STATISTICAL ANALYSIS PLAN

TIGER-2
A Phase 2, Open-Label, Multicenter, Safety and Efficacy Study of Oral CO-1686 as 2nd Line EGFR-Directed TKI in Patients with Mutant EGFR Non-Small Cell Lung Cancer (NSCLC) with the T790M Resistance Mutation

STUDY DRUG: CO-1686

PROTOCOL NUMBER: CO-1686-019

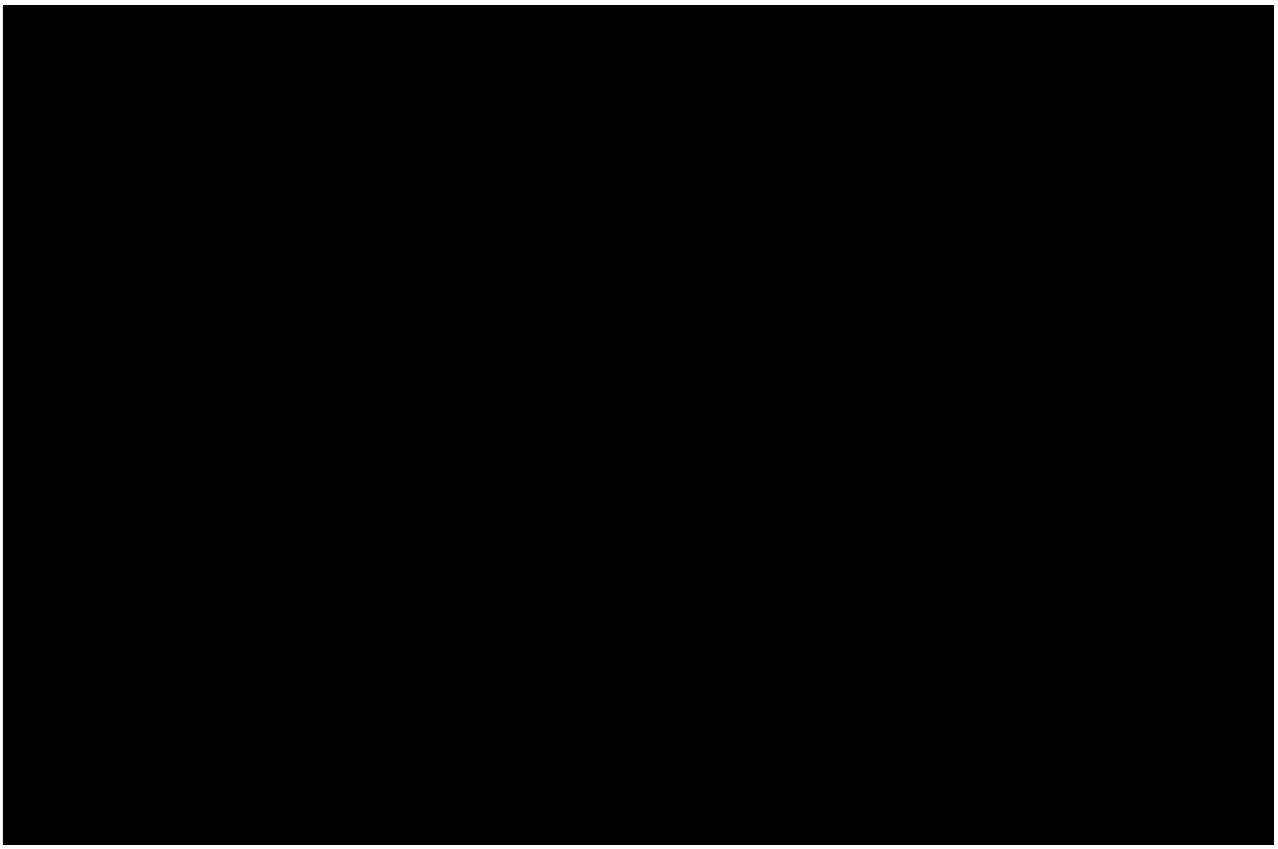
VERSION: Version 1

DATE FINAL: 12 Jun 2015

SPONSOR: Clovis Oncology

[redacted]

APPROVAL PAGE



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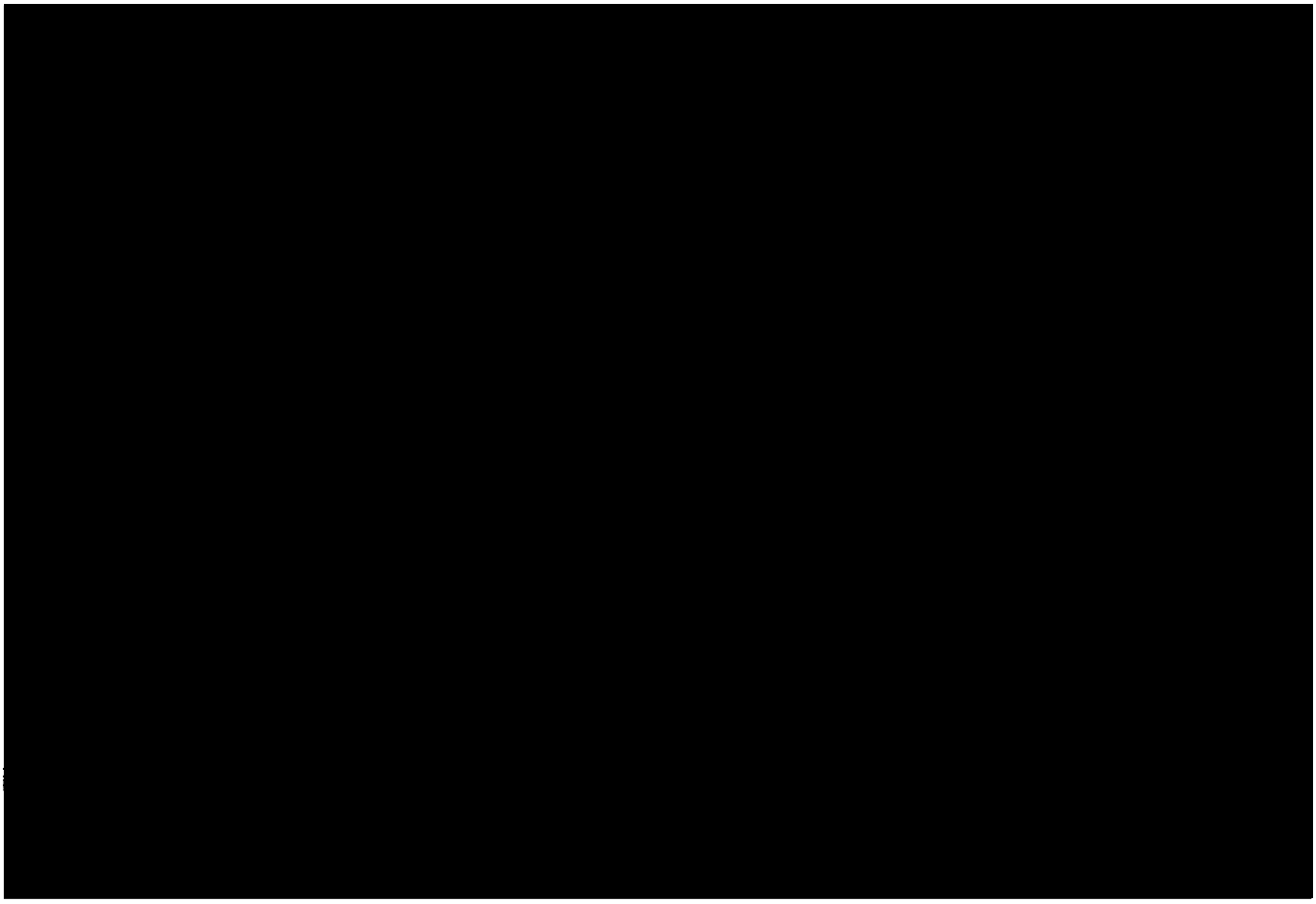

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LIST OF ABBREVIATIONS

AE	Adverse event
CR	Complete response
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLQI	Dermatology Life Quality Index
EORTQLQ-C30	European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
HRQOL	Health-related quality of life
IRR	Independent radiology review
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
PK	Pharmacokinetics
POPPK	Population PK
PR	Partial response
PRO	Patient Reported Outcome
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
WHO	World Health Organization

1 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for Clovis Oncology protocol CO-1686-019 "A Phase 2, Open-Label, Multicenter, Safety and Efficacy Study of

Oral CO-1686 as 2nd Line EGFR-Directed TKI in Patients with Mutant EGFR Non-Small Cell Lung Cancer (NSCLC) with the T790M ".

This version of the Statistical Analysis Plan (SAP) provides detail outlines of the statistical analyses that will be presented for the MAA and NDA, which were originally outlined in the original protocol dated 17th of Feb, 2014, and Amendment 1 dated 1st of May 2014, Amendment 2 dated 9th of May 2014, and Amendment 3 dated 27th of Oct 2014.

All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.3.

2 OVERALL STUDY DESIGN AND OBJECTIVES

2.1 Trial Design and Study Procedures

This is a Phase 2, single arm, open-label, multicenter study evaluating the safety and efficacy of CO-1686 administered orally twice daily to patients with previously treated mutant EGFR NSCLC whose tumor harbors the T790M resistance mutation. The central laboratory will confirm that the patient's tumor harbors the T790M mutation using biopsy material obtained from either primary or metastatic tumor tissue within 28 days of dosing with study drug and after progression on EGFR directed therapy.

CO-1686 will be administered to patients twice daily. Patients will take CO-1686 with a meal or within 30 minutes after a meal. Treatment with CO-1686 is continuous. Each 28 day period of treatment will represent one cycle, with dosing initiated on C1 D1. No dose escalation beyond the starting dose is allowed.

Patients will undergo serial assessments for anti-tumor efficacy, drug safety, and patient reported outcomes (see Section 9 of the Protocol). Sparse blood sampling for population PK analyses will be conducted in all patients treated with CO-1686. Serial blood sampling for longitudinal quantitative assessment of ctDNA will be conducted. Central laboratories will be used for hematology and chemistry, as well as for ECG interpretation.

Tumor scans will be acquired by the investigative site and evaluated locally for patient treatment decisions; however, copies of tumor scans will be sent to a independent radiological review (IRR) vendor. Protocol-specified treatment will continue until there is RECIST or clinical tumor progression or unacceptable toxicity as assessed by the investigator. Following disease progression on CO-1686 and discontinuation of protocol-specified treatment, patients who provide additional consent will undergo tumor biopsy before subsequent-line therapy is initiated. After discontinuation of protocol-specified treatment, subsequent anticancer therapy will be recorded.

All patients should return to the clinic for end-of-study assessments 28 (±7) days after the last dose of oral CO-1686 has been administered. The trial will be completed when all enrolled patients have discontinued treatment in this protocol and completed the end-of-study follow-up visit.

All patients will be followed at approximately two monthly intervals to monitor survival status and subsequent NCSLC cancer therapy until death or sponsor decision, whichever comes first.
After discontinuation of protocol-specified treatment, subsequent anticancer therapy use will be recorded.

2.2 Sample Size used

Approximately 125 patients are planned to be enrolled under the protocol and subsequent Amendments for the MAA and NDA.

For the initial MAA and NDA submissions all patients enrolled in this trial by the 31st of December 2014 with a data cutoff date of April 2015 will be used for both efficacy and safety conclusions. 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.

2.3 Study Objectives and Endpoints

2.3.1 Primary Objectives

- To evaluate the antitumor efficacy of oral single agent CO-1686 , as measured by objective response rate (ORR), when administered to patients with EGFR-mutated,T790M positive, advanced non-small cell lung cancer (NSCLC) after tumor progression on one previous EGFR–directed TKI

2.3.2 Secondary Objectives

The secondary objectives of this study are:

- To assess secondary measures of clinical efficacy (disease control rate (DCR), duration of response (DR), progression free survival (PFS), overall survival (OS) following CO-1686 treatment
- To evaluate the safety and tolerability of 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

2.3.3 Primary Endpoints

- ORR according to Response Criteria in Solid Tumors (RECIST) Version 1.1 as determined by independent radiology review (IRR)

2.3.4 Secondary Endpoints

- DR, DCR and PFS according to RECIST Version 1.1 as determined by IRR
- ORR, DR, DCR and PFS according to RECIST Version 1.1 as determined by Investigator Assessment
- OS
- Treatment emergent adverse events (AEs), laboratory abnormalities and ECG abnormalities
- Plasma PK parameters for CO-1686 based on sparse sampling

3 GENERAL ANALYSIS CONVENTIONS

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.

The Kaplan-Meier methodology will be used to summarize DR, PFS, and OS. If estimable, the 50th (median) together with a 95% Confidence Interval (CI) 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

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

Efficacy Population—all patients who received at least one dose of CO-1686, have at least one measureable tumor lesion at baseline, and have at least one post-baseline tumor assessment or patients who died before first post-baseline scan. Due to that the efficacy is both assessed by the investigator and the independent radiologist there will be two different efficacy populations:

- Investigator Efficacy-Evaluable Population Flag
- IRR Efficacy-Evaluable Population Flag

5 PATIENT DISPOSITION

The frequency and percentage of patients in each analysis population will be presented. In addition, the number of ongoing patients and the number of patients who have discontinued will be presented, together with the primary reason for discontinuation.

6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

6.1 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.

6.2 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
- Molecular characterization of EGFR mutations.

6.3 Medical History

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

7 STUDY DRUG EXPOSURE

The following variables will be summarized:

- Number of cycles initiated
- Number of days of treatment initiated

The number of days of treatment initiated will be investigated by summarizing the number of days from treatment start date to treatment end date +1 or if the subject is ongoing then we use the date of the data cutoff.

8 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 2015MAR01DDE (Enhanced).

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.

9 EFFICACY ANALYSIS

The efficacy endpoints will be evaluated using RECIST Version 1.1 and presented for the efficacy population.

9.1 Primary Efficacy Analysis

The primary efficacy endpoint of ORR is defined as a best response of CR or PR as determined by the independent radiological review. Response and/or progression are evaluated using the RECIST 1.1 criteria. The ORR will be summarized with frequencies and percentages. The ORR is the best overall response recorded from the start of the treatment until disease progression or the time of the data cutoff. The frequency and percentages of patients with a best overall response of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) will be summarized.

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.

9.2 Secondary Efficacy Analyses

9.2.1 ORR by Investigator Assessment

The ORR is the best overall response recorded from the start of the treatment until disease progression or recurrence as assessed by the investigator.

The frequency and percentages of patients with a best overall response of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) will be summarized.

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.

9.2.2 Duration of response

Duration of response (DR) for CR or PR will be calculated as 1+ the number of days from the first response (CR or PR) to documented radiographic progression. Patients without a documented event of radiographic progression will be censored on the date of their last adequate tumor assessment (i.e., radiologic assessment) or date of first response if no subsequent tumor assessments have been performed.

Duration of response will be summarized for both the independent radiology assessment and the investigator assessment.

9.2.3 Time to first response

The frequency and percentages of patients with a response (CR or PR) will be summarized by the first occurrence using the following time points; ≤ 9 weeks (Cycle 2), ≤ 17 weeks (Cycle 4), ≤ 25 weeks (Cycle 6), ≤ 33 weeks (Cycle 8), and > 33 weeks.

9.2.4 Population PK analyses

Sparse blood sampling for population PK analyses will be conducted in all patients treated with CO-1686. A specific population PK data analysis plan will be developed and will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation,

10 STATISTICAL/ANALYTICAL ISSUES

10.1 Handling of Dropouts or Missing Data

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

10.2 Pooling of Centers in Multi-Center Studies

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

10.3 Multiple Comparison/Multiplicity

No adjustments for multiple comparisons will be made.

11 SAFETY ANALYSIS

The safety analyses will be performed using the safety population.

11.1 Adverse Events

Adverse events will be classified using the Medical Dictionary version 16.1 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 (SAE);
- 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 events that results in a reduction, delay, 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, delay, 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.

11.2 Clinical Laboratory Evaluations

In this study, blood will be sent for analysis to a central laboratory for all cycles Day 1 visits, in addition to collecting the local lab results. The focus of the report will be based on these central laboratory results for all summary tables. Listings will be presented with both the central and local lab results. In addition, since glucose is a laboratory variable of interest the analyses around glucose will include both the central laboratory results and the local laboratory results.

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. Laboratory values will be presented in Standard International units. The baseline laboratory value will be defined as the last value prior to or on the day of the first dose of oral CO-1686. The on-treatment period will be defined as the day after the first dose of

oral CO-1686 to 28 days after the last dose of CO-1686. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the maximum, minimum, and last value during the treatment period by dose group and study phase. 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 by dose group and study phase. Separate listings will be produced for clinically significant laboratory abnormalities (i.e., those that meet Grade 3 or 4 criteria according to CTCAE).

The time to first Glucose value > 13.875 mmol/L will also be summarized. The time to first occurrence of a glucose value > 13.875 mmol/L will be calculated as 1+ the number of days from study drug start date to the first date of the glucose value > 13.875 mmol/L. Patients who do not have an observed glucose value > 13.875 mmol/L will be censored on the date of their last visit or data cutoff date for ongoing subjects.

11.3 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, standard deviation, minimum, median, third quartile and maximum) of the maximum, minimum and last value during the on-treatment period. Summaries using descriptive statistics (N, mean, standard deviation, 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.

11.4 12-Lead Electrocardiograms

The electocardiograms (ECGs) will be centrally read for this study. The ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. QT intervals will be corrected for heart rate (QTc) using standard correction factors of both Fridericia's (QTcF) and Bazett's (QTcB).

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 msec, >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.

Descriptive statistics may be used to summarize other ECG parameters of PR, QRS, QT, and RR interval, and the corresponding changes from pretreatment ECG visit at each time point.

12 SUMMARY OF CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Due to the accelerated approval strategy with the NDA submission, the data presented in the NDA will be a subset of the overall study with patients enrolled up to the 31st of December with a visit data cutoff of 29 April 2015. Hence, due to the ongoing nature of the data in this trial the following analyses will not be performed at the time of the NDA version but will be performed when the study is completed:

Secondary endpoints:

- Progression-Free Survival as determined by the Investigator
- Progression-Free Survival as determined by the Independent Radiology Review
- Overall survival
- Disease control rate will be summarized for both the independent radiology assessment and the investigator assessment
- To assess quality of life (QoL) by patient-reported outcomes (PRO) following CO-1686 treatment

Exploratory Objectives

- To evaluate clinical benefit of continued CO-1686 treatment following disease progression
- To evaluate concordance of mutant EGFR detection between tissue and plasma and assess CO-1686 mediated alterations in mutant EGFR levels over time using ctDNA obtained from plasma
- To explore tissue and blood-based biomarkers that may be predictive of response or primary resistance to CO-1686 and investigate mechanisms of acquired resistance in the tissue and blood of patients who experience clinical progression during treatment with CO-1686.