STATISTICAL ANALYSIS PLAN

A Phase 2, randomized, open-label, multicenter, safety and efficacy study of oral lucitanib in patients with FGF aberrant metastatic breast cancer

STUDY DRUG:	Lucitanib
PROTOCOL NUMBER:	CO-3810-025
DATE FINAL:	15 February 2017
SPONSOR:	Clovis Oncology 5500 Flatirons Pkwy Boulder, CO 80301 [redacted]

APPROVAL PAGE

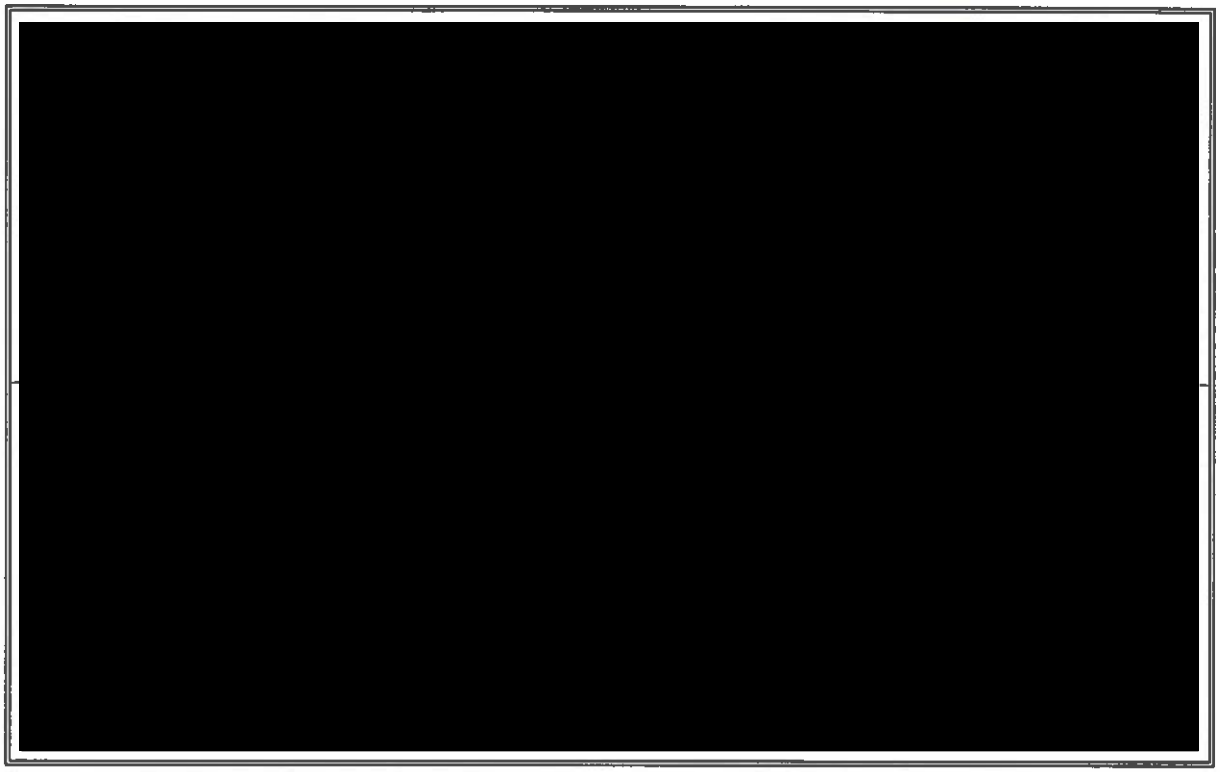


TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

ABBREVIATIONS AND SPECIALIST TERMS

ADME	absorption/distribution/metabolism/excretion
AE	adverse event
AUC_{0-t}	area under the curve from time zero to time t
BP	blood pressure
CGH	comparative genomic hybridization
CI	confidence interval
CISH	chromogenic in situ hybridization
C_{max}	maximum concentration
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CTCs	circulating tumor cells
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DCR	disease control rate
DR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
e.g.	exempli gratia (for example)
EOS	end of study
ER+	estrogen receptor positive
FACT-B	Functional Assessment of Cancer Therapy- Breast
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FISH	fluorescence in situ hybridization
HER2	human epidermal growth factor receptor 2
i.e.	id est (that is)
ICF	informed consent form
kg	kilogram
MUGA	multi gated acquisition scan
mg	milligram
NA	not applicable
NCI	National Cancer Institute
NE	not evaluable
NGS	next generation sequencing
ORR	objective response rate
OS	overall survival
qPCR	quantitative polymerase chain reaction

QT_CB	QT interval corrected using Bazette's method
QT_CF	QT interval corrected using Fridericia's method
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetics
POPPK	population pharmacokinetics
PR	partial response
PRO	patient reported outcomes
RECIST	response evaluation criteria in solid tumours
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system (company)
SD	stable disease
SI	Systeme International
$t_{1/2}$	elimination half-life
t_{max}	time to maximum concentration
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization

1 INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for Clovis Oncology protocol CO-3210-025 "A Phase 2, randomized, open-label, multicenter, safety and efficacy study of oral lucitanib in patients with FGF aberrant metastatic breast cancer". 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 lucitanib administered orally to patients with metastatic breast cancer.

The purpose of the SAP is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of study data prior to database lock for the final analysis. This SAP provides additional details concerning the statistical analyses that were originally outlined in the protocol.

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

2 OVERALL STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

2.1 Study Objectives and Endpoints

From the original protocol through amendment 5 of the protocol, there were three cohorts planned for which objectives and endpoints where defined. Cohort A was to have a starting dose of 10 mg daily of lucitanib; Cohort B was to have a starting dose of 15 mg daily of lucitanib; and Cohort C was added in amendment 2 and was to initially receive 15 mg daily of lucitanib. However, the major protocol amendment #4 discontinued the use of 15 mg as an initial starting dose thereby changing the initial starting dose for all subsequently enrolled patients in Cohort C to 10 mg of lucitanib as well as advising all investigators with patients receiving 15 mg lucitanib to dose reduce to 10 mg. Due to the significant changes to the protocol defined Cohorts and corresponding objectives and endpoints throughout the study, Table 1 below will only indicate those objectives and endpoints outlined in amendment #5 of the protocol.

Table 1. Primary, Secondary, and Exploratory Objectives and Endpoints

Primary Objectives	Primary Endpoints
To estimate the anti-tumor efficacy of oral single-agent lucitanib as measured by investigator assessed PFS, when administered to patients with *FGFR1*- or 11q-amplified breast cancer after failure of currently available standard therapies	Progression-free Survival (PFS) per RECIST Version 1.1 as determined by the investigator

Secondary Objectives	**Secondary Endpoints**
To estimate the anti-tumor efficacy of oral single-agent lucitanib as measured by investigator assessed PFS, when administered to patients with *FGFR1*- or 11q-amplified breast cancer after failure of currently available standard therapies	• ORR according to RECIST Version 1.1 • DR and DCR according to RECIST Version 1.1 • OS
To estimate patient-reported outcomes (PRO) following treatment with lucitanib	Change from baseline in PRO using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire
To evaluate the safety and tolerability of lucitanib	Treatment emergent AEs, laboratory abnormalities, physical examinations including vital signs and electrocardiogram (ECG) abnormalities
To assess the comparative pharmacokinetics (PK) of the lucitanib tablet formulation with the lucitanib capsule formulation	PK parameters including area under the concentration curve from time zero to time t (AUC_{0-t}), maximum concentration (C_{max}), time to maximum concentration (t_{max}), elimination half-life ($t_{1/2}$), volume of distribution at steady state (V_{SS}/F), and total plasma clearance (Cl/F) for lucitanib, if data allow
Exploratory Objectives	**Exploratory Endpoints**
To explore tumor tissue and blood-based biomarkers that may be predictive of response or primary resistance to treatment with lucitanib	• Concordance of tumor tissue *FGFR1* and 11q amplification assessed across different technical platforms (fluorescence in-situ hybridization [FISH], Next Generation Sequencing [NGS], comparative genomic hybridization [CGH], chromogenic in-situ hybridization [CISH], quantitative polymerase chain reaction [qPCR], or circulating tumor cells [CTCs/ctDNA]) • Exploration of different cut-off values for determining *FGFR1* and 11q amplification in tumor tissue by FISH and correlation with clinical efficacy • Ribonucleic acid (RNA) expression of *FGFR1*, FGF3/4/19, and additional FGF family members; correlation with *FGFR1* and 11q amplification status and clinical efficacy

	• Protein expression of *FGFR1* as determined by immunohistochemistry (IHC) in tumor tissue; correlation with *FGFR1* amplification status • Genomic analysis of circulating tumor DNA (ctDNA)
To explore blood-based pharmacodynamics (PD) biomarkers of lucitanib activity	• PD biomarker analysis measurement of circulating plasma biomarker levels including but not limited to FGF-2, FGF-23, sVEGFR1, VEGF-A, sCSF-1R, and CSF-1 • Pharmacogenomic analysis of variations in genes encoding proteins involved in absorption/distribution/ metabolism/excretion (ADME)

2.2 Table 2. Overall Study Design Plan

The following is the study design plan information contained in amendment 5 of the protocol. Please see the original protocol and amendments 1 through 4 to see the changes made to the design and plan throughout the course of the study.

This is a phase 2, open-label, multicenter study evaluating the efficacy and safety of lucitanib administered orally to patients with metastatic breast cancer. Patients with *FGFR1*- or 11q (FGF3, FGF4, Cyclin D1, or FGF19)-amplified metastatic breast cancer may be enrolled into one of two different cohorts (Cohort A: FGF-amplified or Cohort C: FGF non-amplified, both receiving 10 mg daily).

For patients with local *FGFR1* or 11q test results, a central laboratory will confirm the presence or absence of the *FGFR1* and/or 11q amplification. Central testing prior to enrollment for these patients is not required for study enrollment.

Patients with local *FGFR1* and 11q results for whom the central reading does not confirm the amplification status can continue the study at the discretion of the investigator if clinical benefit is observed. If there are a significant number of patients with discordant local and central testing results, additional patients may be enrolled.

For patients without a local *FGFR1* or 11q test result, tissue may be submitted for central testing under a prescreening process, and a positive central laboratory test result is required for screening and subsequent enrollment of these patients.

FGFR1-amplified and 11q-amplified patients will be enrolled* as follows:

- Cohort A (10 mg): approximately 80 patients

FGF non-amplified patients will be enrolled as follows:

- Cohort C (10 mg): up to 40 patients

The dose assigned to patients enrolled into Cohort C depends on the version of the amendment approved at the time of patient enrollment (Amendment #3: 15 mg; Amendment #4: 10 mg).

*Amendment #4 removed the 1:1 randomized treatment assignment (10 mg vs. 15 mg) and accrual of patients to Cohort B (15 mg). Up to 80 patients were expected enrolled into Cohort B under the previous versions of this protocol.
Up to 20 patients enrolled will participate in a PK sub-study to assess the comparative PK of the lucitanib tablet formulation taken at Day –7 with the lucitanib capsule formulation taken at Day 1.
Patients in Cohorts A or C will be enrolled in the PK sub study at participating sites, as follows:

- Participation in the PK sub study will be optional for patients participating in Cohort A

Participation in the PK sub study will be required for patients participating in Cohort C until enrollment of the PK sub study is completed

2.2.1 Screening Period

FGF-amplified (Cohort A) and FGF non-amplified (Cohort C) patients will undergo screening assessments within 28 days of the first dose of lucitanib.

Cohort A or C patients enrolled into the PK sub-study must undergo screening assessments within 21 days of the first dose of lucitanib, i.e., prior to Day –7.

For all patients, AEs will be assessed from the time of first dose of lucitanib through 28 days after the last protocol-specified treatment administration. Study-procedure-related AEs that occur after signing of the Informed Consent Form (ICF) and before administration of lucitanib will also be collected as AEs. AEs that occur after signing of the ICF and before lucitanib should be captured on the Medical History eCRF.

2.2.2 Treatment Period

Lucitanib will be administered once daily and swallowed with water. Patients should take lucitanib at approximately the same time each day, on an empty stomach, at least 2 hours before and 2 hours after a meal (fasting window is a total of four hours). Treatment with lucitanib is continuous but cycles will be defined as 28 days in duration. Dosing will be delayed or reduced according to protocol-specified toxicity criteria. Protocol-specified treatment will continue until there is clinical tumor progression or unacceptable toxicity.

Patients will undergo serial assessments for anti-tumor efficacy, drug safety, and PROs. Tumor scans will be acquired by the investigative site and evaluated locally for patient treatment decisions. Electronic copies of tumor scans will be uploaded to a central

radiological vendor and held for review, if deemed necessary. Sparse blood sampling for POPPK analyses will be conducted in all patients treated with lucitanib. Serial blood sampling for PD evaluation will be conducted. Local laboratories will be used for standard hematology and chemistry tests. Echocardiogram (ECHO)/multiple-gated acquisition (MUGA) will be done locally. ECGs will be stored and may be analyzed centrally. Patients will be asked to self-monitor their BP at least two times per week and instructed to contact the study site in the event of a BP reading equal or above 160 mmHg systolic and/or greater than 100 mmHg diastolic.

Patients with SD or better after their Cycle 6 scan will continue to have tumor scans every 12 ± 1 weeks until tumor progression. After discontinuation of protocol-specified treatment, subsequent specific anticancer therapy used at the investigator's discretion will be recorded. Patients will be encouraged to undergo an optional post-treatment tumor biopsy at time of progression and before subsequent-line therapy is initiated.

2.2.3 End-of-Study

All patients should return to the clinic for end-of-study assessments 28 (±7) days after the last dose of lucitanib has been administered.

The trial will be completed when all enrolled patients have discontinued treatment and completed the end-of-study follow-up visit.

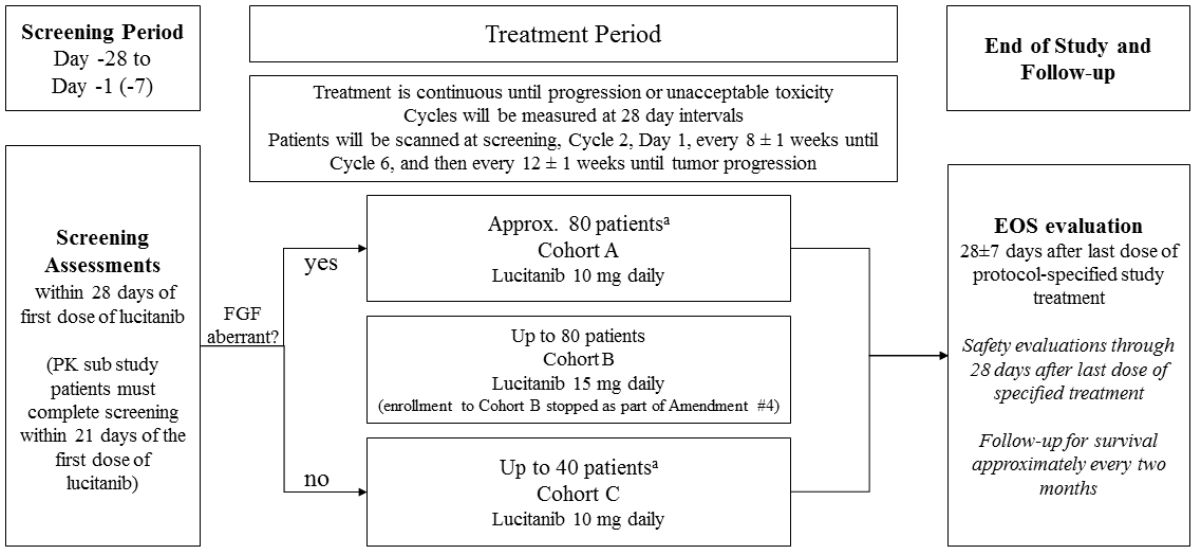
2.2.4 Long Term Follow-Up

All patients will be followed at approximately two monthly intervals to determine survival status, until death or sponsor decision to end the trial, whichever comes first.

2.2.5 Study Schema

The study schemas in Figure 1 summarizes the updated treatment design of the study.

Figure 1: Study Schema



[a] Up to 20 patients enrolled into Cohort C will participate in a PK sub study. Patients enrolled into Cohort A should also be considered for inclusion in the PK sub study at selected sites.

2.2.6 Number of Patients and Sites

FGFR1-amplified and 11q-amplified patients will be enrolled* as follows:

- Cohort A (10 mg): approximately 80 patients

FGF non- amplified patients will be enrolled into Cohort C as follows:

- Cohort C (10 mg): up to 40 patients

*1:1 randomization to Cohorts A and B was removed with Amendment #4.

Up to 20 patients will participate in a PK sub study to assess the comparative PK of the lucitanib tablet formulation with the lucitanib capsule formulation. Additional patients may be added to the PK sub-study to account for patients with incomplete PK sampling profiles at either Day –7 or Day 1, or to account for higher than expected variability in the observed PK profiles.

Enrollment into the PK sub study may only be opened at a limited number of sites based on study requirements and operational feasibility.

Patients in Cohorts A or C will be enrolled in the PK sub study at participating sites, as follows:

- Participation in the PK sub study will be optional for patients participating in Cohort A
- Participation in the PK sub study will be required for patients participating in Cohort C until enrollment of the PK sub study is completed

There will be approximately 30–40 investigative sites in the United States. All patients enrolled in Cohort C are required to participate in the PK sub study. Accrual to Cohort C will

be limited to 10-15 sites participating in the PK sub study, until enrollment in the sub study has been filled.

3 SAMPLE SIZE

Under the original protocol, approximately 160 patients were to be randomized 1:1 to the 10 mg and 15 mg daily dosing groups (Cohorts A and B).

Under protocol amendment 5, the following are the revised sample size considerations.

Up to 200 patients will be enrolled.

A total of at least 80 patients in the 10 mg arm is sufficient to reliably estimate the median PFS and 6 month PFS rate in these heavily pre-treated patients. An observed median PFS greater than 4 months or a 6-month PFS rate of at least 40% will be sufficient to consider the 10 mg dose group worthy of further study. Therefore, with at least 80 patients treated at 10 mg, the width of the 90% confidence interval for the 6 month PFS rate will be less than ±10%, so that if the observed 6 month rate is 50% then the lower limit on the confidence interval will be greater than 40%.

The treatment effect in Cohort C (biomarker negative sub-group) is not expected to be as large as in Cohorts A and B; however, the same target of 40% will be used to evaluate Cohort C. With 40 patients, the width of the 90% confidence interval for the 6 month PFS rate will be less than ±15%, so that if the observed 6 month rate is less than 25% then the upper limit on the confidence interval will be less than 40%, which is evidence that subsequent studies of 10 mg should exclude biomarker negative patients.

4 GENERAL ANALYSIS CONSIDERATIONS

Due to significant changes to the study design throughout the study, all summaries of data will be presented by initial study drug dose level (10 mg, 15 mg) regardless of a patient's enrollment into study cohorts A, B, and C. Initial dose groups will be referred to as treatment groups (10 mg, 15 mg). An overall column combining all patients from both treatment groups will be included in the data summaries, where applicable.

Quantitative variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) and/or frequency and percentages for medically relevant categories. Categorical variables will be presented using frequencies and percentages. Exact 95% confidence intervals may be presented for frequencies.

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

All statistical analyses will be conducted with the statistical analysis software (SAS®) System, Version 9.3 or higher.

5 ANALYSIS POPULATIONS

Per Amendment #5 of the protocol, the following analysis populations were defined for the study:

Efficacy Population – all patients who have received at least one dose of lucitanib and are confirmed as *FGFR1-,* 11q-amplified, or FGF non-amplified per the central laboratory.

Safety Population – all patients who have received at least one dose of lucitanib.

For the final statistical analyses to be conducted in support of the clinical study report, the **Efficacy Population** is redefined as all patients who have received at least one dose of lucitanib and have at least one post-baseline tumor scan.

6 PATIENT DISPOSITION

The frequency and percentage of patients in each analysis population will be presented. The primary reason for discontinuation of lucitanib will be summarized.

7 INCLUSION / EXCLUSION VIOLATIONS

The number of patients that violate each inclusion or exclusion criteria will be listed.

8 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics and demographic data will be summarized for the safety population.

8.1 Demographics

The demographic variables will be summarized with frequency tabulations. Descriptive statistics may also be used to summarize age, height, and weight. The categorical variables presented will include age, weight, sex, race, and ethnicity. Variable categorizations will be as follows:

- Age (years): ≤ 40, 41-60, 61-80, > 80;
- Weight (kg): ≤ 50, > 50-75, > 75-100, > 100-125, > 125-150, > 150;
- Sex: Male, Female
- Race: American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other
- Ethnicity: Hispanic or Latino, not Hispanic or Latino

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

8.2 Baseline Clinical Characteristics

Baseline characteristics variables to be summarized will include ECOG performance status, Hormone Receptor and Human Epidermal Growth Factor Receptor Status at diagnosis, location of metastatic disease, FGF status, breast cancer stage at diagnosis, number of prior anticancer therapies, number of prior adjuvant anticancer therapies, number of prior neoadjuvant anticancer therapies, and number of prior metastatic anticancer therapies, and time since diagnosis. Categorizations are provided below:

- ECOG: 0, 1, 2
- HR/HER2 Status at Diagnosis: HER 2-positive, ER-positive (and not HER 2-positive), PR-positive (and not HER 2-positive and not ER-positive), Triple Negative (note the hierarchical nature of these four categories)
- FGF status: 11q, FGFR1, FGFR1 & 11q, Negative
- Breast cancer stage: Occult, 0, I, IIA, IIB, IIIA, IIIB, IIIC, IV
- Number of prior metastatic anticancer therapies: <3, 3-6, >6
- Location of metastatic disease: bone only, visceral only, bone and visceral
- Time since diagnosis (months): ≤12, >12-24, >24;

8.3 Medical History

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

9 STUDY DRUG EXPOSURE AND COMPLIANCE

The following analyses will be provided as a summary of study drug exposure and compliance:

- Duration of exposure (days): number of days from first dose of study drug to the last dose of study drug.
- Total study drug taken (mg): Number of milligrams of study drug taken during the study.
- Mean daily dose (mg): Total study drug taken / duration of exposure

The number of days on which drug was actually taken will also be summarized.

10 PRIOR AND CONCOMITANT MEDICATIONS

All concomitant treatments documented during the study period will be summarized in frequency tabulations. Prior/concomitant medication coding will utilize the World Health Organization (WHO) Drug Dictionary

Any prior medications not considered prior anticancer medications will be listed along with concomitant medications. 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. Concomitant medications will be tabulated and summarized.

11 EFFICACY VARIABLES

The following are the efficacy variables of interest:

11.1 Primary Efficacy Variable

The primary efficacy variable is the investigator determined PFS per RECIST Version 1.1.

11.2 Secondary Efficacy Variables

Secondary variables include:

- Objective Response Rate (ORR) according to RECIST Version 1.1
- Duration of Response (DR) according to RECIST Version 1.1
- Disease Control Rate (DCR)
- Overall Survival (OS)
- Change from baseline in PRO using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire
- Treatment emergent AEs, laboratory abnormalities, physical examinations including vital signs and electrocardiogram (ECG) abnormalities
- Plasma PK parameters for lucitanib based on sparse sampling for POPPK analysis

12 EFFICACY ANALYSIS

12.1 Primary Efficacy Analysis

Kaplan-Meier methodology will be used to summarize the time to event variables including the estimated 50th (median) percentile by treatment group.

12.1.1 Progression Free Survival (PFS)

PFS is defined as 1+ the number of days from the date of first dose of study drug to disease progression or death due to any cause, whichever occurs first. Patients without a documented event of progression will be censored on the date of their last adequate tumor assessment (i.e., radiologic assessment), or the date of randomization if no tumor assessments have been performed. Progression events will be determined by the investigator.

12.1.2 Objective Response Rate (ORR)

ORR is the proportion of patients with a best response of CR or PR according to RECIST Version 1.1. The best response is recorded from the start of treatment (Day 1) until disease

progression or recurrence. The ORR will be summarized with frequencies and percentages. The number and frequency of confirmed responses (CR+PR) will also be tabulated.

12.2 Key Secondary Efficacy Analyses

12.2.1 Duration of Response (DR)

DR for CR and PR will be measured from the date that any of these best responses is first recorded until the first date that PD is objectively documented. DR will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum).

12.2.2 Disease Control Rate (DCR)

The DCR is defined as the percentage of patients with a best response rate of CR, PR, or SD for at least 12 weeks. The DCR will be summarized with frequencies and percentages.

12.2.3 Overall Survival (OS)

OS is defined as 1+ the number of days from the date of first dose of study drug to the date of death due to any cause. Patients without a documented date of death will be censored on the last date the patient was known to be alive.

12.2.4 PK Sub Study (Cohort C)

Comparative PK parameters will include AUC_{0-t}, C_{max}, T_{max}, $T_{1/2}$, V_{SS}/F, and Cl/F for lucitanib and will be determined using noncompartmental methods. AUC_{0-t} will be calculated using the trapezoid rule. The PK parameters will be compared between the tablet and the capsule formulations.

13 POPULATION PK ANALYSES

A specific POPPK data analysis plan will be developed and will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques. Results will be presented in a separate PK report to be appended to the clinical study report (CSR).

14 EXPLORATORY ANALYSES

The exploratory endpoints will be summarized descriptively.

15 PATIENT REPORTED OUTCOMES

PROs will be measured using the FACT-B questionnaire in all patients with both a baseline assessment and at least one post-baseline assessment.

The baseline PRO measurement will be defined as the last value prior to or on the day of the first dose of lucitanib. The on-treatment period will be defined as the day after the first dose of lucitanib to 28 days after the last dose of protocol-specified treatment. PRO measurements collected during the on-treatment period will be included in the summary tables.

The summary of PRO data will include descriptive statistics (N, mean, standard deviation, median, minimum, 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 by relevant cohort.

16 STATISTICAL / ANALYTICAL ISSUES

16.1 Handling of Dropouts or Missing Data

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

16.2 Interim Analysis

A data monitoring committee (DMC) consisting of two external investigator advisors and specified Clovis personnel was to meet approximately quarterly after the first patient was enrolled to review the efficacy and safety data.

A detailed description of the composition, roles and responsibilities, and functioning of the DMC is provided in the DMC Charter.

17 SAFETY ANALYSIS

The safety analyses will be performed using the Safety Population.

17.1 Adverse Events

The severity of the toxicities will be graded according to the NCI CTCAE whenever possible. Treatment-emergent AEs are defined as AEs with an onset date on or after the date of first dose of lucitanib until the date of the last dose of protocol-specified treatment plus 28 days. AEs will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

The number and percentage of patients who experienced treatment-emergent AEs for each system organ class and preferred term will be presented by treatment group. Multiple instances of the treatment-emergent AEs 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 treatment-emergent AE will also be summarized by treatment group. Separate tables will present the following by cohort:

- All treatment-emergent AEs
- Treatment-emergent AEs by CTCAE grade
- Treatment-related, treatment-emergent AEs by CTCAE grade
- Grade 3 or greater treatment-emergent AEs
- Treatment-related, treatment-emergent AEs
- Serious treatment-emergent AEs
- Serious treatment-related, treatment-emergent AEs
- Treatment-emergent AEs of Grade 3 or higher
- Treatment-related, treatment-emergent AEs of Grade 3 or higher
- Treatment-emergent AEs with an outcome of death
- Treatment-related, treatment-emergent AEs with an outcome of death
- Treatment-emergent AEs leading to discontinuation of study drug
- Treatment-related, treatment-emergent AEs leading to discontinuation of study drug
- Treatment-emergent AEs resulting in interruption of study drug
- Treatment-related, treatment-emergent AEs resulting in interruption of study drug
- Treatment-emergent AEs resulting in study drug dose reduction
- Treatment-related, treatment-emergent AEs resulting in study drug dose reduction
- Treatment-emergent AEs resulting in interruption or reduction/delay of study drug
- Treatment-related, treatment-emergent AEs resulting in interruption or reduction/delay of study drug
- Treatment-emergent AEs resulting in interruption, reduction, or discontinuation of study drug
- Treatment-related, treatment-emergent AEs resulting in interruption, reduction, or discontinuation of study drug

The incidence of treatment-emergent AEs will be summarized by relationship to lucitanib using “treatment-related” and “not treatment-related” categories. If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once in the relationship category of treatment-related.

If a patient experiences multiple occurrences of the same AE with different intensity toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing intensity 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

treatment-emergent AE of the given grade will be summarized.

Non-treatment-emergent AEs (pretreatment and post treatment) will be presented in the data listings.

17.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include variables for hematology, serum chemistry, and urinalysis. Laboratory values will be presented in Systeme International (SI) units. The baseline laboratory value will be defined as the last value prior to or on the day of the first dose of oral lucitanib. The on-treatment period will be defined as the day after the first dose of oral lucitanib to 28 days after the last dose of lucitanib. 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 treatment group. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be presented by treatment group.

17.3 Vital Signs

The baseline vital sign measurement will be defined as the last value prior to or on the day of the first dose of lucitanib. The on-treatment period will be defined as the day after the first dose of lucitanib to 28 days after the last dose of protocol-specified treatment. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

The summary of vital sign data will include descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the maximum, minimum, and last value during the on-treatment period by treatment 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 presented by treatment group. Shift tables and graphical representations of vital signs parameters may be provided.

17.4 12-Lead Electrocardiograms

Descriptive statistics will be used to summarize all ECG parameters of heart rate, PR, QRS, QT (QTcF, QTcB), and RR interval, at each nominal collection time point.

17.5 Other Safety Measurements

Shifts from baseline in body weight by CTCAE criteria will be summarized.

18 REFERENCES