Statistical Analysis Plan

Protocol Title: A Double-Masked, Placebo-Controlled, Dose Ranging Study to Evaluate the Efficacy of Oral AKST4290 with Loading Doses of Aflibercept in Patients with Newly Diagnosed Neovascular Age-Related Macular Degeneration (PHTHALO – 205)

Protocol Number: AKST4290-205

Protocol Version number and date:	V3.0 12JUN20
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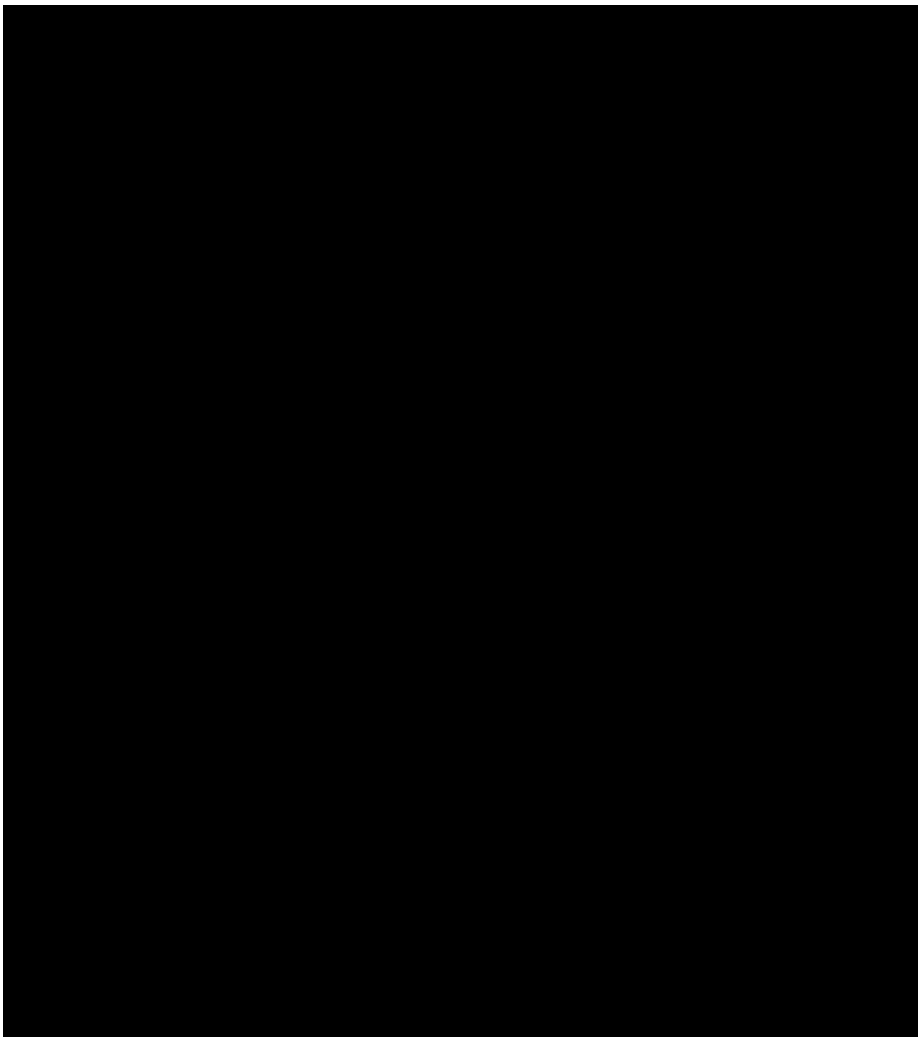

2. REVISION HISTORY

2.1. SUMMARY OF CHANGES

Key revisions from previous finalized versions will be summarized below, when available.

Section	Description	Justification
Cover Page	Modify SAP version number and date, Biostatistics Vendor, and added a "Revised by:" section	Change of biostatistics vendor from the original authors of the SAP [redacted]
7 & 8	Modify secondary and exploratory objectives and endpoints	Modifications due to availability of data or sponsor request.
10.3	Visit mapping for end of treatment visits for subjects who terminate the study early added	Details were required to address analysis of the end of treatment visit for subjects who terminate the study early
10.6	Added text to describe covariates used in primary, secondary, or exploratory efficacy	Clarifying text was added to further describe the MMRM used and the appropriate covariate to apply
10.7	Add study site effect analysis on primary endpoint	The primary endpoint will include an assessment of study site effect per sponsor request
10.11	Modify interim analysis timing and description of delivery	Interim analysis will be provided in May 2021, and not December 2020. Per sponsor request, interim analysis outputs will be developed, but not delivered as described in section 10.11
10.11	Modification from v2.0: Modify interim analysis description of delivery	Modified the delivery details to reflect the modified scope
10.13	Reporting conventions modified	Conventions have been modified to reflect [redacted] standards for analysis
11	Summary of study population details have been modified for analyses	Modifications due to availability of data, sponsor request, or [redacted] standard.
12	Add extent of exposure analyses, additional AE summarizations, and liver function test analyses.	Modifications due to sponsor request and [redacted] standard to include extent of exposure analysis
13	Efficacy analysis modified to include description of BCVA and CST AUC intervals, change from week 12 in BCVA analysis, change to BCVA categorical, median number of injections, and exploratory efficacy analyses sections. Minor clarifying changes made to Section 13.4. Modification to MMRM described for the primary efficacy endpoint.	Modifications due to sponsor request to add efficacy analyses, as well as availability of data. Section 13.1 modified to include treatment group as fixed effect and a treatment group by visit interaction in the MMRM.
14	Add reference to M373 metabolite, modify planned table and figure analyses	Sponsor request to remove age and weight categories from analysis. Addition of plots to present plasma concentration data per [redacted] standard.
15	Added section 15, Changes in the Conduct of the Study or Planned Analyses	[redacted] standard to include– used to describe modifications to Section 7 and 8

3. TABLE OF CONTENTS

4. ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical
BCVA	best corrected visual acuity
BMI	body mass index
CI	confidence interval
CNV	choroidal neovascularization
CRT	central retinal thickness
CST	Central Subfield Thickness
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDTRS	Early Treatment Diabetic Retinopathy Study
EOT	End of Treatment
FA	fluorescein angiography
FAF	fundus autofluorescence
FP	fundus photography
IAI	Intravitreal Aflibercept Injection
iReST	International Reading Speed Texts
IRF	intraretinal fluid
ITT	intent to treat
LLVA	low-luminance visual acuity
MedDRA	Medical Dictionary for Regulatory Activities
mERG	multifocal electroretinogram
MMRM	mixed effects model for repeated measures
nAMD	neovascular age-related macular degeneration
NEI-VFQ-39	National Eye Institute – Visual Functioning Questionnaire-39
PK	pharmacokinetic
PP	per-protocol
RPED	retinal pigment epithelial detachment
SAP	statistical analysis plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SRF	subretinal fluid
ULN	upper limit of normal
WHO	World Health Organization

5. DEFINITIONS

Incidence (of an event, among a group) – proportion of subjects experiencing at least one event of the specified type.

Adverse event surveillance period (for a subject) – time from start of study treatment until trial completion.

6. PROTOCOL SUMMARY

This is a Phase 2, double-masked, placebo-controlled, dose-ranging, multicenter study to assess the efficacy and safety of AKST4290 administered orally at 400 mg twice per day (b.i.d.) (total daily dosage of 800 mg) (Arm 1) or 800 mg b.i.d. (total daily dosage of 1600 mg) (Arm 2) in combination with intravitreal aflibercept injections (IAI), in subjects with newly diagnosed neovascular age-related macular degeneration (nAMD) who are naïve to treatment with anti-vascular endothelial growth factor (anti-VEGF) medications in the study eye. Subjects will be treated with AKST4290 800 mg daily (Arm

1), 1600 mg daily (Arm 2), or placebo (Arm 3) for a total of 36 weeks. All subjects will receive 3 loading doses of IAI, with the initial dose administered on Day 1 (Visit 2) followed by 2 additional doses every 4 weeks (q4w) at Visits 3 and 4. Starting at 12 weeks (Visit 5), subjects in Arms 1 and 2 will be evaluated for IAI on a pro re nata (PRN) basis per strict injection criteria q4w. Subjects in Arms 1 and 2 who do not meet PRN injection criteria will receive a sham injection for masking purposes. Starting at 12 weeks (Visit 5), subjects in Arm 3 will receive IAI every 8 weeks (q8w) (at 16, 24, and 32 weeks [Visits 6, 8, and 10]) with PRN IAI evaluations conducted at every visit for masking purposes. In Arm 3, at 12, 20, 28, and 36 weeks (Visits 5, 7, 9, and 11) subjects that do not meet PRN injection criteria will receive sham injections for masking purposes. All subjects that meet PRN injection criteria will be administered IAI. For masking purposes, all PRN IAI assessments will be performed by a masked investigator and IAI or sham injections will be performed by an unmasked injector. Treatment will be discontinued after Week 36 in all study arms, and subjects will then be followed for an additional 4 weeks.

Approximately 120 subjects will be enrolled with the intent of obtaining approximately 100 evaluable subjects. Subjects will be randomized to active treatment in Arm 1 (approximately 33 evaluable subjects) or Arm 2 (approximately 33 evaluable subjects), or to placebo in Arm 3 (approximately 33 evaluable subjects). All subjects will be masked as to their dose of AKST4290 by using a combination of active or placebo tablets. All subjects will orally self-administer AKST4290 or placebo b.i.d. The randomization schema is 1:1:1, stratified for study site and Early Treatment Diabetic Retinopathy Study (EDTRS) best-corrected visual acuity (BCVA) category for letters read at screening (< 55 vs. ≥ 55).

7. STUDY OBJECTIVES

7.1. PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the potential therapeutic effects of a 36-week, b.i.d. oral dosing regimen of AKST4290, with loading doses of IAI, by assessing the improvement in BCVA using ETDRS method.

7.2. SECONDARY OBJECTIVES

The secondary objectives include the time to PRN injection (Arms 1 and 2 only), time to the first visit where PRN injection criteria are met, median number of injections received beginning at Baseline and Week 12, proportion of subjects with a mean change in BCVA letter score of 0-5, 6-10, 11-15, > 15 letters lost or gained, mean change in central subfield thickness (CST) on spectral-domain-optical coherence tomography (SD-OCT) compared to control through Week 12, mean AUC change in BCVA and CST from Baseline to Week 36, and overall safety. Additionally, a secondary objective will be the comparison of the mean change from baseline in BCVA in Arms 1 and 2 to Arm 3 (control) through Week 12 as well as mean change from Week 12 in BCVA per the ETDRS testing method.

7.3. EXPLORATORY OBJECTIVES

Exploratory objectives will include the evaluations of changes in visual field (as available), low-luminance visual acuity (LLVA), and reading speed. Evaluations of multifocal electroretinogram (mERG) will also be performed at select sites, as available. Morphologic changes in central retinal thickness (CRT), subretinal fluid (SRF), intraretinal fluid (IRF), retinal pigment epithelial detachment (RPED) height, and cube volume will be evaluated by SD-OCT, and total CNV area will be evaluated by fluorescein angiography (FA). Biomarker, PK, and pharmacogenomic evaluations will be conducted on blood and plasma samples. Dose response will be investigated by assessing the mean change in BCVA and the number of injections in Arms 1-3 by study visit. Changes in the National Eye Institute-Visual Functioning Questionnaire-39 (NEI-VFQ-39) will also be assessed. Optional aqueous humor testing for markers of inflammation will be conducted in select subjects.

8. STUDY ENDPOINTS

8.1. PRIMARY ENDPOINT

Mean change from baseline in BCVA per the ETDRS testing method.

8.2. SECONDARY ENDPOINTS

1. Time to PRN injection (Arms 1 and 2 only).
2. Time to first visit where PRN injection criteria are met.
3. Median number of injections received beginning at Baseline and Week 12.
4. Proportion of subjects with BCVA change of 0-5, 6-10, 11-15, > 15 letters lost or gained.
5. Mean change in CST compared with control through Week 12.
6. Mean change in BCVA per the ETDRS testing method compared with control through Week 12.
7. Mean change from Week 12 in BCVA per the ETDRS testing method.
8. Mean AUC change in BCVA and CST from Baseline to Week 36.
9. Safety as assessed by incidence and intensity of AEs.

8.3. EXPLORATORY ENDPOINTS

1. Changes in visual field (as available), LLVA, and reading speed.
2. Evaluation of mERG at select sites, as available.
3. Changes in CRT, SRF, IRF, RPED height and cube volume as measured by SD-OCT, and total CNV area as measured by FA.
4. Biomarker, PK, and pharmacogenomic assessments.
5. Dose response as assessed by mean change in BCVA and mean number of injections in by study visit.
6. Change in NEI-VFQ-39 score by study visit.
7. Optional aqueous humor testing for markers of inflammation will be conducted in select subjects.

9. SAMPLE SIZE

The primary efficacy analysis objective is to observe an improvement in the mean number of letters read from baseline to Week 36 in the AKST4290 treatment groups of at least seven letters. A sample size of 33 subjects achieves approximately 85% power to detect a difference of -7.0 letters between the null hypothesis mean of 0.0 and the alternative hypothesis mean of 7.0 letter improvement, with an estimated standard deviation of 13 and with a significance level (alpha) of 0.025 using a one-tailed one-sample t-test. The combined power of testing each AKST4290 treatment group separately as described in Section 10.9 is approximately 72%.

To ensure a sufficient number of subjects are enrolled to effectively assess the mean change in letters read within each AKST4290 group and within the two AKST4290 groups combined, the total sample size for this study will be 100 evaluable subjects (i.e., approximately 33 subjects in each individual treatment group).

10. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

10.1. GENERAL PRINCIPLES

All summary statistics will be descriptive unless noted otherwise. Descriptive summaries will include mean, standard deviation, median, quartiles and range for continuous variables and counts and percentages for categorical variables. Two-sided 95% confidence intervals (CIs) will be provided for the means and percentages as needed. For key outcome measures, the difference between the treatment arms along with 95% CI of the difference will be computed.

The assumptions for any planned parametric testing will be assessed for appropriateness. If any are violated and inhibit the interpretation of the results, appropriate data transformations or non-parametric analyses will be performed in addition to other planned sensitivity analyses to support the interpretation of the treatment effect.

The primary analysis will evaluate within-group tests for each of the AKST4290 treatment arms (Arms 1 and 2) separately; as a secondary analysis, each of the AKST4290 groups and the pooled AKST4290 treatment arms will be compared to the control arm (Arm 3) for data collected through Week 12. All study population, safety, and efficacy tabulations will include summaries of each of the three treatment arms and a summary for the combined AKST4290 arms.

Subjects will be analyzed in the treatment group assigned at randomization for the intent-to-treat (ITT) and per protocol (PP) data sets (see definitions below). For the Safety Evaluable data set, subjects will be grouped according to actual treatment received.

10.2. ANALYSIS POPULATIONS

10.2.1. Intent-to-Treat

Intent-to-Treat (ITT) set will include all randomized subjects.

10.2.2. Safety Evaluable

Safety Evaluable set (Safety Population) will include all randomized subjects who receive at least one dose of the study agent (placebo or AKST4290).

10.2.3. Per Protocol

Per Protocol (PP) set is a subset of ITT subjects (who receive at least one dose of the study agent) with sufficient compliance to the protocol. The following are grounds for exclusion from the PP population:

1. Deviation of inclusion/exclusion criteria
2. Intake of any prohibited medications listed in Protocol Sections 17.2.1 and 17.2.2 during the study period.
3. Any other major protocol deviation deemed by the Sponsor to warrant exclusion from the PP set

The inclusion or exclusion of ITT population subjects to PP population will be finalized before unblinding the study.

10.3. DATA TRANSFORMATIONS AND DERIVATIONS

Values will be presented for all scheduled study visits according to the nominal visit obtained from the eCRF. Visit windows are defined in Section 15 (Schedule of Events) of the study protocol. Each visit after Day 1 is associated with a target visit day and allows for a ±3 day window for visit completion around the target day. If an unscheduled visit falls in a visit window with an existing nominal visit assessment, the nominal assessment will be used for summary presentation. If no nominal visit assessment exists for a visit window with unscheduled visit(s), then the unscheduled visit within the visit window and closest to the target day will be used. If multiple nominal assessments are collected within the same visit, the nominal visit closest to the target day will be used for summary presentation. Based on these rules, if two visits are equidistant from the target day, the later of the two will be used. Data collected at unscheduled visits will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). Subjects that terminate early from the study will have their Week 36/end of treatment (EOT) visit mapped and summarized with the next scheduled nominal visit, according to the schedule of events, based on the last visit completed per protocol.

10.4. MISSING DATA AND IMPUTATION

The analysis of the primary endpoint will be based on a mixed effects model for repeated measures (MMRM) that uses a likelihood-based estimation method assuming data to be missing at random to account subjects who dropout prior to Week 36. The Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. The MMRM model used to compare the AKST4290 treatment groups to control through Week 12 will include similar methods for accounting for missing data.

For the secondary responder endpoints (e.g., subjects with ≥ 15 letters gained at Week 12 or Week 36), subjects missing the Week 12 or Week 36 evaluation will be considered as having not achieved the success criterion of interest.

10.5. SUB-GROUPS

Subgroups will be defined for the following:

- BCVA randomization stratification level: <55 vs ≥ 55 letters read at screening
- PRN injection criteria on study: subjects who never meet the criteria for PRN IAIs vs subjects who meet the PRN injection criteria at least once

The primary endpoint analysis will be repeated separately for the BCVA randomization stratification levels. Select efficacy endpoints will be defined for the PRN IAI subsets as described in Section 13.4.

10.6. COVARIATES

The MMRM models to assess the within-group change from baseline to Week 36 and to compare treatment groups through Week 12 for the primary efficacy analysis will include a covariate adjustment for the baseline number of letters read. The MMRM used to analyze any secondary or exploratory efficacy analysis will include a covariate for the baseline value of the parameter of interest.

10.7. MULTICENTER STUDIES

This is a multicenter study and efficacy data collected from all study sites will be pooled for data analysis. The effect of study site on the primary endpoint will be explored as discussed in Section 13.3. The effect of study site on other efficacy analysis results may be explored post-hoc, as needed.

10.8. SIGNIFICANCE LEVEL

The primary analysis utilizes a one-sample test with one-sided significance level 2.5%.
All other statistical tests and confidence intervals will be two sided (where relevant) and have significance level of 5%.

10.9. MULTIPLE COMPARISONS

The primary analysis will be performed separately for each of the two AKST4290 treatment arms (Arms 1 and 2) as within-group tests for the change from baseline to Week 36 in BCVA letters read. To account for multiple within-group comparisons, Arm 1 (400 mg b.i.d.) will be evaluated first at the one-sided 2.5% level of significance. If the null hypothesis is rejected, the test will be carried out for Arm 2 (800 mg b.i.d.). Analysis of secondary endpoints will not be adjusted for multiple endpoint or treatment comparisons and will be evaluated based on a two-sided significance level of 5%. This study is exploratory in nature and analysis of secondary endpoints in a potential subsequent pivotal study will include appropriate methods for adjusting for multiple comparisons.

10.10. TIMING OF ANALYSES

Safety monitoring will be conducted on an ongoing basis, albeit not by means of statistical comparisons, unless the Safety Evaluation Meeting is convened and so decides.
An interim analysis of efficacy will be performed (see Section 10.11).
The final analysis will be performed when the enrollment is completed, all the subjects are either completed or discontinued, and the database is locked. However, statistical programming for the final analysis based on blinded (mock) data will commence before database lock.

10.11. INTERIM ANALYSES

Safety will be monitored on an ongoing basis. If a Safety Evaluation Meeting is triggered (see Section 8.5 in Protocol), an ad hoc interim safety analysis will be performed. If such an ad hoc safety interim analysis is conducted, the treatment assignment will remain masked, unless aggregate unmasking is deemed necessary by the Sponsor for safety evaluation.

An interim analysis of primary and key secondary and exploratory efficacy endpoint data is planned to be performed in May 2021, with all available data collected up to an appropriate prior data cut date included. Select safety data will be provided as well. Results of the interim analysis will be utilized to assist in making decisions for more advanced studies on subjects with nAMD (e.g., a Phase 3 program), and to assess further clinical development of AKST4290 in other indications.

Analysis of the efficacy endpoints described in Section 13 will be performed in a similar manner for the interim analysis. Endpoints collected over time will be summarized at select time points where scheduled for evaluation up to the end of study, Week 40, in addition to the primary analysis time point at the end of treatment, Week 36.

Tabulated results of the efficacy and safety data will be prepared by treatment group using blinded study data. The unblinded statistician will have access to the unblinded subject treatment assignments and will run the tabulated results utilizing the unblinded assignments for the interim analysis. For the purposes of the interim analysis, the unblinded statistician will prepare an assessment of each endpoint, to include relevant statistics for the parameters of interest, defined by Alkahest as required for the interim analysis. In addition to tabulated summaries, subject level data will be reported for the primary endpoint to support review of the assessment provided; subject identifiers will be randomly sorted and then excluded from presentation in the output. The unblinded statistician will not be involved in any ongoing site monitoring, data management, or data handling decision making activities following the interim analysis data review up through final database lock. Among specific endpoints for inclusion in the interim analysis are the following:

- Mean change from baseline in BCVA ETDRS letters read by post-baseline visit
- Comparison of BCVA change from baseline between each active arm (or pooled) and control for data collected through Week 12
- Mean change from baseline in LLVA and Reading Speed by post-baseline visit
- Mean change from baseline in Visual Field (Mean Deviation and Pattern Standard Deviation) and mERG (Central Rings 1-5) by post-baseline visit
- Mean change from baseline in NEI-VFQ-39 sub-scales and composite score by post-baseline visit
- Area under the curve (AUC) for mean change from baseline in BCVA and CST for specific study visit intervals
- Time (weeks) to first PRN IAI (Arms 1 and 2 only)
- Time (weeks) to first date where PRN injection criteria is met on or after Week 12
- Mean number of injections received (scheduled or PRN) per week beginning at Baseline and Week 12 through the end of treatment
- Liver function tests upper limit of normal (ULN) categories
- Adverse events (AEs) occurring in ≥ 5% of subjects in either AKST4290 treatment group (Arm 1 or Arm 2)

No adjustments to the current protocol are planned as a result of the interim analysis. Therefore, the overall type 1 error (alpha) in the in the final analysis will be maintained at 0.025, one sided, for the primary endpoint.

10.12. SOFTWARE

Data analyses will be performed with SAS® version 9.4.

10.13. REPORTING CONVENTIONS

10.13.1. General

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the eCRF or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data. P-values will be presented with four decimal places and values less than 0.0001 will be presented as <0.0001.

For all fitted statistical models, generally:
1. Goodness-of-fit will be examined;
2. Results will be displayed in a table of parameters containing at least the parameter estimate, standard error of the estimate, and the p-value of a test of null hypothesis of whether the parameter is zero

10.13.2. Tables

Tables will represent summaries and results of other analyses. All summary tables will be structured with a column for each treatment group, unless treatment group is clearly irrelevant for the summary (e.g., reasons for screening failures), as well as a column for the combined AKST4290 treatment groups. Tables summarizing subject disposition, demographics, and other baseline characteristics will also include a column for all treatment groups combined. All summary tables be annotated with the analysis population and total population size relevant to that table. Confidence intervals and corresponding p-values are reported within (or in the captions of) relevant summary tables.

10.13.3. Listings

Listings will generally present the data as it appears on the eCRFs without any further grouping or pooling as used in the analyses.

Any listings that are “by subject” have all the results of one subject in one row. Any listings that are “by subject by visit” have one row per subject per visit. Otherwise, different results of one subject may be organized to separate rows in some other way (e.g., one medical history element per row). All listings include the subject ID and treatment group.

11. SUMMARY OF STUDY POPULATION

ITT population will be used for all of the following analyses and tabulations, except for the summary of screening failures.

11.1. SUBJECT DISPOSITION

Subject disposition will be presented for all subjects. Numbers of subjects randomized, complete or discontinue from the study, and reasons for study discontinuation will be summarized. Subject disposition by study center will also be presented. Number and reasons of screening failures are also summarized with descriptive statistics.

11.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic variables include age, sex, ethnicity, race, and gender. Baseline characteristics include height, weight, body mass index (BMI), study eye, study eye color, and time since nAMD diagnosis (days). Body mass index will be calculated as: weight (kg) / [height (cm) / 100]^2. Time since nAMD (days) is calculated as the date of informed consent – date of nAMD diagnosis. Each of these variables will also be summarized with descriptive statistics.

Time (days) since nAMD diagnosis will be computed for partial nAMD diagnosis dates based on the following rules:

- Day missing but month and year present: The difference in months between the nAMD diagnosis date and informed consent date will be calculated based on the available date entries, and then multiplied by 30.4 (rounded to the nearest whole number): {[(year of informed consent – year of nAMD diagnosis) x 12] + (the month of informed consent – the month of nAMD diagnosis)} x 30.4.
- Day and month missing but year present: The difference in years between nAMD diagnosis date and informed consent date will be calculated based on the available date entries, and then

multiplied by 365.25 (rounded to the nearest whole number: (year of informed consent – year of nAMD diagnosis) x 365.25.

11.3. MEDICAL HISTORY

Medical history elements will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Incidence of each preferred term will be reported by treatment group.

11.4. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded with the World Health Organization (WHO) drug dictionary version Global B3 September 2018. Prior and concomitant medications will be summarized with descriptive statistics by drug Anatomical Therapeutic Chemical (ATC) Classification System (level one) and generic name.

11.5. TREATMENT COMPLIANCE

Treatment compliance is assessed by the number of tablets dispensed to and returned by the subject, expressed as a percentage of the intended intake during the study period. The number and percentages of subjects who are < 80% compliant and ≥ 80% compliant within each treatment group will be summarized.

11.6. PROTOCOL DEVIATIONS

Subject-specific protocol deviations will be summarized by category, importance (minor, major) and treatment group.

12. SAFETY ANALYSES

The Safety Analysis Set will be used for all analyses and tables of safety data.

12.1. EXTENT OF EXPOSURE

Extent of exposure to study treatment will be summarized by treatment group. The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. Total number of IAIs (PRN and scheduled), number of PRN IAIs, and number of sham injections per subject will also be presented. Duration of exposure, total number of IAIs, PRN IAIs, and sham injections will be summarized using descriptive statistics.

12.2. ADVERSE EVENTS

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized by treatment group. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA).
Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent serious adverse events (SAEs) and subject incidence of TEAEs meeting various criteria
- Subject incidence of TEAEs by MedDRA system organ class and preferred term
- TEAEs occurring in ≥ 5% of subjects in either AKST4290 treatment group (Arm 1 or Arm 2)
- Subject incidence of TEAEs by severity grade, MedDRA system organ class, and preferred term
- Subject incidence of TEAEs by relationship to study drug, MedDRA system organ class, and preferred term

- Subject incidence of severe TEAEs related to study drug by MedDRA system organ class and preferred term
- Subject incidence of injection-related TEAEs by MedDRA system organ class and preferred term
- Subject incidence of SAEs by MedDRA system organ class and preferred term
- Subject incidence of TEAEs of special interest by MedDRA system organ class and preferred term

At each level of summarization (e.g., any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once. In the summary of TEAEs by severity grade, subjects will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, subjects will be counted once at the closest relationship to study drug. Related events include those reported as “Possibly Related” or “Definitely Related” to study drug; events considered not related are those reported as “Unrelated” to study drug.

Adverse event data will be presented in data listings by subject, treatment group, and event. Serious AEs, AEs leading to discontinuation of the study drug, injection related AEs, and AEs of special interest will be presented in separate data listings.

12.3. LABORATORY EVALUATIONS

Clinical laboratory measurements, including serum chemistry and hematology, will be summarized by treatment group. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the study protocol.

Shift tables of baseline value (high abnormal, normal, or low abnormal) to worst post-baseline value (high abnormal, normal, or low abnormal) will be presented by treatment group. In the case where both abnormal high and abnormal low values are present, the direction of the worst measurement is determined by whether any measurement is Panic High or Panic Low, and then by its distance from nearest normality limit. Laboratory measurements identified as abnormal will also be listed separately by subject, laboratory test, and unit. Normality interpretation (Normal, High, Low, Panic High, Panic Low) will be obtained from the Clinical Status assessment from the central lab (see Data Transfer Plan section 14 – EDF-Format). Liver function tests (ALT, AST and total bilirubin) will be summarized by the ULN categories of 2-3 x ULN, 3-5 x ULN, 5-8 x ULN, and >8 x ULN using counts and percentages. Summarizations within each ULN severity category will include the highest ULN severity category per subject, the highest ULN severity category by visit per subject, and the number of subjects who meet any of the ULN severity categories by visit. For the analysis of highest ULN severity category by visit per subject, if a subject experiences multiple instances of the same ULN category across different study visits, the first visit of the highest ULN category will be reported. A plot of all subjects with at least one liver function test ≥ 3 x ULN will also be provided.

12.4. VITAL SIGNS

Vital sign parameter measurements will be summarized by treatment group. Descriptive statistics will be presented for results and change from baseline at each visit where parameters were scheduled to be collected.

12.5. PHYSICAL EXAMINATION

Results of the physical examination will be presented in subject data listings by subject, study visit, and body system.

12.6. 12-LEAD ECG

Twelve-Lead ECG interval parameters including heart rate, QT interval, and QT interval corrected with Fridericia’s formula will be summarized by treatment group. Descriptive statistics will be presented for

observed values and changes from baseline at each visit where parameters were scheduled to be collected.

Twelve-lead ECG will be classified by the investigator as “normal,” “abnormal, not clinically significant,” or “abnormal, clinically significant.” Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline category. Summary results will include the count and percentage of subjects within each shift category and treatment group.

Prolonged QTcF intervals will be summarized as QTcF measurements (msec) that are >450, >480, and >500 at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change >30 or >60 relative to the baseline value. Summary results will include the percentage of subjects within each category and treatment group.

12.7. PREGNANCIES

No pregnancies are expected to occur during the study. If any, these will be listed without any quantitative analysis.

13. EFFICACY ANALYSES

All efficacy analyses will be performed in the ITT Population. Primary and secondary efficacy analyses will also be performed on the PP Population. All efficacy analyses of ocular measurement will reflect data collected specific to the study eye unless otherwise specified.

13.1. PRIMARY EFFICACY ANALYSIS

The primary estimand is the mean change from baseline to Week 36 in BCVA ETDRS letters read for each AKST4290 group for subjects in the ITT Population. The primary analysis will consider all BCVA data collected regardless of the number of PRN IAI received. The null hypothesis to be tested for each AKST4290 treatment group is that the mean change from baseline to end of treatment, Week 36, in BCVA ETDRS letters read less than or equal to seven letters gained. The alternate hypothesis is that the mean change from baseline is at least seven letters gained within an AKST4290 treatment group.

Within each treatment group and for the AKST4290 combined groups, a restricted maximum likelihood (REML)-based MMRM analysis will be performed for the change from baseline in BCVA ETDRS letters read. Because model convergence is questionable with this sample size and all post-baseline visits included, the model will include data beginning at Week 4 and collected at visits scheduled every eight weeks thereafter up to the Week 36 visit (i.e., weeks 4, 12, 20, 28, and 36). The model will include treatment group and visit as fixed effects, a treatment group by visit interaction term, subject as a random effect, and the baseline letters read as a covariate. An appropriate covariance structure will be selected prior to the interim analysis and final database lock and the Kenward Rogers method will be used to calculate the denominator degrees of freedom for the text of fixed effects. Within each AKST4290 treatment group, the mean change from baseline to Week 36 in letters read will be tested against the null value of seven letters gained based on one-sided alpha = 0.025. To control the Type 1 error associated with the within-group testing of two treatment groups, the tests will be performed in sequence as described in Section 10.9. Within each treatment group, the least-squares mean (LSM) and associated 95% CI will be presented for the observed and change from baseline values. A plot of mean BCVA letters read, to include the corresponding AUC interval p-values (see Section 13.2.5), by study visit will also be provided.

The primary endpoint will be summarized by subgroups as described in Section 10.5. Sensitivity analysis to assess the impact of PRN IAI on the primary endpoint is described in Section 13.4.

13.1.1. Additional Analyses of the Primary Endpoint

The primary endpoint will also be analyzed to compare each AKST4290 treatment group and the pooled AKST4290 groups to control through Week 12 using a REML-based MMRM model to include fixed effects for treatment group, categorical visit, and the treatment group by visit interaction; with the

baseline letters read as a covariate. Estimates for the least-squares mean differences (LSMD), 95% CI of the LSMD, and the associated p-value to test for a difference between groups will be presented. A descriptive assessment of non-inferiority between the AKST4290 treatment groups and Arm 3 (control) for the mean change from baseline to Week 36 will be considered a secondary analysis. This assessment will be made by computing the two-sided 95% CI for the difference in LSMs between each AKST4290 group and control, and the pooled AKST4290 group and control.

Change from Week 12 in BCVA ETDRS letters read will also be reported for each treatment group and for the AKST4290 combined group and will include a similar REML-based MMRM analysis as described for the primary endpoint; a covariate of letters read at Week 12 will be included in lieu of baseline letters read.

13.2. SECONDARY EFFICACY ANALYSES

Secondary endpoints will be evaluated both within treatment group through the end of treatment, Week 36, and as a comparison of each AKST4290 group and the pooled AKST4290 groups to control through Week 12. Sensitivity analyses to assess the impact of PRN IAI on the secondary endpoints is described in Section 13.4.

13.2.1. BCVA Categorical Change

The estimand for categorical change in BCVA is the proportion of subjects who meet each BCVA category of interest at Week 12 or Week 36 for subjects in the ITT Population. The BCVA categories for assessment include 0 to 5, 6 to 10, 11 to 15 and >15 letters gained from baseline, as well as 0 to 5, 6 to 10, 11 to 15 and >15 letters lost from baseline.

The percent of subjects meeting each BCVA category of interest from baseline to Week 12 and Week 36 will be summarized by treatment group, and for the pooled AKST4290 groups. Subjects with missing data at the Week 12 or Week 36 visit will be considered to have not achieved the BCVA category of interest relative to that visit. Within each group, the exact 95% CI (Clopper-Pearson) will be presented for the proportion of subjects with the BCVA category of interest met. The proportion of subjects who meet each BCVA category will be further evaluated at Week 12 and Week 36 for a difference in proportions between each AKST4290 treatment group and the pooled AKST4290 groups against control (Arm 3), using the Fisher's exact test. A descriptive assessment of non-inferiority between the groups at each of these time points will be based on an interpretation of the CIs.

13.2.2. Time to First PRN Injection/First Visit Where PRN Injection Criteria are Met

Time to the first PRN injection will be calculated in weeks for subjects assigned to the AKST4290 treatment groups (Arm 1 and Arm 2) as the date of first PRN injection (ie, rescue) minus the first dose of study drug plus one, divided by seven. Time to the first visit where PRN injection criteria are met starting at Week 12 will be calculated in weeks as the first date where PRN injection criteria are first met minus the date of first dose of study drug plus one, divided by seven. Subjects who do not experience the event of interest (i.e. receive a PRN injection, meet the criteria for PRN IAI) while on the study will be censored at their last visit completed. Kaplan-Meier estimates of the distribution of time-to-event will be tabulated and plotted by treatment group, and for the combined AKST4290 groups. The tabulation will include the KM estimate of the median, 25th and 75th quartiles, and 95% CIs (if estimable). The number and percent of subjects with events and number and percent of subjects censored, including reason for censoring, will be presented. In the analysis of time to first visit where PRN injection criteria are met, each AKST4290 treatment group and the pooled AKST4290 groups will be compared to control using a log rank test.

13.2.3. Median Number of Injections Received per Week

The number of injections received per week for each subject from Baseline and Week 12 to study visits Week 12 (from Baseline only), Week 24 and Week 36 will be reported. The number of injections per week will be standardized for their time on study by dividing the number of injections by the subject duration on study in weeks. This may include PRN injections or scheduled injections (Arm 3). The number of injections received per week from Baseline is defined as the number of IAIs received on or after Baseline (PRN or scheduled injections) divided by (the analysis Week visit date [or end of study

date for those subjects who terminate early] minus the date of Baseline visit plus one, divided by seven). The Baseline visit is defined as the visit where the first dose of study drug is taken. If the subject's end of study date is later than the target visit day for the analysis visit, the subject's duration is set as the target day for the visit defined in the protocol schedule of events. The number of injections received per week from Week 12 will use a similar definition, with the reference start date as the subject's Week 12 visit. The median number of injections received per Week will be summarized using descriptive statistics for each treatment group and for the pooled AKST4290 groups and each AKST4290 treatment group and the pooled AKST4290 groups will be compared to control using a Wilcoxon rank-sum test

13.2.4. Mean Change from Baseline in CST and Compared to Control at Week 12

The mean change from baseline to Week 36 and mean change from Week 12 to Week 36 in CST will be summarized using descriptive statistics for each treatment group and for the pooled AKST4290 groups. Treatment group comparisons will be made through Week 12 using a model similar to the primary endpoint. A plot of CST values, to include corresponding AUC interval p-values (see Section 13.2.5), by study visit will also be provided.

13.2.5. Mean AUC Change from Baseline in BCVA ETDRS Letters Read and CST

Mean AUC change from baseline for BCVA ETDRS letters read and CST will be provided for study intervals Week 0 to 12, Week 0 to 24, Week 12 to 24, Week 0 to 36, Week 12 to 36 and Week 24 to 36 using actual elapsed time from dosing. For AUC study interval calculations, the linear trapezoidal rule formula will be used:

$$AUC = \frac{1}{2}(C_1 + C_2)(t_2 - t_1)$$

Treatment group comparisons for the mean AUC change will be performed using an ANCOVA model with a covariate for the baseline value of interest. Estimates for the least-squares mean differences (LSMD), 95% CI of the LSMD, and the associated p-value for treatment group comparisons will be presented.

13.3. EXPLORATORY EFFICACY ANALYSES

Exploratory efficacy analysis will include the evaluation of primary and secondary endpoints collected over time at all post-baseline time points through Week 40 (as available). The primary endpoint, BCVA ETDRS letters read will also be assessed for a study site effect; within-group tests and tests to compare treatment groups will be conducted using methods similar to the primary endpoint with study site included as a fixed effect and a treatment group by study site interaction. Low enrolling sites, defined as any site which enrolls ≤ 5 randomized subjects, will be pooled as a single site for the analysis.

Exploratory efficacy endpoints include changes in LLVA, changes in visual field, changes in reading speed, changes in the NEI-VFQ-39 as well as the evaluation of mERG, total CNV area as reported by FA, and the SD-OCT parameters of SRF height, IRF height, RPED height, cube volume and CRT. Reading speed (words/min) will be calculated using the International Reading Speed Texts (iReST) or Radner Test method. Subjects that have reading speed assessed by Radner Test will have the results reported for the study eye, non-study eye and both eyes (OU). Continuous endpoints will be summarized using descriptive statistics by treatment group and visit. Within-group tests and tests to compare treatment groups will be conducted using methods similar to the primary endpoint.

Reading speed is calculated based on the method used:

- iReST: Reading Speed Score (Words/Min) = 60 x (Words Read Correctly – (Words Read Incorrectly + Words Omitted))/Reading Time (sec)
- Radner Test:

- Using the 0.7, 0.8, 0.9 logMAR Reading Times reported on the CRF, calculate the Average Reading Time*
- Reading Speed Score (Words/Min)* = 60 x (14 / Average Reading Time (sec))
- *Note: Average Reading Time and Reading Speed Score (Words/Min) is calculated separately for OD, OS and OU assessments

13.4. SENSITIVITY EFFICACY ANALYSES

Sensitivity analyses of the primary and secondary endpoints will be conducted to better assess the impact of intercurrent events on the efficacy conclusions. Here, the intercurrent events are subject receipt of IAI after Week 12. A distinction is made for subjects who meet the criteria for PRN injection after Week 12 versus those subjects who actually receive PRN IAI, since subjects in the control group (Arm 3) are scheduled to receive injections regardless of criteria met every four weeks beginning at Week 12. The sensitivity analysis will be based on the first time a subject meets the criteria for PRN IAI starting at Week 12, regardless of treatment group assignment. The primary and secondary efficacy analysis of BCVA and CST endpoints will be conducted through Week 36, without regard for whether subjects received PRN IAI or the number of PRN injections received. Sensitivity analyses will be conducted on the following:

- Mean change from baseline to the first time a subject meets the criteria for PRN IAI, or Week 36/End of Treatment (EOT) for those subjects who never meet PRN injection criteria, in BCVA ETDRS letters read
- Mean change from baseline to the first time a subject meets the criteria for PRN IAI, or Week 36/EOT for those subjects who never meet PRN injection criteria, in CST
- Mean change from baseline to Week 36 in ETDRS BCVA by the subset of subjects who never meet the criteria for PRN IAI, and those who meet the criteria at least once while on study
- Mean change from baseline to Week 36 in CST by the subset of subjects who never meet the criteria for PRN IAI, and those who meet the criteria at least once while on study
- Percentage of subjects with a BCVA categorical change of interest at Week 12 and Week 36 and who never meet the criteria for PRN IAI while on study, and those subjects who met the PRN injection criteria at least once while on study.

Treatment group comparison for the mean change endpoints will be performed using an ANCOVA model with a covariate for the baseline value of interest. Treatment group comparison of the BCVA and PRN IAI composite endpoint will be made using the Fisher's exact test.

13.5. BIOMARKER AND AQUEOUS HUMOR ANALYSES

Disease-related markers may include inflammatory mediators or markers of oxidative stress. Biomarkers will be measured in plasma samples to investigate any change in response to treatment. Analysis of biomarkers will be conducted by a separate vendor and are outside the scope of the analysis plan.

13.6. PHARMACOGENOMIC ANALYSES

Analysis of pharmacogenomics will be conducted by a separate vendor and is outside the scope of this analysis plan.

14. PHARMACOKINETIC ANALYSES

Only data from AKST4290 group will be used for pharmacokinetic analyses.
Data handling methods outlined in study protocol section 17.5 will be followed (missing data not included, values below lower limit of quantification replaced with zero, parameter estimates, and descriptive statistics only reported when at least 2/3 data are available).

Descriptive statistics (including mean, median and quartiles) of AKST4290 and its metabolite, M373, will be reported for all timepoints of pharmacokinetic sampling.

For each subject, the average pre-dose plasma concentration of AKST4290 in steady state will be calculated as geometric mean of pre-dose samples from visits 3, 4 and 5. Descriptive statistics of those steady state concentrations will be presented by treatment group and by sex.
The overall mean of AKST4290 pre-dose plasma concentration is also reported along with 95% confidence interval. Mean pre-dose and post-dose plasma concentrations of AKST4290 and M373 will be provided in plots.

15. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The planned analyses outlined in this SAP includes deviations from the protocol as outlined below.

Section 3 (“Objectives and Purpose”) of the study protocol lists the secondary objectives for the study as:

The secondary objectives include the time to PRN injection (Arms 1 and 2 only), time to the first visit where PRN injection criteria are met, median number of injections received beginning at Week 12, proportion of subjects with a mean change in BCVA letter score of ≥ 15 letters, mean change in CST compared with control through Week 12, mean change in BCVA compared with control through Week 12, and overall safety.

Section 4.2.2. (“Secondary Endpoints”) of the study protocol lists the secondary endpoints for the study as:

- Time to PRN injection (Arms 1 and 2 only).
- Time to first visit where PRN injection criteria are met.
- Median number of injections received beginning at Week 12.
- Proportion of subjects with BCVA change of ≥ 15 letters.
- Mean change in CST compared with control through Week 12.
- Mean change in BCVA per the ETDRS testing method compared with control through Week 12.
- Safety as assessed by incidence and intensity of AEs.

Median number of injections received will also be assessed using Baseline as a starting reference point, in addition to Week 12. The proportion of subjects with BCVA change will be assessed by the following categories: 0-5, 6-10, 11-15 and >15 letters gained or lost. Mean change from Week 12 in BCVA per the ETDRS testing method will also be assessed. Mean AUC change in BCVA and CST from Baseline to Week 36 assessing study visit intervals of Week 0 to 12, Week 0 to 24, Week 12 to 24, Week 0 to 36, Week 12 to 36 and Week 24 to 36 will be reported.

Section 3 (“Objectives and Purpose”) of the study protocol lists the exploratory objectives for the study as:

The exploratory objectives include investigation of the changes in visual field (as available), LLVA, and reading speed. Evaluations of mERG and OCT-A will also be performed at select sites, as available. Morphologic changes (CST, SRF, IRF, RPED height, and CNV) will be evaluated by SD-OCT, FP/FAF (FAF to be performed at select sites, as available), and FA. Biomarker, PK, and pharmacogenomic evaluations will be conducted on blood and plasma samples. Dose response will be investigated by assessing the mean change in BCVA and the number of injections by study visit. Changes in the NEI-VFQ-39 will also be assessed. Optional aqueous humor testing will be conducted in select subjects.

Section 4.2.3 (“Exploratory Endpoints”) of the study protocol defines the exploratory endpoints for the study as:

- Changes in visual field (as available), LLVA, and reading speed.

- Evaluation of mERG and OCT-A in select subjects, as available.
- Changes in CST, SRF, IRF, RPED height, and CNV as measured by SD-OCT, FP/FAF (FAF to be performed at select sites, as available), and FA.
- Biomarker, PK, and pharmacogenomic assessments.
- Dose response as assessed by mean change in BCVA and number of injections by study visit.
- Changes in NEI-VFQ-39 by study visit.
- Optional aqueous humor testing will be conducted in select subjects

OCT-A is not available and will not be analyzed. Changes in CRT and cube volume will be reported in addition to SRF, IRF and RPED height. Total CNV area will be analyzed, as measured by FA.

Section 10.4.2 (“Analysis of the Primary Endpoint”) of the study protocol describes the MMRM analysis to include visit as a fixed effect, patient as a random effect, and the baseline letters read as a covariate.

Treatment group will be included as a fixed effect; a treatment group by visit interaction will also be included.

16. LIST OF TABLES, LISTINGS, AND FIGURES

16.1. TABLES

16.2. LISTINGS

16.3. FIGURES