≤ 1
Week 4	28	2-42
Week 8	56	43-70
Week 12	84	71-98
Week 16	112	99-126
Week 20	140	127-154
Week 24	168	155-182
Week 28	196	183-210
Week 32	224	211-238
Week 36	252	239-266
Week 40	280	267-294
Week 44	308	295-322
Week 48	336	323-350
Week 52	364	351-378
Week 56	392	379-406
Week 60	420	407-434
Week 64	448	435-462
Week 68	476	463-490
Week 72	504	491-518
Week 76	532	519-546
Week 80	560	547-574
Week 84	588	575-602
Week 88	616	603-630
Week 92	644	631-658
Week 96	672	659-686
Week 100	700	687-714
Week 104	728	715-742

2.4 Data Conventions

Unless stated otherwise in specific subsequent sections, data conventions and definitions listed below will be applied to all analyses.

- Day 1 is defined as the day when the patient receives the 1st study treatment.
  Study day = visit date – date of the 1st study treatment + 1

- For patients who were randomized but did not receive any study treatments after randomization, the date of randomization will be used as Day 1.

- Study duration will be calculated for each patient as:
  Study duration for the primary DBL = date of the Week 52 visit (or early exit if discontinued before the primary DBL) – date of the 1st study treatment + 1

  Study duration for the final DBL = date of the Week 104 visit (or early exit) – date of the 1st study treatment + 1

- Unless otherwise specified, baseline data refer to assessments performed at the Baseline (Day 1) visit prior to the 1st study treatment. Screening or unscheduled visits prior to Day 1 visit will be used for baseline in the absence of pertinent data at the baseline visit.

- If ungradable images result in missing baseline CRT, the manual read data for retinal thickness at the center point, if available, will be used for analysis. If the manual read data at baseline is not available, CRT on confirmation reading at screening will serve as baseline CRT.

- Descriptive statistics include the sample size (N), mean, standard deviation (SD), median, minimum (Min), and maximum (Max) for continuous/ordinal data and the frequency distribution includes sample size (N), frequency count, and percentage for categorical data.

- The difference between groups will be calculated as abicipar minus ranibizumab.

- Medical Dictionary of Regulatory Activities (MedDRA) nomenclature will be used to code adverse events, medical procedures, biomicroscopy, and ophthalmoscopy findings.

- The Anatomical-Therapeutic-Chemical classification text from World Health Organization (WHO) Drug Dictionary will be used to code all medications for drug class and for drug name.

- Whenever applicable, the metric system will be used (eg, kilograms [kg] and centimeters [cm]) and all clinical laboratory data will be presented with the Standard International (SI) units.

3. Disposition and Exit Status

3.1 Disposition and Exit Status

Patient disposition will be summarized as a frequency distribution by treatment group using the ITT and PP populations. For the Week 52 analysis, patients who are still in the study will be classified into the ongoing category. Reasons for early exit will be summarized into the following categories as captured on the study exit eCRF.

3.2 Significant Protocol Deviations

Significant protocol deviations will be classified based on the type of deviation for each treatment group. Summary of significant protocol deviations will be done for the ITT population.

4. Demographics and Other Baseline Characteristics

4.1 Demographics

Demographic data are collected at the screening visit. Patient's age (years), sex, and race will be summarized for each treatment group using the ITT and PP populations. Patient age will be classified into categories of less than or equal to 65 years and greater than 65 years.

4.2 Baseline Characteristics

Baseline characteristics include height (cm), weight (kg), iris color, lesion type (predominantly classic, minimally classic, or occult), lesion size, subretinal or intraretinal fluid, intraretinal cysts, pigment epithelial detachments, polypoidal choroidal vasculopathy, and smoking status. Ocular characteristics of the study eye at baseline include lens status, study eye as the better-seeing eye (defined as baseline $BCVA_{study\text{-}eye} > BCVA_{non\text{-}study\ eye}$), BCVA, CRT, and intraocular pressure. Summaries of baseline characteristics will be done for the ITT and PP populations.

4.3 Prior Medications/Procedures

Prior medications are defined as those received prior to the first study treatment. For analysis purposes, a medication will be considered as a prior medication if it satisfies at least one of the following:

- The start date is prior to Day 1, regardless of the stop date;
- The start date is unknown but marked as > 1 year; or
- The stop date is prior to or on Day 1, regardless of the start date

For medications with a partial start or stop date where > 1 year is not marked for the start date or ongoing is not marked for the stop date and the day and/or the month is unknown, comparison to the 1st study treatment date (Day 1) will start with the year followed by the month, if applicable, for determination of prior medications. In cases where a full determination cannot be made based on the partial information, the start date will be assigned to the 1st day of the month if the day of the month is missing or to January if the month of the year is missing; conversely, the stop date will be assigned to the last day of the month if the day of the month is missing or to December if the month is missing. This missing data imputation will only be used to determine whether a certain medication is considered a prior medication. Prior medications will be summarized by treatment group under each drug class and drug name. A separate analysis for prior ophthalmic medications used in the study eye will be performed based on WHODDE base preferred names.

Summary of prior medications will be based on the ITT population.

4.4 Concomitant Medications/Procedures

Concomitant medications are defined as those non-study medications received after the first study treatment. For analysis purposes, a medication will be considered as concomitant if it satisfies at least one of the following:

- The start date is on or after the Day 1 treatment date regardless of the stop date;
- The stop date is after the Day 1 treatment date, regardless of the start date; or
- The stop date is unknown but marked as ongoing

For medications with a partial start or stop date, the same conventions and algorithms as described for prior medications will be used for determination of concomitant medications.

Concomitant medications will be summarized in the same way as prior medications.

Concurrent procedures including those ocular and nonocular procedures performed after study treatment will be coded using MedDRA. The number and percentage of patients with any concurrent procedures will be tabulated and presented by treatment group as a frequency distribution for each primary system organ class (SOC) and preferred term. A separate summary for ocular concurrent procedures in the study eye will be performed.

The number and percentage of patients who escaped to standard-of-care will be tabulated by medication names for each treatment group.

Summary of concomitant medications/procedures will be based on the ITT population.

4.5 Medical History

Medical history will be coded using MedDRA.

Data will be summarized by frequency distribution for each unique primary SOC and preferred terms using the ITT population based on the following two categories:

- Previous medical conditions, and
- Medical conditions at study initiation

Further, ocular history for the study eye will be summarized similarly.

5. Efficacy Analyses

The primary and secondary efficacy endpoints are listed below.

Primary efficacy endpoint:

- The proportion of patients with stable vision (ie, patients who lose fewer than 15 letters in BCVA) from baseline at Week 52

Secondary efficacy endpoints:

- Mean change from baseline in BCVA at Week 52 (key secondary endpoint)
- Mean change from baseline in CRT as assessed with SD-OCT and quantified by the central reading center at Week 52
- Proportion of patients with a gain of 15 or more ETDRS letters in BCVA from baseline at Week 52
- Mean change from baseline in The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) composite score at Week 52

Analyses of the primary efficacy endpoint and the key secondary endpoint for testing non-inferiority will be performed using the PP population. Analyses of the primary and secondary efficacy endpoints for testing superiority will be performed using the ITT population.

5.1 Collection of Primary Efficacy Measurement and Derivation of Primary Efficacy Variable

BCVA will be recorded on the CRF as the number of letters correctly read. For a given eye, the 4-meter distance (standard) of BCVA is tested first. If the patient correctly reads at least 20 letters at 4 meters, BCVA score will be set as the sum of 30 and the number of letters read correctly. If the patient correctly reads less than 20 letters at 4 meters, the BCVA is measured again at 1 meter. The BCVA score will be set to the number of letters read correctly at 1 meter plus the number of letters read correctly at 4 meters. For each patient, BCVA data will be collected for both eyes at the screening, baseline visit (Day 1 but prior to the study treatment), and at Weeks 12, 24, 36, 52, 76, and 104/early exit visits; and for the study eye only at all other scheduled visits.

For patients who received any non-study anti-vascular endothelial growth factor (VEGF) treatments in the study eye, data after the 1st such treatment will be excluded from all efficacy analyses.

5.2 Primary Efficacy Analyses

The primary efficacy endpoint is the proportion of patients with stable vision at Week 52, defined as vision loss of fewer than 15 letters in BCVA from baseline. Patients who escaped to standard of care by meeting the protocol criteria will be set to failures for the primary endpoint of stable vision at Week 52. Confirmation for meeting the protocol criteria is based on the marked reasons captured on the Standard of Care eCRF, which states: “Loss of ≥ 30 letters in BCVA from baseline (in any post-baseline visit), and persistent fluid (subretinal and intraretinal) by OCT, judged to be the cause of the BCVA loss (not explained by reasons other than the progression of neovascular AMD).”

5.2.1 Statistical Hypothesis

The statistical hypothesis for testing non-inferiority of abicipar to ranibizumab with regard to stable vision at Week 52 can be stated as follows:

Null hypothesis:

Abicipar (2Q12 or 2Q8) is inferior to ranibizumab by the specified non-inferiority margin of 10% or more in the proportion of patients with stable vision at Week 52.

Alternative hypothesis:

Abicipar (2Q12 or 2Q8) is inferior to ranibizumab by less than the specified non-inferiority margin of 10% or is superior to ranibizumab in the proportion of patients with stable vision at Week 52.

The null and alternative hypotheses can be mathematically stated as follows:

$H_{o1}:\ P_{2Q8} - P_{rQ4} \leq -10\%$

$H_{a1}:\ P_{2Q8} - P_{rQ4} > -10\%$

And

$H_{o2}:\ P_{2Q12} - P_{rQ4} \leq -10\%$

$H_{a2}:\ P_{2Q12} - P_{rQ4} > -10\%$

where P_{2Q8}, P_{2Q12} , and P_{rQ4} are the probabilities of stable vision at Week 52 for the abicipar 2Q8, abicipar 2Q12, and ranibizumab treatment groups, respectively.

5.2.2 Primary Analyses of Primary Efficacy Variable

The primary analysis of the primary efficacy variable will be performed using the PP population based on a stratified method with Cochran-Mantel-Haenszel (CMH) weights. Within the framework of this method, the difference in the proportions between each abicipar arm and ranibizumab (abicipar group minus ranibizumab group) and the corresponding 2-sided 95.1% confidence interval for non-inferiority testing will be calculated. Specifically, the confidence intervals for treatment group differences will be calculated using the CMH weighted method with the baseline BCVA (≤ 55 versus > 55 ETDRS letters) as a stratification factor as described in Yan and Su (2010). Missing data for BCVA will be imputed using the last observation carried forward (LOCF). The formal non-inferiority test will be performed at Week 52 with a non-inferiority margin of 10% at an alpha level of 0.049. This alpha reflects an adjustment of 0.001 for the unmasked data review by the data safety monitoring committee (DSMC) for safety assessments. The total alpha spent of 0.001 for the DSMC is based on the assumption of no more than 10 unmasked reviews during the study, with 0.0001 allocated to each review. Thus, the overall alpha for the study is preserved at 0.05 level.

For hypothesis testing, if the lower limit of the 95.1% confidence interval for the difference between an abicipar group and ranibizumab is greater than or equal to -10%, non-inferiority of the abicipar group is established.

Multiplicity for the primary efficacy analysis will be controlled using a gatekeeping procedure defined by the following sequence to control the overall type I error rate at 0.05 level:

Step 1: Testing for non-inferiority of abicipar 2Q8 against ranibizumab
Step 2: Testing for non-inferiority of abicipar 2Q12 against ranibizumab

Hypothesis testing for abicipar 2Q12 against ranibizumab is valid only if non-inferiority for abicipar 2Q8 against ranibizumab is established.

If both abicipar groups have demonstrated non-inferiority to ranibizumab using the PP population, hypothesis testing for superiority will be performed using the ITT population for each abicipar group following the same order as defined above for non-inferiority testing. Superiority of abicipar will be demonstrated if the lower confidence limit for the treatment difference is greater than zero.

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[redacted]

5.3 Secondary Efficacy Analyses

The key secondary efficacy variable is the mean change in BCVA from baseline. Other secondary efficacy variables include the mean change from baseline in CRT as assessed by SD-OCT, proportion of patients with BCVA improvement of 15 letters or more from baseline, and mean change from baseline in Health Outcomes NEI-VFQ-25 composite score.

5.3.1 BCVA Mean Change from Baseline

For the key secondary efficacy endpoint mean change from baseline in BCVA at Week 52, statistical analysis for non-inferiority will be based on the PP population using a mixed-effect model for repeated measures (MMRM), which includes BCVA data from baseline (Day 1) to Week 52. The model will include treatment group, region, baseline BCVA in the study eye, baseline CRT (≤ 400 μm or > 400 μm) in the study eye, lesion type of choroidal neovascularization (predominantly classic versus minimally classic or occult) from the confirmation at screening, visit, visit-by-baseline BCVA interaction, and treatment-by-visit interaction as fixed covariates using an unstructured covariance matrix. The difference in

BCVA mean change from baseline between each abicipar arm and ranibizumab (abicipar group minus ranibizumab group) and the corresponding 2-sided 95.1% confidence interval (CI) will be calculated based on the MMRM model. The formal non-inferiority test will be performed at Week 52 using a margin of 5 letters. Non-inferiority of abicipar will be established if the lower limit of the CI is > - 5.0 letters. Testing for non-inferiority in mean change will also be performed using the ITT population and the same MMRM model as a sensitivity analysis.

Testing for superiority of abicipar over ranibizumab in BCVA mean change will be performed using the ITT population with the same MMRM model.

As a sensitivity analysis, BCVA mean change will be analyzed using an analysis of covariance (ANCOVA) model, which includes the treatment group, region, baseline CRT (≤ 400 or > 400 microns), and lesion type of choroidal neovascularization (predominantly classic versus minimally classic or occult) from the confirmation at screening as fixed effects and baseline BCVA as a covariate. In this model, missing data will be replaced by LOCF and the analysis will be performed for the PP population. Treatment differences between each abicipar group and ranibizumab and the corresponding 2-sided 95.1% confidence intervals for the difference will be calculated based on the least–square means and appropriate contrasts from the same ANCOVA model.

Tipping point analysis as described in Section 5.2.4.2 will be performed for BCVA change using the PP population. The tipping region will be constructed based on the combinations of values for δ_{2Q8}, δ_{2Q12}, or δ_{rQ4} that resulted in a lower bound of the 95.1% CI for the difference of abicipar (2Q8 or 2Q12) minus ranibizumab less than -5 letters.

5.3.2 SD-OCT CRT Mean Change from Baseline

The electronic SD-OCT images will be evaluated and graded by the Fundus Photograph Reading Center (FPRC). The graded results will be captured on the evaluation form and used for statistical analysis. In the event of excess fluid at baseline and ungradable images that result in missing baseline CRT, the manual read data for retinal thickness at the center point, if available, will be used for analysis.

CRT is measured as the thickness of the subfields, which is the central 1000 μm from the center of the fovea.

Analysis of CRT mean change from baseline in the study eye will be performed using the same MMRM model for superiority testing based on the ITT population as described in

Section 5.3.1 for the key efficacy variable of BCVA change. The only difference is that baseline CRT will be included in the model as a continuous variable instead of a dichotomy (eg, ≤ 400 μm or > 400 μm) as used for randomization.

5.3.3 BCVA Improvement of ≥ 15 Letters from Baseline

The proportion of patients with a BCVA improvement of ≥ 15 letters from baseline in the study eye at each postbaseline visit will be calculated for each treatment group. Between-group comparisons and the 95.1% confidence intervals for the between-group difference will be performed using the same method as described for the primary efficacy variable in Section 5.2.2 for superiority testing using the ITT population.

5.3.4 NEI-VFQ-25 Mean Change from Baseline in Composite Score

The NEI-VFQ-25 will be administered at the Baseline/Day 1, and at Weeks 12, 24, 36, 52, 76, and 104/early exit visits. Detailed analyses and analysis visit windows are described in Section 7 for health outcome data analysis.

As a secondary efficacy variable, change from baseline at Week 52 in the overall composite score will be analyzed for superiority testing using the ITT population and MMRM as described in Section 5.3.1 for the key secondary efficacy variable of BCVA change. The model will include the treatment group, region, baseline BCVA in the study eye, baseline VFQ score, visit, and treatment-by-visit interaction as fixed covariates using an unstructured covariance matrix. Treatment differences and the corresponding 95.1% confidence intervals will be constructed using the MMRM model.

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[redacted]

[redacted]

6.1 Study Treatment – Exposure and Administration

6.1.1 Exposure to Study Treatments

Exposure to study treatment will be evaluated by the number of study injections (including sham), the number of active study injections (excluding sham) and exposure days. Patients who have missed any study treatment(s) will be enumerated. Duration of treatment based on the days from the 1st to the last active study injections (excluding sham) will be calculated. Descriptive statistics will be tabulated for each treatment group using the safety population.

6.2 Adverse Events

A TEAE is an adverse event that occurs after the initiation of the study treatment (ie, the onset date is the same as or after the study treatment date), or an adverse event with onset prior to the study treatment that worsened in severity or became serious after the initiation of the study treatment. The incidence of TEAEs will be calculated by treatment group and presented as the number and percentage of patients experiencing the TEAE during the reporting period.

The following summaries of TEAE data will be performed: 1) overall summary, 2) all TEAEs regardless of causality, 3) treatment-related TEAEs, 4) ocular TEAEs (study eye versus non-study eye), 5) nonocular TEAEs, 6) treatment-related ocular TEAEs, and 7) TEAEs of special interest. An additional summary will be provided for 8) treatment-emergent serious adverse events (TE SAEs) and 9) AEs leading to study discontinuation.

The 1) overall summary will present the number and percentage of patients with TEAEs, ocular/nonocular TEAEs in the study eye, treatment-related ocular/nonocular TEAEs, AEs leading to study discontinuation, TE SAEs, and death in each treatment group. Treatment-related ocular TEAEs will also be summarized for injection-related and drug-related TEAEs. Injection-related TEAEs are those TEAEs marked as related to the study treatment administration.

Further, tabulations of TEAEs or TE SAEs based on MedDRA coded terms, primary system organ class (SOC) and/or preferred terms (PTs) will be sorted by the frequency of occurrence as detailed below.

- Summary for 3) treatment-related TEAEs, 5) nonocular TEAEs, 8) TE SAEs, and 9) AEs leading to study discontinuation will be sorted by primary SOC in alphabetical order. Within each SOC name, TEAEs (TE SAEs or AEs) will be tabulated by PT in descending order. A patient with multiple occurrences of the same PT within the reporting period will be counted only once for that PT.

- Summary for 2) TEAEs by severity will be sorted by primary SOC in alphabetical order and by the worst severity (maximum severity) experienced for a given patient. Within each SOC, TEAEs will be tabulated by PT in descending order and by severity. The severity of a TEAE is defined as the greater of the onset severity and maximum severity recorded on the CRF for each unique PT reported by the patient.

- Summary for 4) ocular TEAEs, 6) treatment-related ocular TEAEs, and 7) TEAEs of special interest of intraocular inflammation will be sorted by preferred term in descending order. A patient with multiple occurrences of the same preferred term within the reporting period will be counted only once for that PT.

All tabulations will be sorted in descending order of frequency following this sequence from left to right: starting from abicipar groups 2Q8, 2Q12, and ranibizumab every 4 weeks (rQ4).

For the Week 52 analysis, AEs reported from baseline to Week 52 will be determined by AE onset date using the following criteria:

- For patients who completed the Week 52 visit, include AEs with an onset date ≤ Week 52 visit date

- For patients who did not complete the Week 52 visit due to early dropout or missed visit, include AEs with an onset date ≤ 365 days from the date of the 1st injection prior to early exit

For cases where the AE onset date is partially or completely missing and does not allow for a full determination of whether the AE occurred within the Week 52 period, those AEs will be included in the Week 52 analysis.

6.2.1 TEAEs of Special Interest

TEAEs of special interest include intraocular inflammation and those potentially related to systemic VEGF inhibition. TEAEs related to systemic VEGF inhibition will be categorized by arterial-thromboembolic events (ATEs, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death [including deaths of unknown cause]), hypertension, nonocular hemorrhage, proteinuria, and others. Data for these two types of TEAEs will be summarized by MedDRA preferred terms.

TEAEs included in the intraocular inflammation table will follow a two-step selection process: first to identify the MedDRA preferred terms that may represent an intraocular inflammation followed by a thorough medical review of any relevant details reported for the adverse event including ocular examination findings. The incidence of TEAEs for intraocular inflammation of special interest will be summarized by treatment group and presented as the number and percentage of patients. TEAEs identified based on MedDRA preferred terms but not considered as intraocular inflammation of special interest will be displayed in a separate data listing.

TEAEs included in the events potentially related to systemic VEGF inhibition table will be identified following the same process. A summary for arterial thromboembolic events or other adverse events that are potentially related to systemic VEGF inhibition will be done by the following categories of ATE, hypertension, nonocular hemorrhage, proteinuria, and others by preferred terms.

In addition, TEAEs potentially related to systemic VEGF inhibition will be summarized separately for patients who received the following anti-VEGF injections in the non-study eye: ranibizumab, bevacizumab, pegaptanib, and aflibercept.

The selection and review of all TEAEs of special interest will be performed in a masked fashion and finalized prior to database lock and study unmasking.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8. Subgroup Analyses

Subgroup analyses will be performed on the pooled data from the 2 pivotal Phase 3 studies. Analysis will be carried out for the integrated summaries of safety and efficacy. Subgroup analyses will not be performed for the individual clinical studies.

9. Interim Analyses

No interim analyses are planned for this study. However, an independent DSMC will assess the unmasked safety data during the study. To preserve an overall alpha of 0.05 for the study, an adjustment of 0.001 will be made and an alpha level of 0.049 will be used for testing purposes. Therefore, 95.1% confidence intervals will be constructed for the primary efficacy analysis.

[redacted]

[redacted]

11. Deviations from Protocol

There are no deviations from the current study protocol.

12. References

[redacted]

Yan X. and Su X.G Stratified Wilson and Newcombe confidence intervals for multiple binomial proportions. Statistics in Biopharmaceutical Research. 2010;2(3):329-335.

13. Amendment(s)

[redacted]

13.1 Amendment 1

The following changes are made in Amendment 1:

- [redacted] [redacted]

- [redacted] [redacted]

[redacted] [redacted]

Appendix A: Modified Wald Confidence Interval with Stratifications

Single Imputation (LOCF)

Let *i=1, 2,…, k* index strata and let p_{1i} and p_{2i} denote stratum-specific response rates for treatment 1 and 2 in stratum i, respectively. Let $d_i = p_{1i} - p_{2i}$, where $p_{1i} = {}^{x_{1i}}/_{n_{1i}}$, with x_{1i} being the number of responders and n_{1i} being the sample size for treatment 1 in stratum *i*. Similar definition for $p_{2i} = {}^{x_{2i}}/_{n_{2i}}$.

Let $p_{1i}^{*} = \frac{x_{1i}+2}{n_{1i}+4}$ and $p_{2i}^{*} = \frac{x_{2i}+2}{n_{2i}+4}$

With corresponding variance,

$v_{1i} = \frac{p_{1i}^{*}(1-p_{1i}^{*})}{n_{1i}}$ and $v_{2i} = \frac{p_{2i}^{*}(1-p_{2i}^{*})}{n_{2i}}$

And the variance for the difference in response rates between treatment groups in stratum *i*,

$$v_i = v_{1i} + v_{2i}$$

Define weight $w_i = \frac{n_{1i} * n_{2i}}{n_{1i}+n_{2i}}$

The weighted difference,

$$d = \frac{\sum_{i=1}^{k} w_i d_i}{\sum_{i=1}^{k} w_i}$$

And the variance for the weighted difference is,

$$v(d) = \frac{\sum_{i=1}^{k} w_i^2 v_i}{\left(\sum_{i=1}^{k} w_i\right)^2}$$

The Wald confidence interval for the weighted difference is,

$$d \pm Z_{1-\alpha/2} * \sqrt{v(d)}$$

where $Z_{1-\alpha/2}$ is the critical value corresponding to the 1- α/2 quantile of the standard normal distribution.

Multiple Imputation

Let $V_{(j)}$ denote the variance $V(d)$ for the point estimate from the j^{th} imputed dataset.

Hence, the within-imputation variance over all imputed data can be calculated as following:

$$\bar{V} = \frac{1}{m}\sum_{j=1}^{m} V_{(j)}$$

And the between-imputation variance is $B = \frac{1}{m}\sum_{j=1}^{m}(d_{(j)} - \bar{d})^2$

Where $d_{(j)}$ is the weighted difference for the j^{th} imputation invocation and $\bar{d}$ is the average of weighted differences over all imputation invocations.

The total variance is the combination of within- and between-imputation variance:

$$T = \bar{V} + \left(1 + \frac{1}{m}\right)B$$

For SAS application, plugging in ***d*** as the MODELEFFECTS and $\sqrt{V(d)}$ as the STDERR for PROC MIANALYZE.

The lower bound of the confidence interval is,

$$LB = \bar{d} - Z_{1-\alpha/2} * \sqrt{T}$$

and the upper bound of the confidence interval is,

$$UB = \bar{d} + Z_{1-\alpha/2} * \sqrt{T}$$

where T is the total variance from imputed data.