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Title: Evaluation of Abicipar Pegol in Patients with Neovascular Age-Related Macular Degeneration

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Analysis Plan

Evaluation of Abicipar Pegol in Patients with Neovascular Age-Related Macular Degeneration

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1. Introduction

This document describes the planned analysis that will be used for study 1771-201-008 clinical study report. This is a multicenter, open-label, 28-week study to evaluate abicipar for safety and treatment effect in patients with neovascular AMD.

1.1 Primary Study Objectives and Design

The primary objective is to evaluate abicipar for safety and treatment effect in patients with neovascular age-related macular degeneration (AMD).

This is a multicenter, open-label, 28-week study. Approximately 100 patients will be enrolled to receive 2 mg abicipar administered at Baseline (Day 1) and Weeks 4, 8, 16, and 24. The summary of the Study Design:

Structure: multicenter, open-label, single-arm study

Duration: 28 weeks

Study Treatment Groups: 2 mg abicipar

Controls: not applicable

Dosage/Dose Regimen: intravitreal injections of 2 mg abicipar administered Baseline (Day 1) and Weeks 4, 8, 16, and 24

Enrollment/Stratification: None

1.2 Sample Size

The study will enroll approximately 100 patients. This sample size is determined empirically and is considered as appropriate for the planned assessments.

1.3 Database Lock

The study database will be locked upon study completion.

2. Analysis Populations and Data Conventions

2.1 Analysis Populations

The safety population, consisting of patients who received at least 1 study treatment, will be used for all analyses.

2.2 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 safety and treatment effect 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.

2.3 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 days = visit date – date of the 1st study treatment + 1
- Study duration for the final DBL = date of the Week 28 visit (or early exit) – date of the 1st study treatment + 1
- Unless otherwise specified, baseline data refer to assessments performed at Baseline (Day 1) visit prior to the 1st study treatment. Screening or unscheduled visits prior to Baseline (Day 1) visit will be used for baseline in the absence of pertinent data at the Baseline (Day 1) visit
- Data collected after the 1st administration of any non-study (concomitant/prohibited) ocular anti-VEGF treatment in the study eye will be excluded from all efficacy analyses
- When AE date is partial or missing, the following missing data imputation will be used
  - If AE start date is missing, 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

  - If AE stop date is missing, 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 of the year is missing

- 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

- 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, metric systems 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, Exit Status, and Significant Protocol Deviations

3.1 Disposition and Exit Status

Patient disposition will be summarized as a frequency distribution using the safety population. For Week 12 analysis, patients who are still in the study will be classified into “ongoing” category. Reasons for early exit will be summarized into the following categories as captured on the study exit eCRF:

- Screen Failure
- Adverse Event
- Withdrawal by subject
- Lost to Follow-Up
- Pregnancy
- Death
- Physician decision
- Progressive disease

- Protocol Deviation
- Study Terminated by the Sponsor
- Site Terminated by the Sponsor
- Other

3.2 Significant Protocol Deviations

Significant protocol deviations will be classified based on the type of deviations. Summary of significant protocol deviations will be done for the safety 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. 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), BMI (kg/m^2), iris color, subretinal or intraretinal fluid, intraretinal cysts, pigment epithelial detachments, 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. Baseline characteristics will be summarized using descriptive statistics.

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 prior medication if it satisfies at least one of the following:

- The start date is prior to Baseline (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 Baseline (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, Baseline (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 certain medication is considered as prior medication.

Prior medications will be summarized 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.

In addition, ocular anti-VEGF treatment history will be summarized with two categories, treatment-naïve and treatment-experienced. Ocular anti-VEGF treatment includes the following anti-VEGF injections ranibizumab, bevacizumab, pegaptanib, and aflibercept or treatment with a systemic anti-VEGF agent including bevacizumab, and ziv-aflibercept or VEGF-receptor inhibitor such as sunitinib, sorafenib, and pazopanib.

4.4 Concomitant Medications/Procedures

Concomitant medications are defined as those non-study medications received but 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 first treatment date regardless of the stop date;
- The stop date is after the first 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 non-ocular procedures performed after study treatment will be coded using MedDRA dictionary. The number and percent of patients with any concurrent procedures will be tabulated and presented as a frequency distribution for each primary SOC and preferred term. A separate summary for ocular concurrent procedures in the study eye will be performed.

4.5 Medical History

Medical history will be coded using MedDRA dictionary.

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

- Previous Medical Conditions, and
- Medical Conditions at Trial Initiation

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

5. Efficacy Assessments and Analyses

Efficacy assessments include BCVA and CRT measured in the study eye.

5.1 Efficacy Assessments

5.1.1 Best-Corrected Visual Acuity (BCVA)

Best-corrected visual acuity (BCVA) will be recorded on the CRF as the number of letters correctly read using the Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (Age-Related Eye Disease Study [AREDS] Research Group, 2001). 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 28/early exit visits; and for the study eye only at Weeks 4, 8, 12, 16, 20, and 24.

5.1.2 Central retinal thickness (CRT)

Central retinal thickness (CRT) will be assessed with spectral-domain optical coherence tomography (SD-OCT). The graded results will be captured on the evaluation form and be reported by sites and used for statistical analysis.

The central retinal thickness (CRT) is measured as the thickness of the subfields which is the central 1000 μm from the center of the fovea.

For each patient, CRT data will be collected for both eyes at the screening, baseline visit (day 1 but prior to the study treatment), Week 12, and at 28/early exit visits; and for the study eye only at Weeks 4, 8, 16, 20, and 24.

5.2 Efficacy Analyses

All summary on efficacy variables will be based on observed data and will be presented for the study eye only. Additionally, as part of sensitivity analysis, missing data for BCVA will be imputed using the last observation carried forward (LOCF); additionally, data after the first use of prohibited medications will be also be replaced by LOCF. Efficacy variables include the following:

- Proportion of patients with stable vision (eg, patients who lose fewer than 15 letters in BCVA from baseline)
- Proportion of patients with a gain of 15 or more ETDRS letters in BCVA from baseline
- Proportion of patients with a gain of 10 or more ETDRS letters in BCVA from baseline
- The proportions of patients with BCVA of 70 letters (20/40 Snellen equivalent) or better in the study eye at each post-baseline visit
- Mean change from baseline in BCVA
- Mean change from baseline in CRT as assessed with SD-OCT

For binary response variables (eg, stable vision, 10 or 15 letter gain, and BCVA of 70 letters) the proportion of patients with a response at each post-baseline visit will be calculated. The 95% Confidence Interval (CI) for the proportion will be calculated using the exact method.

For continuous variables, change from baseline in BCVA and in CRT will be summarized by visit with means, medians, standard deviations, minimum, and maximum. The 95% of confidence interval for the mean change will be calculated based on *t*-distribution and presented.

BCVA change from baseline for the study eye at each follow-up visit will be classified into the following 7 categories:

Table 2 BCVA Change Categories

Category	Description
1	≥ 15 letters improvement
2	≥ 10 and < 15 letters improvement
3	≥ 5 and < 10 letters improvement
4	no change (ie, change between +5 and -5 letters)
5	≥ 5 and < 10 letters worsening
6	≥ 10 and < 15 letters worsening
7	≥ 15 letters worsening

The distribution of the 7 categories will be summarized by frequency tabulations based on safety population and observed data.

6. Safety Analyses

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code all adverse events (AEs). The incidence of treatment-emergent AEs (TEAEs, as defined in Section 6.2) will be summarized and presented as the number and percent of patients experiencing the TEAEs during the study period.

Other safety variables include vision loss as measured by decrease of BCVA, IOP, biomicroscopic and ophthalmoscopy findings, post-injection assessment, blood chemistry, hematology, urinalysis, physical examinations, vital signs, and urine pregnancy test outcomes.

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 and exposure days, where exposure days is computed as days between 1st study injection to study exit. Patients who have missed any study treatment(s) will be enumerated. Duration of treatment based on the days from the 1st to the last study injections will be calculated. Descriptive statistics will be tabulated using the safety population.

6.2 Adverse Events

A treatment-emergent adverse event (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 first 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 and presented as the number and percent 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 in the study eye, 5) non-ocular 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 overall summary will present the data by the number and percent of patients with TEAEs, ocular/non-ocular TEAEs, treatment-related ocular/non-ocular TEAEs, AEs leading to study discontinuation, TE SAEs, and death. Treatment-related ocular TEAEs will also be summarized for procedure-related and drug-related TEAEs. Procedure-related TEAEs are those TEAEs marked as related to the "Study Procedure" and drug-related TEAEs are those marked as related to the "Study Drug".

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) non-ocular 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.

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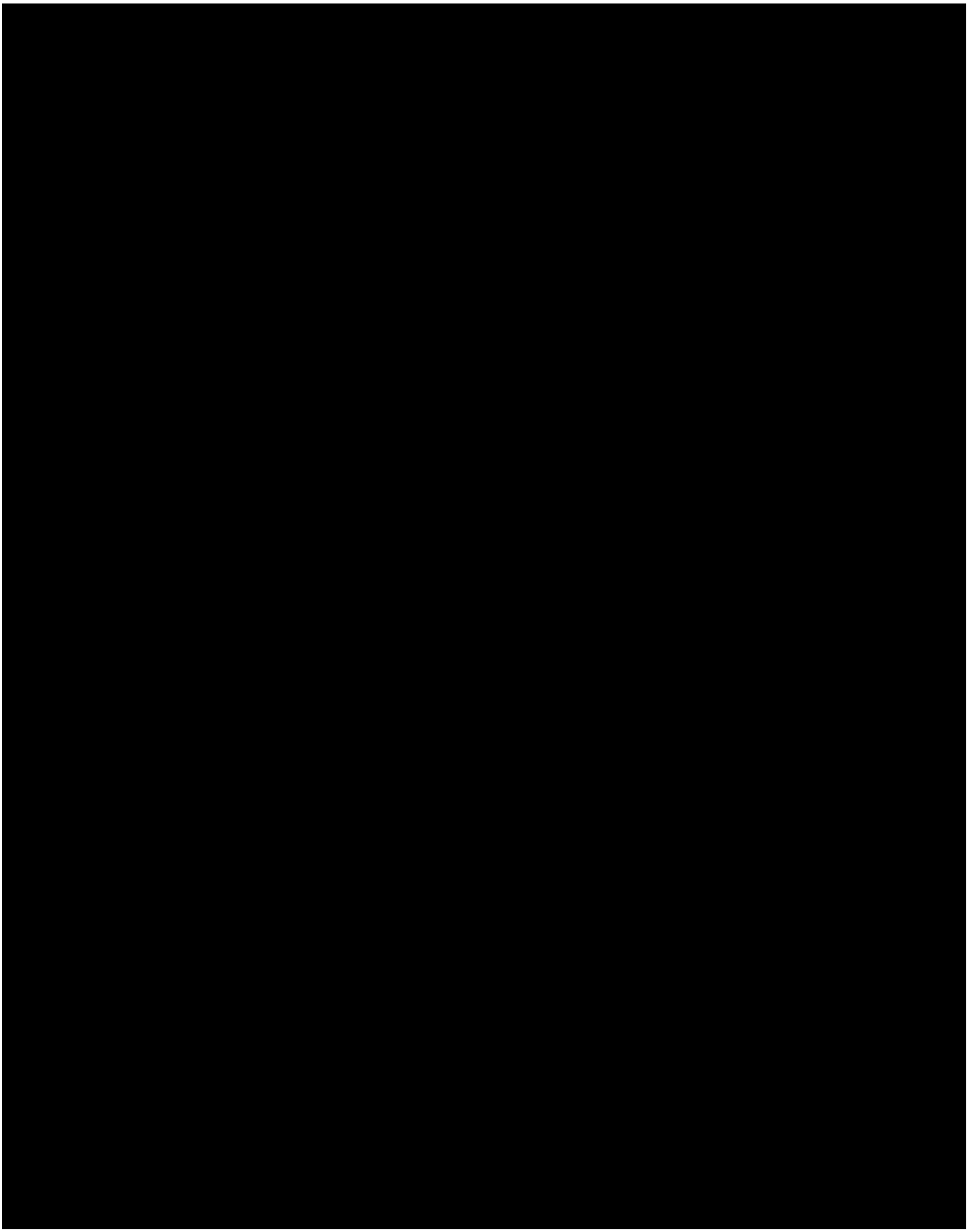

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7. Interim Analyses

An interim analysis (IA) is planned when all patients have completed the Week 12 visit or have exited early from the study.

A data summary will be presented for all available cumulative data by focusing on safety especially intraocular inflammation AE rates.

8. Deviations from Protocol

This is the original analysis plan and there are no deviations from the current study protocol.

9. References

SAS/STAT User's Guide Version 9.3, SAS Institute Inc., Cary, NC

10. Amendment(s)

None.