Study Title	A Single Arm Open-Label Study to Evaluate the Therapeutic Effects and Safety of a 6-Week Treatment Regimen of ALK4290 in Patients with Newly Diagnosed Wet Age-Related Macular Degeneration (wAMD)
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STATISTICAL ANALYSIS PLAN

A Single Arm Open-Label Study to Evaluate the Therapeutic Effects and Safety of a 6-Week Treatment Regimen of ALK4290 in Patients with Newly Diagnosed Wet Age-Related Macular Degeneration (wAMD)

Sponsor: Alkahest, Inc.

Protocol Number: ALK4290-201

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Date: 20 AUG 2018

Version: 1.0

Protocol Title

A Single Arm Open-Label Study to Evaluate the Therapeutic Effects and Safety of a 6-Week Treatment Regimen of ALK4290 in Patients with Newly Diagnosed Wet Age-Related Macular Degeneration (wAMD)

Protocol Number: **ALK4290-201**

Version: **1.0**

Date: **20 AUG 2018**

Statistical Analysis Plan Approval

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Manager of Clinical Data Management
ProTrials Research

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Approved by: _____ _____

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Director of Clinical Operations
Alkahest, Inc.

Date

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List of Abbreviations

AE	Adverse Event
ALT	Alanine Amino Transferase
AMD	Age-Related Macular Degeneration
AP	Alkaline Phosphatase
aPTT	activated Partial Thromboplastic Time
ARM	Age-Related Maculopathy
AST	Aspartate Amino Transferase
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BLQ	Below the Limit of Quantification
Cmax	Maximum Plasma Concentration
CNV	Choroidal Neovascularization
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CS	Clinically Significant
CSR	Clinical Study Report
CST	Central Subfield Thickness
DBP	Diastolic Blood Pressure
DVM	Data Validation Manual
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Early Treatment Diabetic Retinopathy Study
EOT	End of Treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FP	Fundus Photography
FU	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product (Study Agent)
INR	International Normalized Ratio

IOP	Intraocular Pressure
IRF	Intraretinal Fluid
ISF	Investigator Site File
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Drug Regulatory Activities
NCS	Not Clinically Significant
NOA	Not Analyzed
NOP	No Peak Detectable
NOR	No Valid Result
NOS	No Sample Available
OCT	Optical Coherence Tomography
PED	Pigment Epithelial Detachment
pH	Potential of Hydrogen
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
PT	Prothrombin Time
RBC	Red Blood Cell Count
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analytical Plan
SBP	Systolic Blood Pressure
SDC	Statistics & Data Corporation
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System Organ Class
SOP	Standard Operating Procedures
SRF	Subretinal Fluid
TEAE	Treatment-Emergent Adverse Event
wAMD	Wet Age-Related Macular Degeneration
WBC	White Blood Cell Count
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol ALK4290-201, Version 3.0 dated 15MAY2018 and Clarification Memorandum #1 dated 12JUL2018.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the CSR.

2. Study Objectives

The primary objective of this study is to investigate the potential therapeutic effects of a 6-week, twice daily oral dosing regimen of ALK4290 on best corrected visual acuity (BCVA) in newly diagnosed (treatment naïve) patients with Wet Age-Related Macular Degeneration (wAMD) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) testing method. The secondary objectives are to assess the safety of the proposed dosing regimen.

3. Study Variables

3.1 Primary Variable

- Mean change from baseline in BCVA letter score as measured by the ETDRS testing method at 6-weeks

3.2 Secondary Variable

- Safety as assessed by incidence, seriousness, and severity of adverse events (AE)

3.3 Exploratory Variables

- Changes in concentrations of ALK4290 in plasma at various time points
- Changes in central subfield thickness (CST), intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelial detachment (PED) as measured by spectral domain optical coherence tomography (SD-OCT) and fundus photography/fundus angiography (FP/FA)
- Evaluation of pharmacogenomic characteristics and biomarkers in blood and plasma samples

3.4 Statistical Hypotheses

The null and alternative hypotheses for change from baseline in BCVA letter score as measured by ETDRS testing method are as follows:

H_0: Mean change from baseline in BCVA letter score at 6 weeks = 0

H_1: Mean change from baseline in BCVA letter score at 6 weeks ≠ 0

The hypothesis testing will be at a two-sided Type I error rate (α) of 0.20. Specifics of the statistical tests are provided in Section 14.

4. Study Design and Procedures

4.1 General Study Design

This is a single arm, open-label study to evaluate the therapeutic effects and safety of a 6-week treatment regimen of ALK4290 in patients with newly diagnosed (treatment naïve) wAMD. This study enrolls newly diagnosed patients with Choroidal Neovascularization (CNV) secondary to AMD. All subjects will receive the investigational treatment ALK4290 at a daily dosage of 800 mg administered orally twice a day as 400 mg tablets for 6 weeks. At every visit, safety and tolerability assessments will occur. At specified visits, BCVA will be measured by the ETDRS testing method and morphological evaluations will be conducted utilizing SD-OCT and FP/FA.

The study eye is defined as the eye that meets all the inclusion criteria and none of the exclusion criteria. If both eyes meet the inclusion and none of the exclusion criteria, the study is selected by the investigator, per their discretion.

The overall duration of the study is approximately 10 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit) with a targeted recruitment of 30 subjects over the accrual period. The subject participation period is 10 weeks (6-week treatment plus 4-week follow-up), unless prematurely discontinued.

4.2 Schedule of Visits and Assessments

The schedule of event table:

	Screening	Treatment Period							Follow-Up		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/EOT[7]**	**9/FU**	**10/FU**	**Phone/FU**
Day	**-7 to -2**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
Time Window (days)			**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Informed Consent[1]	X										
Informed Consent for Pharmacogenomics[2]	X										
[redacted]	[redacted]										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria[3]	X	X									
Physical examination	X	X		X		X		X[7]		X	
Vital signs (seated)	X	X	X	X	X	X	X	X[7]	X	X	
Laboratory tests	X	X	X	X	X	X	X	X[7]	X	X	
Pregnancy test (as applicable)[9]	X	X						X			
12-lead ECG	X		X			X		X[7]			
SD-OCT	X	X	X	X	X	X	X	X[7]	X	X	
FP/FA	X							X[7]			
Visual acuity	X	X	X	X	X	X	X	X[7]	X	X	
Slit-Lamp	X	X	X	X	X	X	X	X[7]	X	X	
IOP	X	X	X	X	X	X	X	X[7]	X	X	
Administration of study agent[4]		X	X	X	X	X	X	X[7]			
Dispense study agent		X	X	X	X	X	X				
Study agent accountability		X	X	X	X	X	X	X[7]			
Pharmacokinetic (PK) blood sample (for plasma extraction)		X[5]	X[6]	X[6]	X[6]	X[6]	X[6]	X[5,7]	X		
Biomarker plasma aliquots		X[5]				X[5]		X[5,7]	X[5]		
[redacted]		X[2]									
Adverse events[8]	X	X	X	X	X	X	X	X[7]	X	X	X
Concomitant/current medications[8]	X	X	X	X	X	X	X	X[7]	X	X	X
Trial completion											X

1. All subjects must sign an informed consent consistent with ICH-GCP guidelines prior to any trial related procedures, which includes medication washouts and restrictions.
2. [redacted]
3. A preliminary check of inclusion/exclusion criteria will be performed at screening (Visit 1) after obtaining informed consents.
4. Study agent will be self-administered in the clinic under supervision of study personnel during every visit of the treatment period (Visits 2-8) following all safety and ophthalmic assessments. Training on study agent administration will be conducted prior to the initial study agent administration at Visit 2.
5. A pre-dose PK blood sample will be taken to be centrifuged for collection of plasma samples. Biomarker plasma aliquots will be obtained from the PK samples. At Visit 2 only, four post-dose PK blood samples will be taken.
6. A pre-dose PK blood sample will be taken to be centrifuged for collection of plasma samples.
7. End of Treatment (EOT) visit (Visit 8): all study related procedures will be conducted at the conclusion of 6 weeks of treatment on Day 43 ±1. Withdrawal of consent is allowed at any time. For subjects who withdraw consent from the study, no study procedures will be done thereafter. For those that withdraw from the study agent, follow-up visits are to occur as per the protocol. Excluding cases of medical emergency, but prior to the discontinuation of a subject from the clinical study for disease worsening, the study investigator should discuss each case of discontinuation with the sponsor.
8. Adverse events and concomitant medications will be assessed at every study visit as well as recorded at any unscheduled subject contact (e.g., unscheduled phone calls, etc.). Following completion of study agent treatment (Visits 2-8), all current medications will be assessed in the follow-up period.
9. Pregnancy test required in **Poland only** per Inclusion Criteria.

5. Study Treatments

This is a single arm, open-label study. All subjects will receive the investigational treatment ALK4290 at a daily dosage of 800 mg administered orally twice a day as 400 mg tablets for 6 weeks.

6. Sample Size and Power Considerations

A total of 30 subjects will be enrolled in the study with the intent of obtaining approximately 25 evaluable subjects who would complete at least 3 weeks of treatment and evaluations through Visit 5 (Day 22). Subjects who discontinue prior to Day 22 may be replaced. Subjects who withdraw or are withdrawn during screening (prior to completing V2) will be replaced. The study is not powered for detecting statistically significant differences in therapeutic parameters in subjects with wAMD receiving ALK4290.

7. Data Preparation

Data management procedures, including database design and selection of the data dictionary will be performed by the Data Manager and reviewed and approved by the Sponsor. Auto-coding of all AEs, medical histories and concomitant medications will be performed by the IBM Clinical Development EDC system with additional manual coding performed by the Sponsor designated medical coder. Medical coding will be reviewed by the GCT Medical Monitor and confirmed and approved by the Sponsor. All reported study data will be recorded on the electronic Case Report Forms (eCRF) using IBM Clinical Development and transferred to SDC by ProTrials. Clinical personnel at the study site and the CRO are responsible for ensuring that the protocol is followed and that the eCRFs are properly completed.

Additional safety lab data external to the eCRF data will be provided by Synevo to ProTrials to be reconciled with the EDC data and transferred separately to SDC for analysis. External PK data will be transferred from KCAS and will be analyzed by SDC as outlined in the PK plan (separate from the SAP).

[redacted]

All Subject IDs will be assigned automatically within the EDC. The Subject ID consists of 9 numbers: the first set of 3 numbers are specific for the protocol number (i.e., 201); the second set of 3 numbers are specific for the site number (i.e., 001 through 012), and the third set of 3 numbers are the subject specific screening number (e.g., 001, 002, etc.).

After data are entered into EDC, data are reviewed and verified by the clinical monitoring/operations CRO and ProTrials Data Management. Additionally, SAE reconciliation of the Clinical Database is performed against the Alkahest Global Safety Database and any issues are resolved. When the database has been confirmed to be complete, consistent and accurate, the database will be locked according to ProTrials Standard Operating Procedures and study specific Data Management Plan. Any

changes to the database after that time can only be made with the approval of the Sponsor in consultation with ProTrials and SDC.

Final analyses outlined in this document will be performed after:

- All data management requirements are met according to ProTrials' Standard Operating Procedures (SOP), including performance of edit and verification checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate ProTrials' and Sponsor personnel;
- All major protocol deviations and the Per Protocol (PP) set have been determined.

8. Analysis Sets

The presentation of baseline characteristics will be based on the Intent-to-Treat (ITT) set. All safety analyses will be performed using the Safety set. Analyses of the primary and exploratory efficacy endpoints will focus on, but will not be limited to, the Evaluable and/or PP sets, as defined below.

8.1 Intent-to-Treat Set

The Intent-to-treat set includes all enrolled subjects.

8.2 Safety Set

The Safety set includes all subjects who received at least 1 dose of the study agent.

8.3 Evaluable Set

The Evaluable set includes all subjects who complete at least 3 weeks of treatment during the 6-week treatment period.

8.4 Per Protocol Set

The Per Protocol set is a subset of the Evaluable set, comprised of all subjects who completed the study and have no major protocol violations.

9. General Statistical Considerations

Final data analysis will be performed by SDC after the study is completed and the database has been cleaned and locked. One interim analysis will be performed by SDC when two-thirds of all enrolled subjects have either completed Day 15 (Visit 4) or prematurely exited the study; at this time, a snapshot of the database will be extracted (without formal pre-database-lock data cleaning) for inclusion in the interim analysis. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher.

Unless specified otherwise, all ocular assessments and efficacy outcome measures are with respect to the study eye, herehence. Data collected for the fellow eye (non-study eye) will be included in subject listings and may be analyzed.

Study day will be calculated as (Date of Visit) – (Date of Initiation of Investigational Medicinal Product [IMP]) + 1 for visits after initiation of IMP and as (Date of Visit) – (Date of Treatment Initiation) for visits prior to initiation of IMP.

9.1 Missing or Inconclusive Data Handling

In general there will be no imputation of missing data other than for partial or missing dates. Partial start and end dates for medical history, concomitant medications, and AEs will be imputed as outlined in Appendix 1. Completely missing dates will only be imputed for AEs.

The original dates will be displayed in data listings along with the relative study day for complete dates. imputed dates will be used in derivations only (e.g., to determine treatment-emergence status, etc.).

9.2 Definition of Baseline

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 2 (Day 1). For assessments that are not performed at Visit 2 (i.e. FP and FA), the screening Visit 1 measures will be considered as baseline.

9.3 Visit Windows and Visit Mapping

The following table lists the scheduled visits and planned study day along with the corresponding visit window that will be used to map visits occurring outside of the scheduled times.

Scheduled Visit	Planned Study Day	Visit Window
Visit 1 / Screening	Day -7*	<= Day -1
Visit 2	Day 1	Day 1
Visit 3	Day 8	Day 2 to Day 11
Visit 4	Day 15	Day 12 to Day 18
Visit 5	Day 22	Day 19 to Day 25
Visit 6	Day 29	Day 26 to Day 32
Visit 7	Day 36	Day 33 to Day 39
Visit 8 / End of Treatment (EOT)	Day 43	Day 40 to Day 46
Visit 9 / Follow-Up (FU)	Day 50	Day 47 to Day 53
Visit 10 / FU	Day 57	Day 54 to Day 60
Phone / FU	Day 71	>=Day 61

* Visit 1/Screening of Fundus Photography/FA can be performed up to Day -14, per the protocol.

Summary tables will be presented by scheduled visit using the following algorithm. If there are multiple non-missing assessments within a visit window, then the visit closest to the scheduled visit will be used. If multiple visits are equidistant from the scheduled visit, then the scheduled visit and unscheduled visit

will be selected in that order. If multiple visits of the same type are equidistant from the scheduled window, then the earliest visit of that type will be selected.

Subject listings will include all visits.

9.4 Data Analysis Conventions

Quantitative variables will be summarized using descriptive statistics including the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum values. Means, medians, and confidence intervals (CI) will be reported to two decimal places and SDs to three. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Change from baseline will be calculated as the value at follow-up visit minus baseline.

The primary efficacy analysis will be evaluated at a two-sided significance level of 0.20. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as “<0.0001”; p-values greater than 0.9999 will be presented as “>0.9999”.

9.5 Adjustments for Multiplicity

There will be no adjustments for multiplicity for this early phase, exploratory study.

10. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were enrolled, treated, completed the study, and discontinued from the study.

The number and percentage of subjects discontinued from the study and the reasons for study discontinuation will be summarized for all enrolled subjects. The reasons for study discontinuation that will be summarized include: AEs, treatment with prohibited concomitant medications, subject non-compliance, withdrawal of consent, pregnancy, termination of study, and other. A subject listing will be provided that includes the date (and study day) of and reason for premature study discontinuation.

The number and percentage of subjects with protocol deviations will be summarized for the ITT set. A subject listing will be provided that includes the date of the deviation and the deviation description.

Subject listings will be provided to list out informed consent dates, inclusion and exclusion criteria violations, and exclusions from the PP set.

11. Demographic and Baseline

11.1 Demographic and Vital Signs

Demographic variables collected in this study include age in years (at time of screening), sex, race, ethnicity, body mass index (BMI), weight, height, iris color, and study eye (OD or OS). Subjects who record more than one race will be grouped into a single category denoted as 'Multiple Race'.

Age (years) will be summarized using continuous descriptive statistics. Age will also be categorized as follows: <65 years and ≥65 years.

The number and percentage of subjects will be presented for age category, sex, race, ethnicity, iris color and study eye (OD or OS). Percentages will be based on the total number of subjects in the ITTset. A subject listing that includes all demographic variables will be provided.

11.2 Baseline Characteristics

Baseline BCVA letter score as measured by the ETDRS testing method; CST, presence and height of IRF, SRF, and PED as measured by SD-OCT; and presence and size of CNV and leakage from CNV as measured by FP/FA will be included in the relevant summaries (including the demography summary) and listings.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be summarized using discrete summary statistics and presented at the subject level by system organ class (SOC) and preferred term (PT). If a subject reports the same PT multiple times within the same SOC, that PT will only be counted once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, the SOC will only be counted once. Separate tables will be created for ocular and non-ocular medical history. Medical history will be coded using MedDRA, Version 21.0. The summaries will be based on the ITT set.

Listings of relevant medical history, including prior medical history within three months prior to Visit 1 (Screening) will be captured in the appropriate eCRF. A subject listing of reported medical history with start and stop dates (or ongoing) will be provided.

12.2 Prior and Concomitant Medications/Treatments

At the screening Visit 1 (Day -7 to Day -2), subjects will be asked what medications they are taking, as well as those the subject may have taken prior to screening. At each subsequent study visit, subjects

will be asked what concomitant medications they are currently taking or if there have been any changes to their medication since the previous visit.

All prior and concomitant ocular and non-ocular medications will be listed using the ITT set including generic name, route of administration, start date, stop date, dosage, and indication. Prior and concomitant medications will be categorized by WHO Drug Dictionary (B3 Global March 2018 or higher) classification for therapeutic class and drug name.

Counts and percentages of ocular and non-ocular concomitant medications will be summarized separately, and summaries will be displayed for the ITT set. Subjects with multiple medications in the same WHO drug dictionary class or preferred name will be counted only once for that respective WHO drug dictionary class or preferred name.

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

A dose is considered a single 400 mg tablet. Subjects are instructed per protocol to administer a dose twice daily (i.e., once in the morning and once in the evening). Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows:

$$\text{Compliance (\%)} = \frac{\text{Number of Actual Doses Received}}{\text{Number of Expected Doses}} \times 100$$

The number of actual doses received will be calculated from the the number of dispensed and returned tablets as recorded in the eCRF. The number of expected doses that will be used for calculating compliance will be calculated as {2x [date of last dose – date of first dose]} +1 for all subjects, regardless of study completion status. Overall compliance will also be categorized as compliant (≥75%) and non-compliant (<75%).

Treatment compliance (%) will be summarized for the Safety set using continuous descriptive statistics. The compliance categories defined above will be summarized with counts and percentages.

A subject listing of compliance will also be produced.

13.2 Treatment Exposure

Extent of exposure will be calculated in days using the following:

$$\text{Extent of Exposure (days)} = [\text{Date of last dose} - \text{Date of first dose}] + 1$$

Extent of treatment exposure (days) and the total number of doses received for each subject exposed to IMP will be summarized with continuous descriptive statistics using the Safety set. A subject listing of treatment exposure will also be produced.

14. Analysis of the Primary Endpoint

The primary endpoint is the mean change from baseline (Visit 2 / Day 1) to end of treatment (Visit 8 / Day 43) in BCVA letter score of the study eye as measured by the ETDRS testing method using the Evaluable set. BCVA will be measured at the beginning of every study visit and change from baseline for each subject will be calculated as follow-up visit minus baseline visit. Quantitative summary statistics will be used to summarize the BCVA letter score and change from baseline at each visit. A two-tailed, one-sample t-test will be used to assess the mean change from baseline in BVCA letter score at each visit, in which the change from baseline BCVA letter score will be compared to a reference value of zero. The following SAS code will be used to run the one-sample t-test:

```
PROC TTEST H0=0 ALPHA=0.20 DATA=INDATA;
   VAR BCVA_CHG;
RUN;
```

where

- *INDATA* is the name of the input dataset;
- *BCVA_CHG* is the change in BCVA from baseline to the follow-up visit.

A mixed model accounting for repeated measures will also be used to analyze BCVA. This model will include the change from baseline in BCVA letter score as the response variable and baseline BCVA letter score, smoking status and visit as explanatory variables for adjustment. LS means for each visit will be calculated along with corresponding 95% CIs and p-values. SAS code to implement this repeated measures mixed model is as follows:

```
PROC MIXED DATA=INDATA;
   CLASS SUBJID SMOKE VISIT;
   MODEL CHG = BASELINE SMOKE VISIT / DDFM = KR SOLUTION;
   REPEATED VISIT / SUBJECT=SUBJID TYPE=UN;
   LSMEANS VISIT / CL;
RUN;
```

where

- *INDATA* is the name of the input dataset sorted by *SUBJID* and *VISIT*;
- *SUBJID* is the subject ID number;
- *SMOKE* is the subject's smoking history (Never smoked, Ex-smoker, Currently smokes);
- *VISIT* is the visit at which the BCVA letter score was collected;

- *CHG* is the change from baseline in the BCVA letter score;
- *BASELINE* is the baseline BCVA letter score;

The Kenward-Roger method will be used to determine denominator degrees of freedom. An unstructured variance-covariance matrix will be used for the above repeated measures model. If the model does not converge using the unstructured matrix, the first order autoregressive structure and the compound symmetry structure will be employed, in that order.

The above analyses will be repeated on the PP set as a sensitivity analysis.

Additionally, the number of subjects with change from baseline in BCVA letter score for the following categories will be summarized with counts and percentages:

- >=15 letters;
- >=14 and >=10 letters;
- >=9 and >= 5 letters;
- >=4 and >= -4 letters;
- >= -5 and >= -9 letters;
- >= -10 and >= -14 letters;
- <= -15 letters.

BCVA results will also be presented in a data listing. BCVA results in the fellow eye are not included in the analyses but will be included in the listings. BCVA will also be summarized by visit using box plots.

15. Analysis of the Secondary Endpoints

The analyses for secondary endpoints (incidence, seriousness and severity of AEs) will be discussed in the next section as part of the safety analyses. There is no secondary efficacy endpoint for the study.

16. Safety Analyses

Safety will be assessed for the following endpoints using the Safety set:

- Incidence, seriousness, and severity of AEs;
- Observed slit-lamp biomicroscopy values;
- Observed intraocular pressure (IOP) values;
- Changes from baseline in clinical laboratory values;
- Changes from baseline in physical examination;
- Changes from baseline in vital signs.

Adverse events will be presented using frequencies and percentages of subjects.

Other safety endpoints including slit-lamp biomicroscopy, IOP, clinical laboratory values, physical examination, and vital signs will be summarized using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. Assessments performed by eye (study eye and fellow eye) will be summarized separately. No statistical inferential testing will be performed for safety variables.

16.1 Adverse Events

AEs are defined as any untoward medical occurrence associated with the use of an IMP in humans, whether or not considered IMP-related. All AEs, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent through the follow-up period) will be collected, documented, and reported. All AEs that occur or worsen on or after the first use of IMP will be considered as treatment-emergent AEs (TEAE). Reported AEs that begin prior to the first dose of IMP are classified as non-TEAEs; these will only be included in subject listings and not included in summary tables.

When reporting an AE, the event description should use the best matching terminology describing the event as found in the Common Terminology Criteria for Adverse Events (CTCAE v4.03). Standardized terms from the CTCAE will be used to categorize events for reporting to regulatory authorities using the Medical Dictionary for Regulatory Activities (MedDRA, v. 21.0).

The severity of all reported AEs are graded by the investigator into one of the following five (5) CTCAE categories:

- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Life-Threatening)
- Grade 5 (Death)

The relatedness of IMP to AE will be classified as definite, possibly, or unrelated. Documentation of AEs will include start date, end date, seriousness, severity, relatedness, whether or not medication was required, outcome, and action taken with the study agent.

A serious adverse event (SAE) is defined for this protocol as any AE that meets one or more of the following criteria:

- A death (CTCAE Grade 5 event) occurring during the study, whether or not considered treatment-related;
- A life-threatening event (CTCAE Grade 4);

- An event requiring inpatient hospitalization or prolonged hospitalization due to the adverse event;
- An adverse event resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the participant's body function or structure, physical activities or quality of life;
- An event that otherwise required a medical or surgical intervention to preclude permanent impairment or damage (excluding unrelated elective or cosmetic procedures).

An AE of special interest (AESI) is defined for this protocol as any the following outcomes:

- Hepatic injury defined by the following alterations of liver parameters:
  - For subjects with normal liver function at baseline an elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥ 3-fold the upper limit of normal (ULN) combined with an elevation of total bilirubin ≥ 2-fold the ULN measured in the same blood draw sample;
- Abrupt decrease of BCVA (> 15 letters lost from baseline);
- QTc interval prolongation (> +50 ms from baseline and > 450 ms).

An overall tabular summary of TEAEs will be presented that includes the number and percentage of subjects who experienced at least one TEAE. These summaries will also include breakdowns of TEAEs further categorized as ocular or non-ocular, and within these categories as drug-related TEAEs, TEAEs with CTCAE Grade 3/4/5, drug-related TEAEs with CTCAE Grade 3/4/5, TEAEs with an outcome of death, serious TEAEs, drug-related serious TEAEs, TEAEs leading to discontinuation of IMP and drug-related TEAEs leading to discontinuation of IMP.

Furthermore, the number and percentage of subjects with TEAEs by SOC and PT; by SOC, PT and maximal severity; by SOC and PT for TEAEs; by SOC and PT for SAEs; and by SOC and PT for TEAEs leading to subject withdrawal will be presented. Separate summaries will be provided for ocular and non-ocular TEAEs (including systemic). Adverse events of special interest will also be summarized by SOC and PT. These summaries by SOC and PT will be at the subject level. If a subject reports the same PT multiple times within the same SOC, that PT will only be counted once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be counted once.

All AEs (including non-TEAEs) will also be presented in subject listings.

16.2 Slit-Lamp Biomicroscopy Examination

Slit-lamp biomicroscopy examinations will be conducted on both eyes at all scheduled visits. The slit-lamp findings will include examinations of the cornea, conjunctiva, anterior chamber, iris/pupil, lens and

eyelids. Anterior chamber will be graded as +, ++, +++ or none; the other parameters will be graded as normal or abnormal. Abnormal findings will be further classified as not clinically significant (NCS) or clinically significant (CS). All clinically significant values will be recorded as AEs in the eCRF and followed until resolution. Once resolved, the AE eCRF page(s) will be updated

Slit-lamp findings will be summarized by visit, for the study eye and fellow eye separately, using qualitative summary statistics (frequency counts and percentages). Percentages will be based on the number of subjects with non-missing values at a given visit.

A shift table will show changes from baseline Visit 2 (Day 1) to all observations at later study visits. The data for slit-lamp biomicroscopy examinations will be presented in a listing.

16.3 Intraocular Pressure (IOP)

IOP will be measured using applanation Goldmann tonometry or equivalent tonometer in both eyes at all scheduled visits. IOP will be summarized for each eye (study eye and fellow eye) by visit using quantitative summary statistics. The number and percentage of subjects with IOP >= 20 mmHg and the number and percentage of subjects with IOP >= 30 mmHg will be summarized. Results will be listed for both eyes at each visit.

16.4 Clinical Laboratory Values

Blood samples and urine must be collected at every visit. Safety laboratory examinations will include hematology, biochemistry, coagulation, and qualitative urine analysis.

- Serology (screening only): hepatitis A (anti-immunoglobulin M (IgM), anti-IGM)), hepatitis B (hepatitis B antigen, anti-HBs, DNA), hepatitis C (anti-hepatitis C virus (HCV), ribonucleic acid (RNA) if anti-HCV positive), hepatitis D (anti-IgM, anti-immunoglobulin G (IgG)), hepatitis E (anti-hepatitis E virus (HEV), anti-HEV IgM, RNA if anti-HEV IgM positive), anti-smooth muscle antibody (titer), anti-nuclear antibody (titer), anti-liver-kidney microsomes (LKM) antibody, antimitochondrial antibody, Epstein Barr virus (vascularized composite allotransplantation (VCA) IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)
- Hematology: hemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential, platelets
- Biochemistry: glucose, sodium, potassium, calcium, inorganic phosphate, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), total bilirubin (if elevated provide direct bilirubin), urea, total protein, albumin, uric acid

- Coagulation: activated partial thromboplastic time (aPTT), prothrombin time (PT)/international normalized ratio (INR)
- Urine: potential of hydrogen (pH), glucose, erythrocytes, leukocytes, protein, nitrite and glomerular filtration rate (GFR)

All safety laboratory measurements will be performed at all scheduled visits by a central laboratory (except serology which is evaluated at screening only) . Investigators will get guidance and instructions on laboratory sampling and processing through a separate Lab Manual provided by the central laboratory.

The investigator is responsible for determining and documenting if out of range laboratory values are clinically significant or not. All clinically significant values will be recorded as AEs in the eCRF and followed until resolution. Once resolved, the AE eCRF page(s) will be updated.

Continuous biochemistry, hematology, and coagulation assessments will be summarized by visit and changes from baseline using quantitative summary statistics. The data for biochemistry and hematology will also be presented in listings.

Serology and urinalysis will be listed with collection information, and clinically significant findings, but no tabular summaries will be produced.

All laboratory values will be presented using conventional units.

16.5 Electrocardiogram (ECG)

ECGs will be measured at screening Visit 1, Visit 3, Visit 6, and Visit 8/EOT, and graded as normal or abnormal. Abnormal findings or changes from baseline will be further classified as not clinically significant (NCS) or clinically significant (CS).In the event abnormal ECG results requires additional follow up, ECGs may be performed at unscheduled visits or at a study visit that an ECG is not required per protocol. ECG data performed outside of the protocol specified time points will be captured in the EDC on an “Unscheduled Visit” eCRF and mapped to the nearest scheduled visit as defined in Section 9.3. ECG grades and shift from baseline will be summarized with counts and percentages for each visit for the Safety set. All clinically significant findings will be recorded as AEs in the eCRF and followed until resolution. Once resolved, the AE eCRF page(s) will be updated. A subject listing of the ECG results will also be produced.

16.6 Vital Signs

Vital signs (blood pressure, pulse rate and respiration) and temperature will be summarized at all scheduled visits using descriptive statistics for the Safety set. Blood pressure includes systolic blood

pressure (SBP) and diastolic blood pressure (DBP). Change from baseline will also be summarized to each post-baseline visit.

A subject listing of the vital signs results will also be produced.

16.7 Physical Examination

A general physical examination including height (measured only at screening) and weight will be performed at screening Visit 1, Visit 2, Visit 4, Visit 6, Visit 8/EOT and Visit 10/FU.

Physical examination data will be listed to indicate whether the physical examination was conducted or not, but no tabular summaries will be produced.

17. Analysis of the Exploratory Endpoints

17.1 SD-OCT and Fundus Photography/Fluorescein Angiography

SD-OCT will be assessed at all scheduled study visits. The retinal layers and thickness will be visualized and measured by OCT and will be investigated by a trained person using only specified OCT equipment. Reported CST values will be exclusive of the sub-retinal pigment epithelial (RPE) layer fluid.

FP/FA will be conducted on the study eye at Screening (Day -7 to -2; up to 14 days prior to Visit 1 is also acceptable for FP/FA) and Visit 8/EOT (Day 43±1).

The following ophthalmic endpoints described below will be measured in an exploratory manner to investigate the extent, onset, and duration of action. Change from baseline in the study eye of the quantitative endpoints will be analyzed in a manner similar to the primary efficacy endpoint. Qualitative endpoints will be summarized for the study eye using counts and percentages for the Evaluable and PP sets. Subject listings will also be provided for these endpoints and will include collected data for the fellow eye.

- CST (µm) measured by SD-OCT, absolute and change from baseline
  - CST in the study eye will also be summarized for each scheduled visit using box plots.
- Presence and maximum height (microns) of IRF by SD-OCT over time, absolute and change from baseline
- Presence and maximum height (microns) of SRF by SD-OCT over time, absolute and change from baseline
- Presence and maximum height (microns) of PED by SD-OCT over time, absolute and change from baseline
  - Collected in EDC as RPE detachments and maximum height of the detachments are collected when present.

  - Maximum height of PED in the study eye will also be summarized for each scheduled visit using box plots.
- Presence and size (number of disc areas) of CNV measured by SD-OCT and FP/FA, absolute and as change from baseline.
- Presence and size (number of disc areas) of CNV leakage as demonstrated by FP/FA, absolute and as change from baseline

The following ophthalmic endpoints will be captured in EDC as part of standard SD-OCT and FP/FA assessments. These endpoints will not be summarized (except for macular volume, which will be summarized for the study eye at scheduled visits using box plots) but will be presented in subject listings.

- Macular Volume (mm^3) as measured by SD-OCT
- Presence of Intraretinal Cystoid Spaces as measured by SD-OCT
- Presence of Lesion in the CNV (including size of the lesion) as measured by FP/FA
- Presence of RPE atrophy as measured by FP/FA
- Presence of Hemorrhage in the PED (including area of the hemorrhage) as measured by FP/FA
- Presence of Disciform Scar/Retinal Fibrosis as measured by FP/FA

18. Interim Analyses

Continuous data monitoring will be performed. One interim analysis will be performed when two-thirds of all entered subjects have reached Day 15 (Visit 4). The interim analysis will include only a subset of the secondary endpoint (i.e., accumulated AE information).

Recruitment into the trial will be stopped if the interim analysis shows relevant safety problems with ALK4290. No formal futility analysis will be conducted.

19. Pharmacokinetic Analysis

A separate PK plan will be created to describe details pertinent to the analysis of collected PK data.

20. Biomarker Analysis

A separate biomarker plan will be created to describe details pertinent to the exploratory analysis of collected biomarker data.

21. Changes from Protocol-Stated Analyses

Not applicable.

22. References

Not applicable.

23. Revision History

Documentation of revision to the SAP will commence after approval of the Final version 1.0.

24. Tables

Tables that will be included in the topline delivery are shown in boldface font and the tables, listings, and figures for the interim analyses are italicized.

Table Number	Title	Set
14.1.1	***Subject Disposition***	***All Subjects***
14.1.2	***Demographics and Baseline Characteristics***	***ITT Set***
14.1.3.1	Ocular Medical History	ITT Set
14.1.3.2	Non-Ocular Medical History	ITT Set
14.1.4.1	Ocular Concomitant Medications	ITT Set
14.1.4.2	Non-Ocular Concomitant Medications	ITT Set
14.1.5	Compliance with Study Drug	Safety Set
14.1.6	Exposure to Study Drug	Safety Set
Primary and Exploratory Efficacy Analyses		
14.2.1.1	***Summary of Study Eye BCVA Letter Score and Change from Baseline at Scheduled Visits***	***Evaluable Set***
14.2.1.2	***Summary of Study Eye BCVA Letter Score and Change from Baseline at Scheduled Visits***	***PP Set***
14.2.1.3	Categorical Summary of Study Eye BCVA Letter Score Change from Baseline at Scheduled Visits	Evaluable Set
14.2.2.1	***Summary of Study Eye Central Subfield Thickness (µm) and Change from Baseline as Measured by SD-OCT at Scheduled Visits***	***Evaluable Set***
14.2.2.2	***Summary of Study Eye Central Subfield Thickness (µm) and Change from Baseline as Measured by SD-OCT at Scheduled Visits***	***PP Set***
14.2.3.1	Presence of Intraretinal Fluid as Measured by SD-OCT in the Study Eye at Scheduled Visits	Evaluable Set
14.2.3.2	Presence of Intraretinal Fluid as Measured by SD-OCT in the Study Eye at Scheduled Visits	PP Set
14.2.3.3	Summary of Maximum Height of Intraretinal Fluid (microns) and Change from Baseline as Measured by SD-OCT in the Study Eye at Scheduled Visits	Evaluable Set
14.2.3.4	Summary of Maximum Height of Intraretinal Fluid (microns) and Change from Baseline as Measured by SD-OCT in the Study Eye at Scheduled Visits	PP Set
14.2.4.1	Presence of Subretinal Fluid as Measured by SD-OCT in the Study Eye at Scheduled Visits	Evaluable Set
14.2.4.2	Presence of Subretinal Fluid as Measured by SD-OCT in the Study Eye at Scheduled Visits	PP Set

Table Number	Title	Set
14.2.4.3	Summary of Maximum Height of Subretinal Fluid (microns) and Change from Baseline as Measured by SD-OCT in the Study Eye at Scheduled Visits	Evaluable Set
14.2.4.4	Summary of Maximum Height of Subretinal Fluid (microns) and Change from Baseline as Measured by SD-OCT in the Study Eye at Scheduled Visits	PP Set
14.2.5.1	Presence of Pigment Epithelial Detachment as Measured by SD-OCT in the Study Eye at Scheduled Visits	Evaluable Set
14.2.5.2	Presence of Pigment Epithelial Detachment as Measured by SD-OCT in the Study Eye at Scheduled Visits	PP Set
14.2.5.3	Summary of Maximum Height of Pigment Epithelial Detachment (microns) as Measured by SD-OCT in the Study Eye at Scheduled Visits	Evaluable Set
14.2.5.4	Summary of Maximum Height of Pigment Epithelial Detachment (microns) as Measured by SD-OCT in the Study Eye at Scheduled Visits	PP Set
14.2.6.1	Presence of Choroidal Neovascularization as Demonstrated by Fluorescein Angiography in the Study Eye at Scheduled Visits	Evaluable Set
14.2.6.2	Presence of Choroidal Neovascularization as Demonstrated by Fluorescein Angiography in the Study Eye at Scheduled Visits	PP Set
14.2.6.3	Summary of Size of Neovascularization (Number of Disc Areas) and Change from Baseline as Demonstrated by Fluorescein Angiography in the Study Eye at Scheduled Visits	Evaluable Set
14.2.6.4	Suumary of Size of Neovascularization (Number of Disc Areas) and Change from Baseline as Demonstrated by Fluorescein Angiography in the Study Eye at Scheduled Visits	PP Set
14.2.7.1	Presence of Leakage from Choroidal Neovascularization as Demonstrated by Fluorescein Angiography in the Study Eye at Scheduled Visits	Evaluable Set
14.2.7.2	Presence of Leakage from Choroidal Neovascularization as Demonstrated by Fluorescein Angiography in the Study Eye at Scheduled Visits	PP Set
14.2.7.3	Summary of Size of Leakage from Choroidal Neovascularization (Number of Disc Areas) and Change from Baseline as Demonstrated by Fluorescein Angiography in the Study Eye at Scheduled Visits	Evaluable Set
14.2.7.4	Summary of Size of Leakage from Choroidal Neovascularization (Number of Disc Areas) and Change from Baseline as Demonstrated by Fluorescein Angiography in the Study Eye at Scheduled Visits	PP Set
Safety Analyses		
14.3.1.1	***Overall Summary of Treatment-Emergent Adverse Events***	***Safety Set***
14.3.2.1	***Summary of All Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term***	***Safety Set***
14.3.2.2	Summary of All Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set

Table Number	Title	Set
14.3.3.1	***Summary of All Ocular Treatment-Emergent Adverse Events Suspected to be Related to Investigational Medicinal Product by System Organ Class and Preferred Term***	***Safety Set***
14.3.3.2	***Summary of All Non-Ocular Treatment-Emergent Adverse Events Suspected to be Related to Investigational Medicinal Product by System Organ Class and Preferred Term***	***Safety Set***
14.3.4.1	Summary of All Ocular Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
14.3.4.2	Summary of All Non-Ocular Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
14.3.5	Summary of All Adverse Events of Special Interest by System Organ Class and Preferred Term	Safety Set
14.3.6.1	Summary of All Ocular Treatment-Emergent Adverse Events Leading to Subject Withdrawal by System Organ Class and Preferred Term	Safety Set
14.3.6.2	Summary of All Non-Ocular Treatment-Emergent Adverse Events Leading to Subject Withdrawal by System Organ Class and Preferred Term	Safety Set
14.3.7.1	Summary of Ocular Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term	Safety Set
14.3.7.2	Summary of Non-Ocular Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term	Safety Set
14.3.8.1	Summary of Slit Lamp Biomicroscopy	Safety Set
14.3.8.2.1	Shift in Overall Results of Slit Lamp Biomicroscopy	Safety Set
14.3.8.2.2	Shift in Slit Lamp Biomicroscopy Anterior and Vitreous Chamber	Safety Set
14.3.8.2.3	Shift in Slit Lamp Biomicroscopy Hypopyon and Retinal Tear and Detachment	Safety Set
14.3.8.2.4	Shift in Slit Lamp Biomicroscopy Lens Status	Safety Set
14.3.8.2.5	Shift in Slit Lamp Biomicroscopy Lens Opacity for Phakic Eyes	Safety Set
14.3.9	Summary of Intraocular Pressure	Safety Set
14.3.10.1.1	Summary of Clinical Laboratory Values - Biochemistry	Safety Set
14.3.10.1.2	Shift in Clinical Laboratory Values - Biochemistry	Safety Set
14.3.10.2.1	Summary of Clinical Laboratory Values - Coagulation	Safety Set
14.3.10.2.2	Shift in Clinical Laboratory Values - Coagulation	Safety Set
14.3.10.3.1	Summary of Clinical Laboratory Values - Hematology	Safety Set
14.3.10.3.2	Shift in Clinical Laboratory Values - Hematology	Safety Set
14.3.11	Summary of Vital Signs	Safety Set
14.3.12.1	Summary of Electrocardiogram Overall Results	Safety Set
14.3.12.2	Shift in Electrocardiogram Overall Results	Safety Set

25. Listings

Listing Number	Title	Set
16.2.1	Subject Disposition	ITT Set
16.2.2	Protocol Deviations	ITT Set

Listing Number	Title	Set
16.2.3.1	Inclusion and Exclusion Criteria	All Patients
16.2.3.2	Subjects Excluded from Analysis Sets	ITT Set
16.2.3.3	Informed Consent	ITT Set
16.2.4.1	Demographics	ITT Set
16.2.4.2	Ocular Medical History	ITT Set
16.2.4.3	Non-Ocular Medical History	ITT Set
16.2.4.4	Prior and Concomitant Ocular Medications	ITT Set
16.2.4.5	Prior and Concomitant Non-Ocular Medications	ITT Set
16.2.5.1	Study Drug Administration	ITT Set
16.2.6.1	Best Corrected Visual Acuity Scores (ETDRS)	ITT Set
16.2.6.2	Spectral Domain – Optical Coherence Tomography	ITT Set
16.2.6.3	Fundus Photography	ITT Set
16.2.6.4	Fluorescein Angiography	ITT Set
16.2.7.1	All Adverse Events	ITT Set
16.2.7.2	Serious Adverse Events	ITT Set
16.2.7.3	Adverse Events of Special Interest	ITT Set
16.2.7.4	Adverse Events Leading to Subject Withdrawal	ITT Set
16.2.7.5	Deaths	ITT Set
16.2.8.1	Slit-Lamp Biomicroscopy	ITT Set
16.2.8.2	Intraocular Pressure	ITT Set
16.2.8.3	Vital Signs	ITT Set
16.2.8.4	Physical Examination	ITT Set
16.2.8.5	Biochemistry	ITT Set
16.2.8.6	Hematology	ITT Set
16.2.8.7	Coagulation	ITT Set
16.2.8.8	Urine Analysis	ITT Set
16.2.8.9	Serology	ITT Set
16.2.8.10	Electrocardiogram	ITT Set

26. Figures

Figure Number	Title	Set
14.2.1	***By-Visit Box Plot Summary of BCVA Letter Score in the Study Eye***	***Evaluable Set***
14.2.2	***By-Visit Box Plot Summary of Central Subfield Thickness (µm) in the Study Eye as Measured by SD-OCT***	***Evaluable Set***
14.2.3	By-Visit Box Plot Summary of Macular Volume (mm^3) in the Study Eye as Measured by SD-OCT in the Study Eye	Evaluable Set
14.2.4	By-Visit Box Plot Summary of Maximum Height of Pigment Epithelial Detachment (microns) as Measured by SD-OCT in the Study Eye	Evaluable Set

27. Appendix 1

The following algorithms will be used to impute partial dates.

Assessment Type	**Start Date**	**End Date**
Medical History	If only day is missing then impute day as the first of the month ('01'). If missing day and month then impute the first of the year ('01JAN').	If only day is missing then impute day as the last day of the month ('31' for months 01, 03, 05 ,07, 08, 10, 12; '30' for months 04, 06, 09, 11; '29' for month 02 if a leap year; '28' for month 02 if not a leap year). If missing day and month then impute the last of the year ('31DEC').
Prior and Concomitant Medications	If only day is missing and the month and year are the same as the date of IMP initiation, then impute day as the day of IMP initiation. If only day is missing and month and year are not the same as the date of IMP initiation, then impute the first day of the month ('01'). If missing day and month and the year is the same as the date of IMP initiation, then impute day and month as the day and month of IMP initiation. If missing day and month and the year is not the same as the date of IMP initiation, then impute day and month as the first of the year ('01JAN').	If only day is missing then impute day as the last day of the month ('31' for months 01, 03, 05 ,07, 08, 10, 12; '30' for months 04, 06, 09, 11; '29' for month 02 if a leap year; '28' for month 02 if not a leap year). If missing day and month then impute the last of the year ('31DEC').

Adverse Events	Patial start dates for AEs will not be collected. Completely missing start dates for AEs will be imputed as the first dose date unless the corresponding end date indicates the AE could have start earlier, in which case the missing date will be imputed as 01Jan of the same year as the end date.	Patial end dates for AEs will not be collected. Completely missing end dates for AEs will not be imputed.