Protocol Number: REFMAL 265 (X396-CLI-101)

Phase I/II, First in Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer

Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

Final V1.0

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List of Abbreviations

AE	adverse event
ALK	anaplastic lymphoma kinase
ALT/SGPT	alanine aminotransferase
ANC	absolute neutrophil count
AST/SGOT	aspartate aminotransferase
BOR	best overall response
CNS	central nervous system
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ERT	eResearch Technology, Inc.
FISH	fluorescence in situ hybridization
IHC	immunohistochemistry
JAMA	Journal of the American Medical Association
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
msec	millisecond
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall (or Objective) response rate
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetic
PR	progesterone receptor; partial response
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis System
SD	stable disease

TEAEs	Treatment-emergent adverse events
TKI	tyrosine kinase inhibitor
TTP	time to disease progression
ULN	upper limit of normal
WHO	World Health Organization

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1 INTRODUCTION

This document describes the Statistical Analysis Plan (SAP) for Protocol X396-CLI-101 Amendment 9 (29-Jan-2018) titled 'Phase I/II, First in Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer'. Any deviations from this SAP will be noted in the Clinical Study Report.

1.1 Objectives

Primary Objective

The primary objective of this study is:

- To evaluate the safety/tolerability of X-396 (ensartinib) and determine the maximum tolerated dose (MTD) of ensartinib administered as a single agent.

Secondary Objectives

The secondary objectives of this study are:

- To characterize the preliminary pharmacokinetics (PK) of ensartinib administered as a single agent.
- To explore the preliminary biological activity and clinical tumor response after treatment with ensartinib administered as a single agent.

Exploratory Objectives

- To observe the correlation between PK and clinical endpoints.
- To evaluate the status of exploratory biomarkers and correlate with clinical outcome.
- To explore preliminary clinical tumor response in patients with known anaplastic lymphoma kinase (ALK) resistance mutations.
- To obtain germline deoxyribonucleic acid (DNA) samples for possible pharmacogenetic analysis in the event that outliers with respect to efficacy, tolerability/safety, or exposure are identified.

1.2 Study Design

Brief summary of the study design is as follows:

- Open-label, multi-center, non-randomized, dose-escalation and expansion cohort study
- Phase I/II: dose escalation phase (initial accelerated titration followed by 3+3 escalation scheme) with subsequent expansion cohort phase
- Treatment: Ensartinib will be given orally once or twice daily on a 28-day schedule
- Indication: Advanced solid tumors (dose escalation phase) or non-small cell lung cancer patients that are ALK-positive by fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), or United States Food and Drug Administration (FDA)-approved assay (expansion cohort phase) that are not responsive to at least 1

standard therapy or for which there are no effective therapies or for patients that refuse standard therapy. However, patients may be ALK tyrosine kinase inhibitor (TKI)-naïve, and patients may have received prior crizotinib and/or second generation ALK TKI(s).

Treatment Groups

All patients enrolled will take ensartinib orally as a capsule formulation with or without food. The dosing frequency will be once or twice daily based on data evaluation from the previous cohort(s). In order that sufficient PK data are collected at doses below the MTD, additional patients may be enrolled at lower doses.

The actual number of dose cohorts explored during the escalation phase will depend upon the MTD and the safety profile as well as the PK profile observed during the conduct of the trial. During the expansion phase, cohorts are as defined in the protocol.

1.3 Statistical Considerations

Sample Size Justification

This study will enroll up to 190 patients. The number of patients treated will depend upon the need to expand the escalation cohorts from 3 to 6 based on toxicity, the total number of cohorts treated before dose limiting toxicity (DLT) is observed and the MTD is determined, and the number of additional patients enrolled in the expanded cohort phase.

Initially, this sample size was not chosen based on statistical considerations or to obtain adequate power for a particular endpoint analysis, but was chosen to allow for providing a preliminary safety and PK assessment of ensartinib. As of Amendment 8, promising response rates were observed during the Phase II expansion cohort phase that were within the range of historical controls for other agents. As of Amendment 9, to improve the precision of the estimated response rates and to gain more experience with ensartinib in these patient populations, the sample size for selected expansion cohorts was increased, to up to 25 patients for the ALK TKI-naïve cohort, up to 40 patients for the cohort including patients that progressed on prior crizotinib and did not receive another ALK TKI, and up to 50 patients for the cohort including patients that progressed on a second generation ALK TKI. An increase to 40 patients would allow cohort response rates to be estimated within no worse than +/- 15% with 90% confidence. An increase to 50 patients would allow cohort response rates to be estimated within no worse than +/- 12% with 90% confidence. In addition, as of Amendment 9, because of interest in the ALK 1198 mutation, a cohort for patients whose tumor is known to have that mutation is being opened, with up to 20 patients allowed in that cohort.

Randomization

No randomization or stratification will be required. Ensartinib will be administered in an open-label fashion according to cohort assignment. Patients will be allocated to cohorts as defined in the study protocol.

1.4 Analysis Software

Analyses will be performed using statistical Analysis System (SAS®) version 9.4 or higher.

2 DEFINITION OF STUDY POPULATIONS FOR ANALYSIS

The following analysis populations will be defined in this study.

- The safety population will consist of all patients who received at least one dose of ensartinib. The safety population will be used in all safety summaries.
- The efficacy evaluable population will consist of the efficacy population that are ALK positive at 225 mg QD, complete at least 1 cycle of treatment and have a post-baseline response assessment.
- The central nervous system (CNS) efficacy evaluable population will consist of the efficacy evaluable population who have CNS metastasis at baseline.
- DLT evaluable population will consist of all patients who completed DLT evaluation period.
- The PK population will be a subset of the safety population and consists of all patients who have sufficient ensartinib plasma data for PK analysis. PK analysis will be specified in PK SAP as a separate document.

3 EFFICACY PARAMETERS / ENDPOINTS

The primary analysis population for efficacy is the efficacy evaluable population defined in Section 2. Analyses will be carried out for expansion cohorts (e.g., ALK TKI naïve patients, patients that received prior crizotinib only, patients that received ≥ 2 other prior ALK TKIs, patients with CNS metastases at baseline).

Response to treatment will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria (Eisenhauer et al., 2009).

For patients with CNS metastases assessed at baseline, response and progression will additionally be assessed based on modified Response Assessment in Neuro-Oncology (RANO) criteria that allows measurable target CNS lesion to be ≥ 3 mm in diameter.

3.1 Efficacy Parameters / Endpoints

The number of complete responses (CR), partial responses (PR), stable disease (SD), and progressive disease (PD) for each subgroups (e.g., ALK TKI naïve patients, patients that received prior crizotinib only, patients that received ≥ 2 different ALK TKIs, patients with CNS metastases at baseline) and overall total will be listed and summarized, as appropriate. Additionally for patients with CNS metastases, regardless of cohort, the number of CR, PR, SD, and PD will be listed and summarized. The endpoints for tumor response are:

- Proportion of patients with an objective tumor response (CR + PR)
- Duration of response (DOR)
- Proportion of patients with SD as best response
- Proportion of patients with disease control (DCR: CR+PR+SD) as best response

- Time to disease progression (TTP)
- Progression-free survival (PFS)
- CNS response rate (for patients with CNS lesions assessed at baseline)
- Time to CNS progression

The overall tumor response will be reported descriptively, and best response as a percent change from baseline for the sum of the target lesions will be presented as a waterfall plot.

Overall Tumor Response per RECIST 1.1

- **Best Overall Response**

  Best overall response (BOR) is the best tumor response recorded up until PD or the patient withdraws consent or otherwise discontinues treatment. An objective response (CR or PR) should be confirmed at least 4 weeks after the response has been noted as per the RECIST 1.1 criteria, although unconfirmed responses may also be reported.

- **Progression-free Survival**

  PFS is defined as the time in months from date of initiation of study treatment to the first date of progression or death due to any cause. The date of progression is the date of a new lesion or the date of radiological measurements of target lesions that meets criteria for progression. Suspected clinical progression should be confirmed by radiologic assessment.

  Censoring rules will include the following:

  - Patients last known to be alive and progression-free will be censored at the date of the last adequate objective disease assessment.
  - Patients with no on study disease assessments will be censored at the date of randomization unless death occurred prior to the first planned assessment (in which case the death is an event).
  - Patients with inadequate baseline disease assessment will be censored at the initiation of study treatment.
  - Patients who received alternate therapy prior to progression will be censored at the date of the last adequate objective assessment prior to receiving alternate therapy.
  - Patients with an unacceptably long interval (i.e., two or more consecutive objective disease assessments were missed) since the last adequate response assessment and who have a PFS event (death or progression) after the missing assessments and prior to a subsequent adequate objective assessment of non-progression are censored at the time of last adequate objective assessment prior to the missing assessments.
  - Patients who stop treatment discontinuation for undocumented progression, toxicity or reasons other than documented PD will be censored at last adequate disease assessment.

- **Duration of Response**

  DOR is defined as the time from first documentation of response (CR or PR) to documentation of disease progression or death due to any cause. Only patients with measurable disease who have achieved CR or PR in the best overall response will be included in the analysis of duration of response. The same censoring rules for PFS will apply to duration of response.

- **Time to Disease Progression**

  TTP is defined as the time from date of initiation of study treatment to the first observation of documented disease progression or death due to underlying cancer. The same censoring rules for PFS will apply to time to disease progression.

CNS Tumor Response

- **CNS Best Overall Response**

  CNS best overall response is the best CNS tumor response recorded up until PD or the patient withdraws consent or otherwise stops study treatment. A CNS objective response (CR or PR) need not be confirmed.

- **Time to CNS Progression**

  Time to CNS Progression is defined as the time from date of initiation of study treatment to the first observation of documented CNS progression. This includes patients with CNS metastases at baseline as well as those without CNS metastases at baseline but subsequently develop CNS metastases. The same censoring rules for PFS will apply to time to CNS progression except that only CNS disease will be considered.

4 SAFETY PARAMETERS / ENDPOINTS

For all safety analyses, unless stated otherwise, the primary analysis population will be the safety population defined in Section 2.

4.1 Primary Safety Parameters / Endpoints

The safety endpoints to be summarized are:

- Incidence of DLTs (see Section 4.3)
- Incidence of adverse events (AEs) and AEs considered to be drug-related
  - By Highest Grade
  - By Cohort/Dose
- Incidence of grade 3 and grade 4 AEs and related AEs
- Incidence of serious adverse events (SAEs) and SAEs considered to be drug-related
  - By Cohort/Dose
- Incidence of AEs and SAEs leading to treatment discontinuation
- Incidence of AEs and SAEs leading to dose reduction
- Incidence of AEs and SAEs leading to dose omitted/held

- Incidence of all and drug-related AEs and SAEs by Medical Dictionary for Regulatory Activities (MedDRA) System Body Class
- Laboratory values
- Electrocardiogram data, particularly QT interval corrected for heart rate using the Fridericia formula (QTcF) and QT interval corrected for heart rate using the Bazett formula (QTcB) values and their changes from baseline
- Vital Signs
- On study ophthalmology examinations (if any)
- Deaths and related deaths

4.2 Adverse Events

Adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03, using the 5-point severity scale:

NCI-CTCAE Grade	Severity Scale
1	Mild
2	Moderate
3	Severe
4	Life-threatening
5	Death related to the AE

In grading the adverse events, the worst grade observed is to be reported. Adverse events will be coded using MedDRA version 15.

Treatment-emergent adverse events (TEAEs) are defined as those AEs that occur, having been absent before first dose of study treatment, or have worsened in severity after the initiation of study treatment, up to either 30 days after the last dose.

4.3 Dose Limiting Toxicities

The patient population used for determination of a DLT is the safety population noted in Section 2, but only during Cycle 1, and only during the dose escalation phase. A DLT is defined in the study protocol as any one of the following beginning during Cycle 1 and assessed as related to study drug:

- Grade 4 neutropenia (absolute neutrophil count [ANC] <500/μL) for >5 days, or febrile neutropenia (ANC <1000/μL with fever >101°F [38.5°C])
- Grade 4 thrombocytopenia, or grade 3 thrombocytopenia associated with bleeding
- Grade 3 or 4 non-hematologic toxicity (excluding grade 3 rash, diarrhea, nausea, or vomiting if controlled with standard supportive care and lasting ≤48 hours)
- Treatment delay of ≥14 days due to unresolved toxicity

Note that isolated laboratory changes without associated signs or symptoms will be reviewed with the Medical Monitor, investigators, and Sponsor to determine whether they should be considered DLTs.

The MTD is the highest dose at which ≤1 of 6 patients experience a DLT during 1 cycle of therapy. If 2 or more patients in a dosing group experience a DLT, the MTD has been exceeded. At least 6 patients must be treated at the designated MTD, with no more than 1 DLT observed among the 6 patients.

4.4 Laboratory Parameters

Laboratory toxicity grading will be derived from the laboratory values using NCI-CTCAE version 4.03.

4.5 Electrocardiographic Parameters

QTcF/QTcB analysis values are defined as the average of triplicate assessments per protocol time point and do not include any unscheduled or repeat assessments.

Maximum QTcF/QTcB is defined as the largest average QTcF/QTcB at any time point post-baseline and does not include any unscheduled or repeat assessments.

5 STATISTICAL METHODS

Statistical analyses will be primarily descriptive in nature. Statistical hypothesis testing will not be performed.

No imputation of missing data is planned. Collected data will be presented in the data listings by dose cohort.

5.1 Definition of Dates / Days / Cycles

Deriving Study Day and Cycle Day

- Day 1 = Date of First Study Drug Administration
- Study Day = Study Date – Date of First Study Drug Administration + 1
  if study date is on or after date of first dosing, or
  = Study Date – Date of First Study Drug Administration
  if study date is before date of first dosing
- Cycle Day = Cycle Date – Date of Initial Study Drug Administration in cycle + 1

Assigning Treatment Cycle Number

- Cycle n begins when the patient starts the n-th cycle of study drug administration.

5.2 Descriptive Statistics

Discrete (binary, ordinal and categorical) variables will be presented as frequencies and percentages. Continuous variables will be presented with the number of non-missing values, mean/median, standard deviation, minimum and maximum values. Graphical data may also be presented where appropriate and requested by the Sponsor.

5.3 Treatment Groups Comparability

No formal statistical testing to compare the treatment cohorts will be performed on the baseline or post-treatment variables.

Patient Disposition

Study completion and discontinuation information will be listed. The following number of patients will be summarized:

- Screened
- Cohort assignment
- Treated (defined as any patients who have started receiving any part of the study treatment) in each treatment cohort
- Discontinuation from study treatment and the reasons for discontinuation

Demography and Baseline Characteristics

The following patient characteristics will be listed and summarized:

- Demographic variables/baseline characteristics, including age (18-64, 65+), race, gender, height, weight, smoking status, and performance status.
- Disease characteristic variables, including primary tumor type, histology and ALK, MET, EGFR and KRAS statuses.

In addition, medical history and physical examination information will be listed.

Prior Systemic Therapy

- Prior Therapy
  - Number of Patients
  - Number of prior systemic therapy regimens: count distribution (0, 1, 2, 3, >=4); and continuous variable summary statistics
  - Number of prior systemic therapy regimens for metastatic disease: count distribution (0, 1, 2, 3, >=4); and continuous variable summary statistics
  - BOR and duration for the most recent prior systemic therapy
  - BOR and average duration for all prior systemic therapies
  - BOR and longest duration of prior systemic therapy

- Prior Therapy for ALK-positive patients
  - Number of Patients
  - Number of prior systemic therapy regimens: count distribution (0, 1, 2, 3, >=4); and continuous variable summary statistics
  - Number of prior systemic therapy regimens for metastatic disease: count distribution (0, 1, 2, 3, >=4); and continuous variable summary statistics
  - BOR and duration for the most recent prior systemic therapy
  - BOR and average duration for all prior systemic therapies
  - Average duration for all prior ALK TKI therapies
  - BOR and duration for all prior ALK TKI therapies
  - BOR and longest duration of prior systemic therapy
  - BOR and duration of the most recent prior ALK TKI therapy
  - BOR and longest duration of prior ALK TKI therapy

Prior/Concurrent Medications and Pharmacologic Treatments

All medications will be coded using the World Health Organization (WHO) Drug Dictionary.

All prior and concomitant medication data will be listed.

Discontinuation of Study Treatments

Patients who discontinue treatment will continue to be followed for up to 30 days for adverse events.

Patient Follow-up

Patients are expected to be followed from the date of first study drug administration until their end of the study participation or death, whichever occurs first. After the end of study participation, patients will continue to be followed for up to 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these events are not likely to improve because of the underlying disease. In addition, all patients who have CTCAE grade 3 or 4 laboratory abnormalities at the time of withdrawal must be followed until the laboratory values have returned to grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve because of the underlying disease.

5.4 Efficacy Analysis

The primary analysis population for efficacy is the efficacy evaluable population (see Section 2). No formal statistical hypothesis testing will be performed.

Analysis of Response

Best overall response will be presented for overall and by subgroups (e.g., ALK TKI naïve patients, patients that received prior crizotinib only, patients that received ≥ 2 different prior ALK TKIs and patients with CNS metastasis at baseline). BOR information will be presented in the data listings.

The analysis of response rate will be repeated for patients with measurable disease.

Presentations of overall (or objective) response rate (ORR) and DCR will include corresponding 95% confidence intervals using Clopper-Pearson method.

Analysis of Time-To-Event Variables

Survival analysis methods will be used to analyze TTP, PFS, and DOR, and time to CNS progression.

The number of months to event/censoring will be calculated as:

[Date of Event or Censoring – Date of First Dose + 1] / 30.4375

Median DOR, TTP, PFS, and time to CNS progression, with corresponding 95% confidence intervals, will be generated from the Kaplan-Meier analyses.

The confidence intervals will be calculated using the Brookmeyer and Crowley method (1982).

DOR, TTP, PFS, and time to CNS progression information will be presented in the data listings.

Sensitivity efficacy analysis will be performed to examine the robustness of the primary analysis, including:

- Clinical PD assessed by investigators will be considered as PD;
- PFS events will be counted regardless of any missed or inadequate disease assessments prior to the event; PFS events will be counted regardless of any anti-cancer treatment prior to the event; PFS events will be counted if patients discontinued due to toxicity or other reasons other than documented PD; and
- Measurable target CNS lesion will be defined as $\geq$ 10 mm in diameter.

Exploratory / Tertiary Analysis

Exploratory analysis of duration of treatment between ensartinib vs most recent prior systemic therapy will be presented.

In addition for ALK-positive patients, duration of treatment between ensartinib vs duration for all prior ALK TKI therapies, average of prior ALK TKI therapies, most recent prior ALK TKI therapy, and longest duration of prior ALK TKI therapy will also be presented.

Missing Data

In general, missing data will not be imputed for any analysis, unless otherwise specified.

Besides the specified censoring rules, no further imputation for missing data will be applied to the efficacy endpoints.

Missing Dates

To calculate time since disease diagnosis, the date of diagnosis must have at least a non-missing year. A partially missing date of diagnosis will be assigned the middle of the year

(July 1), if day and month are missing and the 15th of the month if only the day is missing. If the year of diagnosis is the same as the randomization year, then January 1 will be assigned if the month is missing, and the 1st of the month will be assigned if only the day of month is missing.

For AEs with partially missing start dates, it may be necessary to impute an AE start date. For the partial date of AE start date (missing day and/or month and/or year), the following imputation rules will be applied:

- If year of the AE start date is missing, no date imputation will be made and the AE will not be considered treatment-emergent unless the investigator has deemed it to be treatment-related.
- If both day and month of the AE start date are missing, the day and month will be imputed with the day and month of the first study dose date if the year is equal to the year of first dose. Otherwise, the month and day is imputed as the first day of the year (01 Jan).
- If only day is missing, and if the year and month are equal to the first dose date, the day will be imputed as day of the first dose date. Otherwise, the day will be imputed as "01."

The same rule for AEs with partially missing dates will be applied to concomitant medications with partially missing dates.

5.5 Safety Analysis

The primary analysis population for safety is the safety population (see Section 2).

Exposure to Study Drugs

Exposure to ensartinib will be summarized by dose cohort in the following ways:

- Total number of Treatment Cycles
- Actual Dose (mg)
- Duration (days)
- Dose Intensity (mg/day)
- Relative Dose Intensity (%)
- Actual Dosing Days during Cycle 1 for dose escalation phase
    - ≥23 Days
    - <23 Days

Swimmer plots showing time on treatment will also be prepared. This may be done for selected cohorts based on population, prior treatment, and/or assigned dose.

By-patient listings will be presented for all exposure and study treatment administration, including any dose modification (reduction, interruption, omission, and/or discontinuation) with reason for the modification.

Definition of terms related to Exposure

- Case Report Form (CRF) captured
  - Assigned Dose Level (mg) = intended dose level applied to the patient according to cohort [note: Assigned Dose Level is captured on the CRF]
  - Administered Dose (mg) = dose actually taken [note: Administered Dose is captured on the CRF]

- Exposure Derivations
  - Actual Dose (mg) = sum (of Administered Doses) from cycle 1 up to and including the final treatment cycle visit
  - Planned Dose (mg) = sum (Assigned Doses) from cycle 1 up to and including the final treatment cycle visit
  - Duration (days) = last dose date – first dose date +1
  - Dose Intensity (mg/day) = Actual Dose (mg) / Duration (days)
  - Intended Dose Intensity (mg/day) = Planned Dose (mg) / Duration (days)
  - Relative Dose Intensity (%) = Dose Intensity (mg/day) / Intended Dose Intensity (mg/day)

Adverse Events

Adverse events will be coded using NCI-CTCAE version 4.03. These will be tabulated within dose cohort, perhaps by selected assigned dose levels, and total and summarized by system organ class and preferred term. Worst grade / maximum severity per patient for adverse events will be summarized by system organ class and preferred term: all adverse events and those considered to be treatment-related. The subsets of AEs leading to treatment discontinuation and AEs leading to dose reduction and doses held will be summarized by system organ class and preferred term.

TEAEs are AEs that occur, having been absent before the first dose of study treatment, or have worsened in severity after initiating the study treatment up to 30 days from the last dose for all AEs and at any time beyond 30 days for AEs, SAEs, or deaths assessed by the investigator as treatment-related.

SAE will also be presented in an analogous manner.

Death and cause of death will be listed, including the relationship to the study treatment.

Dose Limiting Toxicity Data

DLT is characterized in terms of hematological and non-hematological toxicity or treatment delays because of unresolved toxicity, according to the study protocol definition (see Section 4).

The dose limiting toxicity data for the dose escalation phase will be available in the associated patient listings noted above.

Laboratory Data

Collected hematological, clinical chemistry, coagulation, urinalysis, and testosterone laboratory data will be included in the data presentations. Repeat and unscheduled assessments will not be summarized, but will be presented in the data listings.

All laboratory data will be listed. In addition, shift tables displaying End of Treatment results compared to Baseline results, and maximum on-treatment results compared to Baseline results, based on low, normal, or high values, using the Journal of the American Medical Association (JAMA) reference ranges, will be presented. Analogously, maximum on-treatment CTCAE grade changes compared to Baseline results will be presented. Summarization of observed results and changes over time from Baseline, and maximum change from Baseline, will be presented. Graphical displays of select laboratory parameters (hemoglobin, platelets, white blood cells, neutrophils, lymphocytes, total protein, albumin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), creatinine, and testosterone) over time will be provided.

Laboratory data will be further analyzed for evidence of potential drug-induced liver injury. Summary statistics will be tabulated for patients who exhibit each of the following post-Baseline laboratory results:

- AST/SGOT, ALT/SGPT, and (AST/SGOT or ALT/SGPT):
  3x upper limit of normal (ULN) to <5x ULN
  5x ULN to <10x ULN
  10x ULN to <20x ULN
  >= 20x ULN

- Total Bilirubin:
  >2x ULN

- Alkaline Phosphatase:
  >1.5x ULN

- (AST/SGOT or ALT/SGPT) and Total Bilirubin:
  (AST/SGOT or ALT/SGPT) > 3x ULN and Total Bilirubin > 1.5x ULN
  (AST/SGOT or ALT/SGPT) > 3x ULN and Total Bilirubin > 2x ULN

Vital Signs

Collected vital signs data will be included in the data presentations. Repeat and unscheduled assessments will not be summarized, but will be presented in the data listings.

All vital signs data will be listed. In addition, summarization of observed results and changes over time from Baseline will be presented. Graphical displays of select vital signs parameters (systolic blood pressure, diastolic blood pressure) over time will be provided.

Ophthalmology Examination

By-patient listings will be presented for ophthalmology data as defined in the study protocol. It should be noted that the ophthalmology examination is only scheduled to be obtained at baseline, unless clinically indicated during the study.

Electrocardiographic Assessments

QTcF, maximum QTcF, QTcB and maximum QTcB (including changes from baseline), based on the measurements provided by eResearch Technology, Inc. (ERT), will be summarized as both continuous and categorical measurements, where the categorical for QTcF, QTcB, change from baseline QTcF and change from baseline QTcB are as follows, respectively:

- observed: >450-480; >480-500 and >500 (msec)
- change from baseline: >30-60 and >60 (msec)

QTcF and QTcB will be summarized for Screening, Cycle 1 Day 1 and Cycle 1 Day 22 at pre-dose; 0.5, 1, 2, 4, and 8 hours post-dose (as appropriate, per the PK collection schedule), Cycle 2 Day 1 and End of Treatment by cohort. Change from baseline QTcF and QTcB will be summarized for the respective post-baseline assessments by cohort and total.

Maximum QTcF and QTcB and maximum change from baseline QTcF and QTcB will be summarized by cohort, possibly for selected dose levels, and for all patients.

All QTcF and QTcB data (including change from baseline) and interpretations (both from the investigator and ERT, including other noted clinically significant abnormalities), will be listed for each scheduled and unscheduled timepoint by cohort. Graphical displays of QTcF over time will be provided.

By-patient listings will be presented for all ERT data.

5.6 Pharmacokinetic Analysis

The pharmacokinetics analysis report will be provided by Covance Laboratories Inc.

Descriptions of any applicable PK analyses are beyond the scope of this SAP and a separate PK SAP will include the details on PK analyses.

5.7 Pharmacodynamic Analyses

If appropriate, listing and summary outputs will be provided.

5.8 Interim Analyses

Interim analyses may be performed, but formal interim analyses are not part of the protocol.

6 REFERENCES

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