STATISTICAL ANALYSIS PLAN

A PHASE 1/2, OPEN-LABEL, SAFETY, PHARMACOKINETIC AND PRELIMINARY EFFICACY STUDY OF ORAL CO-1686 IN PATIENTS WITH PREVIOUSLY TREATED MUTANT EGFR NON-SMALL CELL LUNG CANCER (NSCLC)

STUDY DRUG: CO-1686

PROTOCOL NUMBER: CO-1686-008

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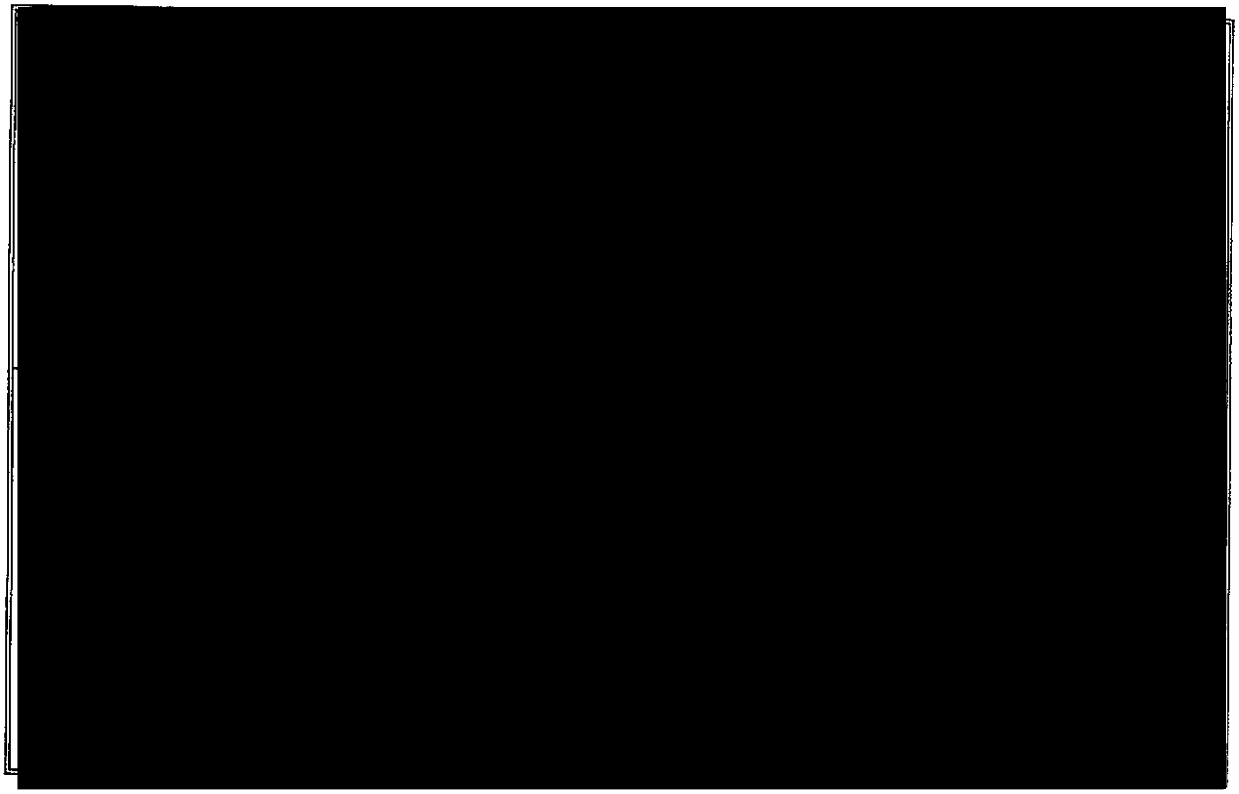
APPROVAL PAGE



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LIST OF ABBREVIATIONS

AE	Adverse event
BSA	Body surface area
CR	Complete response
CRF	Case report form
DCR	Disease control rate
DLT	Dose-limiting toxicity
HRQOL	Health-related quality of life
ICH	International Conference on Harmonization
IRR	Independent radiology review
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Drug Regulatory Activities
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression-free survival
PR	Partial response
QOL	Quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SLD	Sum of longest diameters
StDev	Standard deviation
TEAEs	Treatment-emergent adverse events
ULN	Upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for Clovis Oncology protocol CO-1686-008 "A Phase 1/2, Open-Label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-Small Cell Lung Cancer (NSCLC)". This statistical analysis plan (SAP) provides a comprehensive and detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy and safety of CO-1686 in previously treated mutant EGFR NSCLC patients.

This version of the Statistical Analysis Plan (SAP) provides details of the statistical analyses that will be presented in the NDA and MAA. The majority of the analyses in this SAP are from the original protocol and subsequent amendments.

All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.1 or higher.

2 OVERALL STUDY DESIGN AND OBJECTIVES

2.1 Study Objectives for Phase 1

2.1.1 Primary Objectives

- To evaluate the toxicity profile of escalating doses of CO-1686 and to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D)
- To characterize the PK profile of CO-1686

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To characterize the PK profile of CO-1686 after a high-fat breakfast vs in the fasted state
- To evaluate the effects of CO-1686 on the QT/QTc interval
- To evaluate tumor response (overall response rate [ORR] + duration of response) of CO-1686

2.1.3 Exploratory Objectives

- To characterize lung-cancer and treatment-related symptoms in patients at baseline and in response to CO-1686 using the Dermatology Life Quality Index, the EORTC OLQ-LC13, and the EORTC QLQ-C30
- To explore the concordance of T790M detected in tumor versus that detected in blood
- To determine if T790M is detectable in urine

2.2 Study Objectives for Phase 2

2.2.1 Primary Objectives

- To evaluate tumor response (ORR + duration of response) to CO-1686 in patients with a T790M mutation

2.2.2 Secondary Objective(s)

The secondary objectives of this study are:

- To evaluate objective response rate (ORR), duration of response, and progression-free survival (PFS) in patients treated with CO-1686
- To evaluate the toxicity and tolerability of CO-1686
- To evaluate overall survival (OS), disease control rate (DCR) and progression-free survival in patients treated with CO-1686
- To determine pharmacokinetics (PK) of CO-1686 using population PK (POPPK) methods and explore correlations between PK, exposure, response, and/or safety findings
- To characterize lung-cancer and treatment-related symptoms in patients at baseline and in response to CO-1686 using the Dermatology Life Quality Index, the EORTC QLQ-LC13, and the EORTC QLQ-C30
- To evaluate the effects of CO-1686 on the QT/QTc interval

2.2.3 Exploratory Objective(s)

The exploratory objectives of phase 2 of this study are:

- To evaluate clinical benefit of continued CO-1686 treatment following disease progression
- To explore the concordance of T790M detected in tumor versus that detected in blood

2.3 Trial Design and Study Procedures

This study will include 2 parts:

- Phase 1: Dose-escalation Period with 21-day cycles; optional Treatment Extension Period starting on Day 22
- Phase 2: Evaluation of activity and safety in patients with the T790M EGFR mutation who have:

  Cohort A

  - Progressed on EGFR directed therapy (irrespective of the number and order of previous lines of NSCLC therapy) (Dose levels of 750 mg BID, 625 mg BID and 500 mg BID)

  or

  Cohort B

  - Progression on the first single agent EGFR directed therapy received and also had no more than one previous line of chemotherapy (Dose levels of 750 mg BID, 625 mg BID and 500 mg BID)

  or

  Cohort C

- Signed consent for the study, and fulfils eligibility, but with discordance between local (T790M positive) and central (T790M negative) T790M results, or had no central test result due to inadequacy of the tissue specimen and known to be T790M positive by local test (Dose level of 625 mg BID).

2.3.1 Schedule of Assessments

The procedures and assessments to be performed during the study are outlined in the Schedule of Evaluations in the protocol.

Patients in the Phase 2 portion of this study will receive CO-1686 at 500 mg BID, 625 mg BID or 750 mg BID. Treatment will continue until disease progression, patient withdraws consent for further treatment, or by investigator decision. Treatment can continue post-progression if, in the opinion of the investigator and approved by the sponsor, the patient has indolent progression with evidence of continued clinical benefit from treatment. The study consists of screening, treatment, and follow-up periods.

Within 28 days prior to Cycle 1 Day 1, patients will be screened and evaluated for eligibility for the study. During the treatment period, patients will return to the clinic for study drug and to be evaluated for safety and dosing compliance. Each cycle consists of 21 days. Imaging will be done at the end of Cycles 2, 4, and 6 (between Days 14 and 21) and every 3 cycles after Cycle 6 (between Days 14 and 21).

During the follow-up period, patients will be followed for survival, related serious adverse events (SAEs) and next therapy for NSCLC every 2 months until lost to follow-up, withdrawal of informed consent or sponsor decision. The follow-up data may be collected by visit, telephone or chart review.

2.4 Sample Size

Total number of patients – up to approximately 715 (Phase 1 N≈110; Phase 2 N≈605)

- Phase 1: CO-1686 free base (completed) - 57 patients

  CO-1686 HBr - approximately 53 patients

- Phase 2:

  - Cohort A: approximately 40 patients for dose level 750 mg BID, up to approximately 275 patients for combined dose levels of 500 mg BID and 625 mg BID

  - Cohort B: approximately 40 patients for dose level 750 mg BID, up to approximately 150 patients for combined dose levels of 500 mg BID and 625 mg BID

  - Cohort C: up to approximately 100 patients at 625 mg BID

For the initial MAA and NDA submissions all patients enrolled in this trial at a dose of 500mg BID or 625mg BID by the 31st of December 2014 with a data cutoff date of April 29, 2015 will be used for both efficacy and safety conclusions. All other patients treated in CO-1686-008 enrolled by the 31st of December 2014 have a data cutoff date of December 31, 2014. The efficacy and safety profile for CO-1686 will be established by the combined patients treated in this study and Phase 1 study, CO-1686-008.

3 GENERAL ANALYSIS CONVENTIONS

The summary tables will be presented for all patients treated with at least one dose of CO-1686 (safety population). Particular dose groups of interest, including patients from both Phase 1 and Phase 2, may be presented in the summary tables.

Quantitative variables will be summarized using descriptive statistics and may also be summarized categorically with frequencies and percentages. For variables registered on a continuous scale, the following will be presented: N, mean, standard deviation, median, minimum and maximum. Categorical variables will be presented using frequencies and percentages and the randomized treatment groups may be compared using Fisher's exact test. The Kaplan-Meier methodology will be used to summarize time-to-event variables. If estimable, the median together with a 95% confidence interval will be presented. The number of patients with events and the number of censored patients will also be presented.

All data will be used to their maximum possible extent but without any imputations for missing data.

Unless otherwise specified, baseline is defined as the last measurement on or prior to the first day of study drug administration.

4 ANALYSIS POPULATIONS

PK-Evaluable Population—all patients who have received at least one dose of CO-1686 and have had adequate PK assessments drawn for determination of the PK profile. Adequacy will be determined on a case-by-case basis and will be assessed prior to analysis of the blood samples.

Food-Effect PK Population—all patients participating in the food-effect PK evaluation in Phase 1 of the study who received CO-1686 on both Day -7 and Day 1 (Cycle 1) complied with the fed and fasted requirements, and have sufficient PK data for a comparison to be made between the fasted and fed state.

ECG/PK Comparison-Evaluable Population—all patients in Phase 1 and Phase 2 who have received CO-1686 and have had adequate PK and ECG assessments performed for determination of the ECG effects and the relationship between PK and ECG

Safety Population—all patients who have received at least one dose of CO-1686.

DLT-Evaluable Population—all patients enrolled into Phase 1 of the study who received at least 80% of Cycle 1 scheduled doses of CO-1686 and completed Cycle 1 or who experienced a DLT in Cycle 1.

Tumor-Evaluable Population—all patients who received at least one dose of CO-1686, have measurable tumor lesions at baseline, and have at least one postbaseline disease assessment. Patients that died prior to receiving at least one postbaseline disease assessment will also be included.

5 PATIENT DISPOSITION

Patient disposition (analysis population allocation, dose group, treated, discontinued study drug, along with primary reason for discontinuation of study drug) will be summarized using frequency counts, and the corresponding percentages.

6 INCLUSION / EXCLUSION VIOLATIONS

The number of patients that violate each inclusion or exclusion criteria will be summarized with frequencies and percentages.

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All demographic and baseline characteristics will be summarized for the safety population.

7.1 Demographics

The demographic variables will be summarized with frequency tabulations that will focus on identifying the extreme values of the distributions. Descriptive statistics will also be used to summarize the quantitative variables. The demographic variables presented will include age, height, weight, gender, race, and ECOG Performance Status using the following categorizations:

- Age (years): ≤50, 51-65, 65-80, 81-95, >95;
- Height (cm): ≤75, >75-100, >100-125, >125-150, >150-175, >175;
- Weight (kg): ≤50, >50-75, >75-100, >100-125, >125-150, >150;
- Gender: Male, Female
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
- ECOG Performance Status: 0, 1, 2.

These categorizations may be adjusted for a variable if the majority of the data lies in only 2 or 3 of the categories.

7.2 Baseline Clinical Characteristics

The following variables will be summarized with descriptive statistics and may also be summarized with frequency tabulations, as indicated:

- Time since diagnosis of NSCLC (months): ≤3, >3-6, >6-12, >12-24, >24;
- Baseline laboratory parameters: graded based on CTCAE grading
- T790M status
- Method used for detection of T790M status; local tissue test, central tissue test, or plasma test
- Molecular characterization of EGFR mutations.

7.3 Medical History

Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

8 STUDY DRUG EXPOSURE AND COMPLIANCE

The following variables will be summarized:

- Number of cycles initiated (Phase 1 and 2)
- Duration of exposure (Phase 1 and 2).

The duration of exposure will be summarized with descriptive statistics and frequency counts for relevant categories. The number of cycles initiated will be investigated by summarizing the number of cycles started by each patient.

9 PRIOR AND CONCOMITANT MEDICATIONS

All concomitant treatments documented during the study treatment period will be summarized with frequency tabulations. Prior/concomitant medication coding will utilize World Health Organization (WHO) Drug version March 1, 2007 or later.

Separate data summaries of prior medications will be provided. Prior medications will be defined as those medications with both a start and a stop date that is before the day of the first dose of study drug administration. If either the start date and/or the stop date of the medication is missing so that it is unclear whether the medication was stopped prior to first dose of study drug administration then the medication will be included in the summary of the concomitant medications.

10 EFFICACY VARIABLES

10.1 Primary Efficacy Variables

The primary efficacy variables are the objective response rate (ORR) [CR+PR] and duration of response as determined by RECIST 1.1 criteria

10.2 Secondary Efficacy Variables

Secondary variables include:

- Objective response rate per independent radiology review (IRR)
- Disease control rate (DCR) per investigator and IRR
- Overall survival (OS)

10.3 Exploratory Efficacy Variables

Exploratory variables include:

- Time to treatment failure
- Concordance of the presence of T790M mutation in blood and tumor tissue samples

11 EFFICACY ANALYSIS

All efficacy evaluations will be conducted in patients that are centrally confirmed to be T790M positive using the efficacy-evaluable and safety populations, unless otherwise specified.

11.1 Primary Efficacy Analysis

The primary efficacy endpoint of ORR is defined as a best response of CR or PR as determined by the investigator. Response and/or progression are evaluated using the RECIST 1.1 criteria. The ORR will be summarized with frequencies and percentages.

The confirmed response rate will be calculated for patients with sufficient data to determine if the patient has a confirmed response or has progressive disease, otherwise patients will be classified as inevaluable for confirmed response at the time of analysis.

As a secondary endpoint, ORR will be evaluated per the IRR.

11.2 Secondary Efficacy Analyses

11.2.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent disease or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

The duration of overall response and the duration of overall CR will be summarized with Kaplan-meier methodology. Only patients with a PR and/or CR will be included in the summary.

The duration of response will be summarized for the both the investigator assessment and the independent radiology review.

11.3 Exploratory Endpoints

11.3.1 Change from Baseline in Sum of the Longest Diameters (SLD) of Target Lesions

The largest decrease from baseline in the sum of the longest diameters (SLD) of target lesions will be displayed graphically for all patients and relevant subgroups using a waterfall plot.

11.3.2 Time to Treatment Failure

The time to treatment failure will be computed as 1+ the number of days from the first dose of study drug to the last dose of study drug.

The subgroup of patients that continue receiving study drug past an event of disease progression will be summarized separately.

11.3.3 Concordance of the presence of T790M mutation in blood and tumor tissue samples

An exploratory pharmacodynamic endpoint is the detection and quantification of mutant EGFR cell-free DNA in blood collected at baseline and with every tumor assessment. The presence of the T790M mutation at baseline and subsequent time points will be presented both with frequencies and percentages. In addition, the relationship between T790M detected in tumor compared with that detected in blood, and urine where applicable, will be explored. This will involve determining the sensitivity, specificity, positive and negative predictive values with 95% confidence intervals (CIs) of blood with respect to tumor.

11.3.4 Detection of T790M in Urine Samples

The frequency and percentage of Phase 1 patients with T790M present in urine samples will be presented for the subgroup of patients that provide samples.

11.3.5 Metabolite Profiling

The association between the key efficacy and safety parameters and the CO-1686 metabolite profile will be evaluated in the subset of patients with available metabolite pharmacokinetic data.

The metabolite PK parameters will be summarized for patients with and without an objective response of CR/PR. Similarly, the metabolite PK parameters will be summarized for patients with and without key adverse events, e.g., hyperglycemia and QTc prolongation.

11.3.6 Duration of Treatment in Patients with a Response

The duration of treatment in patients with at least one investigator assessment of CR or PR is defined as 1+ the number of days from the first dose of study drug to the last dose of study drug.

The duration of response will be summarized with Kaplan-meier methodology.

12 STATISTICAL/ANALYTICAL ISSUES

12.1 Handling of Dropouts or Missing Data

All available data will be used to the greatest extent possible without any imputations for missing data.

12.2 Pooling of Centers in Multi-Center Studies

The data from all study centers will be pooled for analysis.

12.3 Multiple Comparison/Multiplicity

No adjustments for multiple comparisons will be made.

12.4 Examination of Subgroups

Subgroup analyses of the key efficacy endpoints based upon the following variables may be performed for the safety and efficacy-evaluable populations:

1. T790M status
2. EGFR activating mutation
3. Method used for detecting T790M status
4. ECOG Performance Status
5. Age
6. Race
7. Gender
8. Presence of brain metastases at baseline
9. History of glucose intolerance.

12.5 Interim Analysis and Data Monitoring

No formal interim analyses are planned.

13 PHARMACOKINETICS / PHARMACODYNAMIC ANALYSIS

Pharmacokinetic (PK) parameters will be determined using noncompartmental methods. AUC from Time 0 to the last observation will be calculated using the trapezoid rule. The k_{el} will be calculated using log-linear regression on the terminal part of the concentration time curve. The terminal half-life and the AUC from the last observation to infinity will be calculated from the estimated k_{el}. Other parameters to be determined are $AUC_{(0\text{-}t)}$, C_{trough}, C_{max}, T_{max}, V_{ss}/F, and Cl/F.

14 SAFETY ANALYSIS

The safety analyses will be performed using the safety population.

14.1 Adverse Events

Adverse events will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE whenever possible. Treatment-emergent adverse events (TEAEs) are defined as AEs with onset date on or after the date of first dose of study medication until the date of the last study medication dose plus 28 days. Adverse events will be considered treatment-emergent if all or part of the date of onset of the adverse event is missing and it cannot be determined if the adverse event meets the definition for treatment-emergent.

The number and percentage of patients who experienced TEAEs for each system organ class and preferred term will be presented. Multiple instances of the TEAE in each system organ class and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least one TEAE will also be summarized.

Separate tables will be presented as follows:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;
- Treatment-related TEAEs;
- Serious TEAEs;
- Serious treatment-related TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study medication; and
- TEAEs resulting in reduction, delay, or interruption of study medication
- Time to the first adverse event that results in a reduction, interruption or discontinuation of study drug.

The incidence of TEAEs will be summarized by relationship to study drug according to the following categories: "treatment-related," or "not treatment-related". The category of treatment-related is defined as a relationship of "Possible/Probable", "Definitely", or missing. If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once, as a relationship category of treatment related.

If a patient experiences multiple occurrences of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing toxicity grade will be presented in the summary table with a toxicity grade of "Missing." For each toxicity grade, the number and percentage of patients with at least one TEAE of the given grade will be summarized.

The time to the first adverse event that results in a dose reduction, interruption or discontinuation of study drug is defined as 1+ the number of days from the first dose of study drug to the start of the first adverse event. Patients without an event will be censored on the date of their most recent visit date.

14.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The on-treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of study drug. Laboratory values collected during the on-treatment period will be included in the summary tables.

The summary of laboratory data will include descriptive statistics (N, mean, StDev, minimum, median, and maximum) of the maximum, minimum and last value during the on-treatment period. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given.

Shift tables from baseline to the worst CTCAE grade on-treatment will also be summarized.

Graphs of the mean values over time may also be provided.

Glucose values will also be stratified into categories indicative of clinical significance. Each patient's maximum glucose value on treatment will be classified as

- >200 mg/dL
- >250 mg/dL
- >500 mg/dL.

The frequency of patients that achieve each of these levels at least 1 time or at least 2 times will be summarized.

The time to the initial use of a glucose lowering concomitant medication will be summarized with Kaplan-meier methodology. Patients that have not taken any glucose lowering medications will be censored on the last visit date.

14.3 Vital Signs

The on-treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of study drug. Vital sign measurements collected during the on-treatment period will be included in the summary tables.

The summary of vital sign data will include descriptive statistics (N, mean, StDev, minimum, median, third quartile and maximum) of the maximum, minimum and last value during the on-treatment period. Summaries using descriptive statistics (N, mean, StDev, minimum, median and maximum) of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given.

Graphs of the mean values over time may also be provided.

14.4 12-Lead Electrocardiograms

Electrocardiogram (ECG) intervals will be stratified into categories indicative of potential clinical significance. Each patient's maximum QT and QTc intervals from the pretreatment visit and treatment period visits will be classified as

- ≤450 msec,
- >450 to ≤480 mscc,
- >480 to ≤500 msec, and
- >500 msec.

For each patient's maximum change from the pretreatment ECG visit for QT and QTc, intervals will be classified into

- <30 msec,
- ≥30 to <60 msec, and
- ≥60 msec.

Patients will also be classified according to the CTCAE grade 3 criteria of at least 2 on treatment QTc values >500ms. The number and percentage of patients in each classified category will be presented.

Additional endpoints may include abnormal T waves and U waves and other ECG intervals and diagnostic parameters.

Plots of the mean QT/QTc over time may also be provided.

15 SUMMARY OF CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Due to the conditional/accelerated approval strategy, the initial MAA and NDA submission data sets will focus on the subset of patients treated at 625mg BID or 500mg BID and enrolled up to the 31st of December with data as of April 2015.

The following changes from the protocol specified analyses are contained in this SAP:

1. The patients with death before first post-baseline scan will be included in the ORR analysis with the category of 'Death before first post-baseline scan'. This means that the tumor evaluable population was changed to an efficacy analysis population including those with death before first scan
2. Clarified how ongoing patients are analyzed for ORR
3. Added the duration of treatment in patients with a CR or PR
4. PFS analyses are not included since the study is still ongoing
5. PRO analyses are not included since the study is still ongoing
6. Analyses of the time to adverse events that results in a dose reduction, interruption, or discontinuation of study drug are included.