STATISTICAL ANALYSIS PLAN

Calithera Biosciences, Inc.

CX-839-005

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing CB-839 in Combination with Everolimus (CBE) vs. Placebo with Everolimus (PboE) in Patients with Advanced or Metastatic Renal Cell Carcinoma (RCC)
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1 STATISTICAL ANALYSIS PLAN APPROVAL

Sponsor:	Calithera Biosciences, Inc.
Clinical Protocol Number:	CX-839-005
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3 LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AP	alkaline phosphate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BMI	body mass index
BOR	best overall response
CBE	CB-839 in combination with everolimus
ccRCC	clear cell renal cell carcinoma
CO_2	carbon dioxide
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
DRS-E	disease-related symptoms - emotional
DRS-P	disease-related symptoms - physical
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ 5D-5L	EuroQol 5D
ET	Early Termination
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
FKSI-19	Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index
FWB	function and well-being
HR	heart rate
ICH	International Conference on Harmonization
IxRS	Interactive voice/web response system
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mRCC	metastatic renal cell carcinoma
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer

Abbreviation	Definition
ORR	overall response rate
OS	overall survival
PboE	placebo in combination with everolimus
PD	pharmacodynamics
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	once every two weeks
QTcF	corrected QT interval by Fridericia's Formula
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI	Système International
TEAE	treatment-emergent adverse event
TFT	thyroid function test
TKI	tyrosine kinase inhibitor
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization

4 INTRODUCTION

The statistical analysis plan (SAP) provides details of the planned analyses and statistical methods for the study CX-839-005 (A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing CB-839 in Combination with Everolimus [CBE] vs. Placebo with Everolimus [PboE] in Patients with Advanced or Metastatic Renal Cell Carcinoma [mRCC]). The background and rationale for the study can be found in the study protocol.

5 STUDY DESIGN

Protocol CX-839-005 is a randomized, Phase 2, multicenter, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of CBE compared with PboE in patients with advanced or mRCC. Figure 1: Study Design SchemaFigure 1 illustrates the study design.

Patients eligible after completing all screening evaluations will be randomly assigned in a 2:1 ratio to receive one of the following treatments:

- CBE - The glutaminase inhibitor CB-839 [4 x 200 mg tablets (800 mg) twice daily (BID)] and the mTOR inhibitor everolimus [10 mg once daily (QD)]
- PboE - Placebo tablets [4 tablets BID] and everolimus [10 mg QD]

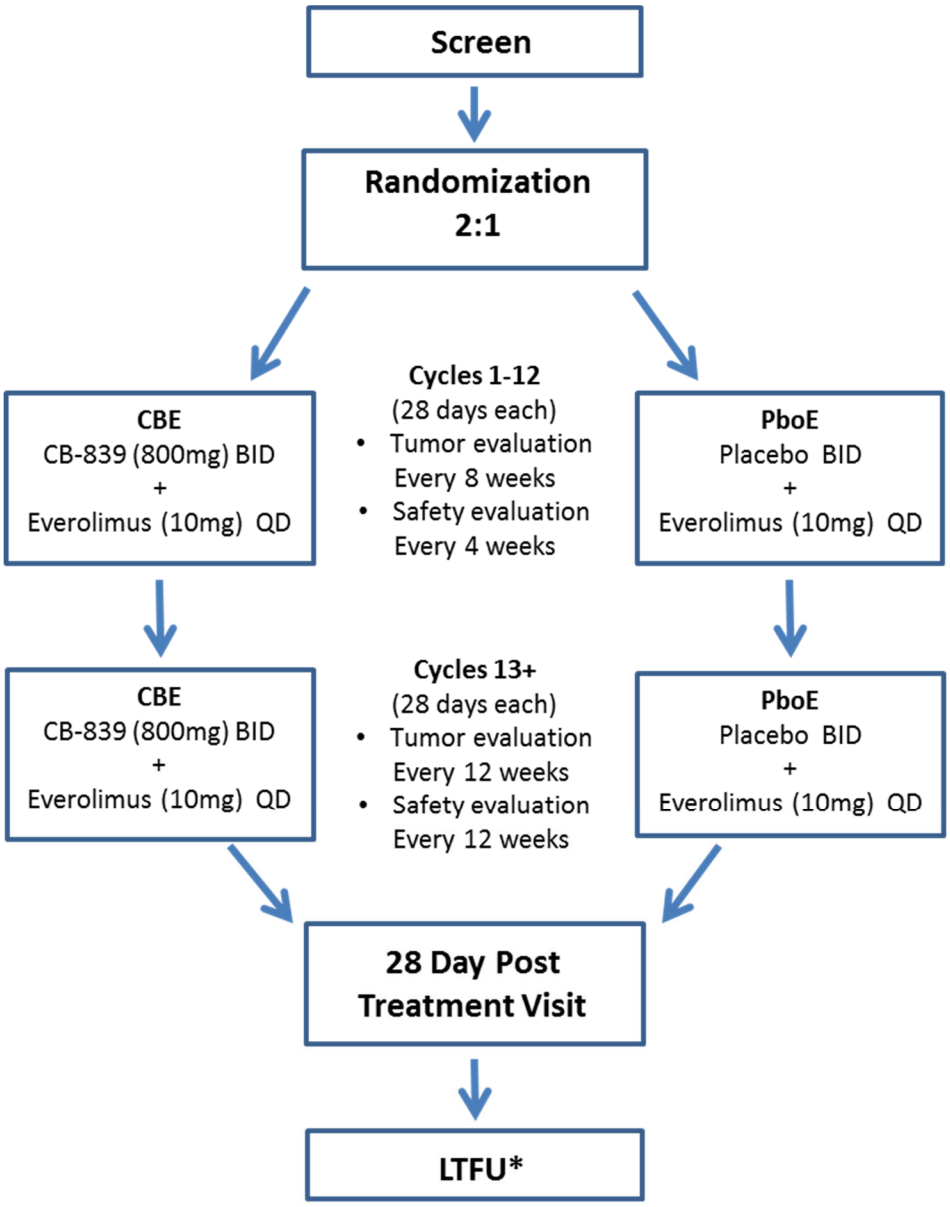
Randomization will be stratified by the following factors:

- Number of prior VEGFR-targeting TKI therapies: 1 vs. >1
- Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria for previously treated patients with mRCC: favorable vs. intermediate/poor risk

Treatment administrations are per the instructions and schedule of events outlined in the protocol. Crossover between treatment arms will not be allowed.

CB-839 or placebo will be administered BID with food. Everolimus will be administered QD at the same time every day. Patients will receive the treatment determined by randomization in 28-day cycles until disease progression or unacceptable toxicity (whichever occurs first). Patients will be followed for 28 additional days from last dose date or early discontinuation of treatment for safety follow-up. Patients who discontinue study treatment for reasons other than disease progression or death will remain in follow-up including protocol-defined imaging. Long-term follow up for survival will continue until death or withdrawal of consent to follow-up.

Figure 1: Study Design Schema



*Long-term follow-up every 3 mo for 1 year from discontinuation of treatment, every 6 mo thereafter

5.1 Protocol Synopsis

6 THE PROTOCOL SYNOPSIS IS IN APPENDIX A: PROTOCOL SYNOPSIS. FOR ADDITIONAL DETAILS, SEE THE SCHEDULE OF ASSESSMENTS IN

Appendix B: Schedule of Study Assessments.

6.1 Study Endpoints

6.1.1 Efficacy Endpoints

6.1.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is investigator-assessed PFS defined as the time from randomization to the earlier of documented disease progression or death due to any cause, whichever occurs first. Radiographic disease progression will be assessed using the RECIST 1.1 criteria per investigator.

6.1.1.2 Secondary Efficacy Endpoints

The secondary endpoint OS is defined as the time from randomization to death due to any cause.

6.1.1.3 Additional Efficacy Endpoints

The additional efficacy endpoints are:

- Overall response rate (ORR), defined as the percentage of patients with complete response (CR) or partial response (PR) according to the RECIST 1.1 criteria per investigator.
- Duration of response (DOR), defined as the time between the first documentation of a PR or a CR to the first documentation of progressive disease (PD) or death, whichever occurs first as determined by RECIST 1.1 criteria per investigator.
- Disease control rate (DCR), defined as the summed percentage of patients with best overall response (BOR) of CR, PR and stable disease (SD) according to RECIST 1.1 criteria per investigator documented at least 8 weeks following treatment initiation.
- Patient reported outcomes using the NCCN-Functional Assessment of Cancer Therapy (FACT) Kidney Symptom Index (FKSI-19) questionnaire and the EuroQoL 5D utility score (EQ-5D-5L).

6.1.2 Pharmacokinetic Endpoint

- Maximum observed serum CB-839 concentration (C_{max}) after dosing (CBE arm)
- Minimum observed serum CB-839 concentration (C_{min}) prior to dosing at selected cycles, at treatment discontinuation (CBE arm)

Additional pharmacokinetics may be summarized in a separate report and may be outside the scope of the CSR.

6.1.3 Safety Endpoints

The safety endpoints are:

- Type, incidence, seriousness, nature, severity, and drug-relatedness of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0)

- Changes in vital signs, physical findings, and clinical laboratory test results and following study treatment administration

6.2 Determination of Sample Size

A median PFS of 3.7 months is estimated for the everolimus control group based on published data for 3rd line treatment of advanced ccRCC (7). The proposed study of CBE vs. PboE will enroll approximately 63 patients with a 2:1 randomization between experimental and control arms with an accrual period of 8 months and additional follow-up of 6 months. If the control arm's median PFS is 3.7 months and the true PFS hazard ratio of experimental patients to control patients is 0.60, the study will require approximately 48 PFS events in order to reject the null hypothesis of equal PFS between the two treatment arms with a power of 0.80 and 1-sided type I error rate of 0.2 (exponential PFS distribution and log-rank test for PFS comparison).

6.3 Analysis Timing

There is no interim analyses planned for the primary endpoint of PFS in this study. The PFS primary analysis will be conducted when approximately 48 events (PD or death) have occurred in the intention-to-treat (ITT) population, which is approximately 20 months from the first patient randomized. The number of events correspond to a minimum detectable difference in HR of approximately 0.77 for one-sided alpha-level of 0.2.

7 STUDY CONDUCT

7.1 Data Monitoring

Since there is no efficacy interim analysis planned prior to the study unblinding, no data monitoring was set up for efficacy.

Safety data from the study is monitored on an ongoing basis via routine PrimeVigilance activities. In addition to real time medical review of emergent SAEs, a cross functional sponsor safety review team performs regular periodic aggregate data reviews across all CB-839 studies.

8 STATISTICAL METHODS

8.1 Analysis Populations

The analysis populations are defined as follows:

- The ITT population is defined as all randomized patients, whether or not the patients receive the assigned treatment per the interactive voice/Web response system (IxRS). Patients in the ITT set will be analyzed according to the treatment group to which they are randomized regardless of post randomization protocol deviations.

- Safety Analysis Population: Includes all patients who receive at least 1 tablet of any study-specific treatment (CB-839, placebo or everolimus) and will be analyzed according to the actual treatment received. Patients randomized to the placebo arm having taken any CB-839 will be analyzed in the CB-839 with everolimus combination arm. Similarly, patients randomized to the CB-839 with everolimus combination arm without receiving any CB-839 will be analyzed in the placebo plus everolimus arm.

8.2 Analysis of Study Conduct

Subject disposition, including enrollment, analysis populations, major protocol deviations (including major deviations of inclusion and/or exclusion criteria), reason for discontinuation from the study, and on-study status will be summarized by treatment arm and overall for all subjects combined for the ITT.

8.3 Analysis of Treatment Group Comparability

Demographic and baseline characteristics, including age, sex, race, ethnicity, baseline medical history, prior medications, disease characteristics, histology subtype, current disease status, and stratification factors will be summarized by treatment arm and overall subjects combined for the ITT and safety populations.

Baseline values are defined as the last available data obtained prior to the patient receiving the first dose of any study treatments on Cycle 1 Day 1 visits unless otherwise noted.

8.4 Efficacy Analysis

8.4.1 Primary Analysis of Progression-Free Survival

Progression free survival is defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Additional censoring applies for missing scans. The duration of primary analysis of PFS will be censored as outlined in **Table 2**. A sensitivity analysis will be

performed by handling patients having a PFS event at any time by data cutoff as an event regardless of missing scans. See **Table 3** for details for censor/event rules for PFS sensitivity analysis.

Treatment comparisons will be based on the stratified log-rank test in the ITT population. The stratification factors will be those used for randomization and will be obtained from the IxRS (MSKCC and number of prior therapies with TKI). A 1-sided log-rank $p < 0.2$ in favor of the CBE experimental treatment will be regarded as a positive result. The null and alternative hypotheses can be phrased in terms of the survival functions $S_{PFS\_CBE}(t)$ and $S_{PFS\_PboE}(t)$ in arm CBE and arm PboE, respectively:

$$H_0: S_{PFS\_CBE\,(t)} = S_{PFS\_PboE\,(t)} \text{ versus } H_1: S_{PFS\_CBE\,(t)} > S_{PFS\_PboE\,(t)}$$

Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm and construct survival curves for the visual description of the difference between the treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm (1).

The hazard ratio (HR), $\lambda_{PFS\_CBE}/\lambda_{PFS\_PboE}$, where λ_{PFS_CBE} and λ_{PFS_PboE} represent the hazard of PFS in arm CBE and arm PboE, respectively, will be estimated with a stratified Cox regression model and the same stratification variables used for the stratified log-rank test. To prevent a stratification cell having too few events, if a stratification cell has less than 10 PFS events (two arms combined), the stratification factor that contributes the least number of events for that cell will be removed. Stratification factors for the analyses will be removed until all stratification cells have at least 10 PFS events in two arms combined.

Results from an unstratified analysis will also be provided.

Table 2 Primary Analysis: The Censor/Event Rules for Progression Free Survival and Duration of Response[a]

Situation	Date of Event or Censoring	Outcome
No baseline disease assessment	Date of randomization	Censored
No post-baseline assessments and no death	Date of randomization	Censored
No progression and no death	Date of last evaluable tumor assessment	Censored
Additional cancer therapy prior to documentation of disease progression or death	Date of last evaluable tumor assessment	Censored
Documented RECIST progression per investigator or death within 2 scheduled scan intervals following previous evaluable radiological tumor assessment	First date of evaluation of overall response of PD or death is determined	Event
RECIST progression or death documented to occur after missing 2 scheduled disease assessments (including an overall response of non-evaluable) following previous evaluable radiological tumor assessment	Date of last evaluable tumor assessment with no progression prior to the first of these missed visits	Censored

PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors
[a]RECIST progression or death can occur either on study or during the survival follow up period after treatment discontinuation for symptomatic deterioration, adverse event, or other reason not related to disease and prior to the initiation of new cancer therapy.

Table 3 Sensitivity Analysis: The Censor/Event Rules for Progression Free Survival and Duration of Response[a]

Situation	Date of Event or Censoring	Outcome
No baseline disease assessment	Date of randomization	Censored
No post-baseline assessments and no death	Date of randomization	Censored
No progression and no death	Date of last evaluable tumor assessment	Censored
Additional cancer therapy prior to documentation of disease progression or death	Date of last evaluable tumor assessment	Censored
Documented RECIST progression per investigator or death within 2 scheduled scan intervals following previous evaluable radiological tumor assessment	First date of evaluation of overall response of PD or death is determined	Event
RECIST progression or death documented to occur after missing 2 scheduled disease assessments following previous evaluable radiological tumor assessment	First date of evaluation of overall response of PD or death is determined	Event
PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors [a]RECIST progression or death can occur either on study or during the survival follow up period after treatment discontinuation for symptomatic deterioration, adverse event, or other reason not related to disease and prior to the initiation of new cancer therapy.		

PFS (month) = (date of event / censor – date of randomization + 1) / 30.4375

8.4.2 Secondary Analysis

8.4.2.1 Overall Survival

Overall Survival (OS) is defined as the time from randomization to death from any cause. Patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization. Because OS may require longer follow up than the primary PFS analysis, additional OS analyses may be performed after the time of PFS primary analysis.

OS will be analyzed with the same methodologies as PFS.

8.4.3 Additional Analyses

8.4.3.1 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients who had an objective response (unconfirmed). An objective response is defined as either complete response (CR) or partial response (PR), as determined by the investigator with use of RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessments, will be considered non-responders. Confirmation is not required in this double-blind protocol, but for exploratory purposes ORR with confirmation by investigator will also be summarized. ORR must be sustained 28 days, when confirmation is reported.

The analysis population for ORR will be the ITT population. An estimate of BOR and ORR and its 95% CI will be calculated with the Clopper-Pearson method for each treatment arm. The difference in ORRs between the two treatment arms and 95% CI will be computed using the normal approximation to the binomial distribution and wald with continuity correction. The ORR will be also be compared between the two arms using stratified logistic regression. The sensitivity analysis will be computed using the stratified Cochran-Mantel-Haenszel test, stratified by the same factors used in the primary PFS and OS analyses (see Section 7.5.1).

8.4.3.2 Duration of Response

Duration of Response (DOR) is defined as the time from the first documented objective response (PR or CR) to documented PD as determined by the investigator with use of RECIST v1.1 or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of the analysis will be censored at the date of the last evaluable tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. Censoring rules for DOR will follow those in **Table 2.** The determination of DOR is based on a non-randomized subset of patients (responders only), and formal hypothesis testing will not be performed. The subset of responders are defined based on post randomization outcomes therefore the responder population is not balanced across the two treatment arms. DOR will be estimated using Kaplan Meier (KM) methodology. Comparisons between treatment arms will be made using the stratified and unstratified log-rank test for descriptive purposes only.

DOR will be reported for patients with confirmed ORR.

8.4.3.3 Disease Control Rate

Disease Control Rate (DCR) is defined as the summed percentage of patients with CR, PR and stable disease (SD) according to RECIST v1.1 per investigator criteria documented at least 8 weeks following treatment initiation.

8.4.3.4 Patient Reported Outcomes

Patient-reported outcomes (PRO) for the NCCN-FACT FKSI-19 (Version 2) will be summarized by treatment group. Summary statistics (mean, SD, median, range) of the change from baseline will be provided. Mean score for each endpoint will be displayed graphically. The analysis will be performed for patients in the PRO-evaluable population, which is defined as ITT with a non-missing baseline assessment and at least one non-missing post-baseline assessment until treatment discontinuation.

With the exception of the VAS score and index score for EQ 5D-5L questionnaire, descriptive statistics summarizing the proportions of patients who reported having "no," "slight," "moderate," "severe," or "extreme/unable" problems at each time point will be reported. The VAS score and the US specific Index score for EQ 5D-5L questionnaire will summarized and analyzed as continuous measures. Patients without post-baseline assessments will be excluded from this analysis. EQ-5D-5L data will not be reported in the CSR.

8.4.3.5 Subgroup Analyses

The consistency of PFS results in subgroups will be examined in the populations where PFS benefit has been demonstrated. To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., KPS performance status, number of previous TKI therapies, MSKCC prognostic criteria, prior anti-PD-1/PD-L1 immunotherapy, etc.), on study proton pump inhibitors, nivo/ipi and nivo use, number of prior lines, and the duration of PFS in these subgroups will be examined. Summaries of PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS, will be produced separately for each level of the categorical variables for the comparisons between treatment arms and displayed in a forest plot (**Error! Reference source not found.**).

8.5 Pharmacokinetic Analyses

PK analyses will be performed for the PK-evaluable population, defined as all CBE patients who have received at least one dose of CB-839 and at least one evaluable PK sample. CB-839 serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

8.6 Safety Analyses

Unless specified otherwise, safety analyses described in this section will be conducted for the Safety population, with patients grouped according to whether they received any CB-839 treatment.

8.6.1 Exposure of Study Medication

Study drug exposure statuses, which include treatment duration, total dose received (mg), number of cycles, dose intensity (mg/day), and relative dose intensity (%), will be summarized for each treatment arm for the Safety population.

8.6.2 Adverse Events

Verbatim description of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA, v19.1) preferred terms and system organ classes, and graded by the investigator according to NCI CTCAE v4.03. Treatment-emergent adverse events (TEAEs) will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade, and treatment arm. In addition, serious adverse events, severe adverse events (Grade ≥ 3), and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum grade. All deaths are reported as SAEs per study conduct. In order to accurately summarize the true SAE rate, all SAE summaries will not count grade 5 events for patients who died due to progressive disease.

For reporting purposes, "treatment emergent" is defined as adverse events occurring on or after the first dose of study drug is administered until the clinical cutoff date, or existing events that worsened after the first dose during the study.

All listings of adverse events will also include all adverse events.

Deaths reported during the study treatment period and the follow-up period after treatment completion and/or discontinuation will be listed by treatment arm.

8.6.3 Laboratory Data

Laboratory data will be summarized by treatment arm. Values outside the normal ranges will be summarized by treatment arm. In addition, selected laboratory data will be summarized by treatment arm and NCI CTCAE v4.3 grade.

8.6.4 Vital Signs

Changes in selected vital signs will be summarized by treatment arm and by change over time, which includes change from baseline at each visit where parameters are scheduled to be collected. Baseline is defined as the measurement obtained on Cycle 1, Day 1 before the first dose of study drug is administered.

8.7 Missing Data

See Section 7.5 for methods for handling missing data for primary and secondary endpoints.

8.8 Unblinding

As directed by Calithera, Precision and Calithera will be unblinded at the time of the PFS primary analysis when approximately 48 events (PD or death) have occurred in the ITT population, prior to final database lock.

9 REFERENCES

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10 APPENDIX A: PROTOCOL SYNOPSIS

Name of Sponsor:
Calithera Biosciences, Inc.

Name of Investigational Product:
CB-839/placebo and everolimus

Title of Study:
A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing CB-839 in Combination with Everolimus (CBE) vs. Placebo with Everolimus (PboE) in Patients with Advanced or Metastatic Renal Cell Carcinoma (RCC)

Protocol Number: CX-839-005

Study Centers:
Multicenter: Unites States and Europe

Study period (years):
Estimated 35 months including enrollment and follow-up

Phase of development:
Phase 2

Objectives:
Primary Objective
The primary objective is to compare the progression free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 of patients treated with CB-839 + everolimus (CBE) versus placebo + everolimus (PboE) for advanced or metastatic clear cell RCC (ccRCC) previously treated with:

- At least 2 lines of therapy, including at least one vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI)
- Radiographic progression of mRCC must have occurred (per investigator assessment) on or after the most recent systemic therapy and within 6 months prior to C1D1.

Secondary Objective
The secondary objective is to compare the overall survival (OS) of study patients treated with CBE vs. PboE.

Additional Objectives
The additional objectives are to:

- To compare the objective response rate (ORR), Duration of Response (DOR), and Disease Control Rate (DCR) of CBE vs. PboE
- To compare the safety and tolerability of CBE vs. PboE
- To investigate the population pharmacokinetics (PK) of CB-839

- To investigate the relationship of genetic variants and response to CBE vs. PboE
- Change in kidney-cancer related symptoms
- Change in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health

Study Design:
Protocol CX-839-005 is a randomized, Phase 2, multicenter, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of CBE compared with PboE in patients with advanced or mRCC. Figure 1: Study Design SchemaFigure 1 illustrates the study design.

Patients eligible after completing all screening evaluations will be randomly assigned in a 2:1 ratio to receive one of the following treatments:

- CBE - The glutaminase inhibitor CB-839 [4 x 200 mg tablets (800 mg) twice daily (BID)] and the mTOR inhibitor everolimus [10 mg once daily (QD)]
- PboE - Placebo tablets [4 tablets BID] and everolimus [10 mg QD]

Randomization will be stratified by the following factors:

- Number of prior VEGFR-targeting TKI therapies: 1 vs. >1
- Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria for previously treated patients with mRCC: favorable vs. intermediate/poor risk

Treatment administrations are per the instructions and schedule of events outlined in the protocol. Crossover between treatment arms will not be allowed.

11 APPENDIX B: SCHEDULE OF STUDY ASSESSMENTS

(1 cycle = 28 days)	Pre-randomization	Post-randomization				
Visit	**Screening[1]**	**Cycle 1**		**Cycle 2+**	**Cycle 13+ (Every 3 cycles)[13]**	**End of Treatment/ Follow up**
	≤21 days prior to C1D1	Day 1[2] (≤3 days post randomization)	Day 15 (± 2 days)	Day 1 (± 5 days)	Day 1 (± 7 days)	EOT: Within 28 days post treatment discontinuation
Written Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Demographics and Medical History	X					
Physical Examination[3]	X	X	X	X	X	X
Height	X					
Weight	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X
Karnofsky Performance Status	X	X		X	X	X
12-lead ECG with QTcF	X					
Urinalysis[5]	X					
HbA1c levels[5, 6]	X					
Triglyceride and total cholesterol levels[5, 7]	X			X		
Coagulation tests[5]	X					
Serum Chemistry levels	X	X	X	X	X	X
Hematology	X	X	X	X	X	X
Serum or Urine Pregnancy Test[8]	X					X
Pharmacokinetic (PK) Assay[9]			X	X		
CB-839 or Placebo Dosing		CB-839 or Placebo will be administered twice daily (BID) with food				
Everolimus Dosing		Everolimus will be administered once daily (QD) at the same time every day				
Optional Tumor Biopsy	Can be collected any time on study. Patients must sign the optional tumor biopsy consent					
Archival Tumor Collection	X					
Radiographic Evaluation of Tumor Burden (diagnostic CT with intravenous contrast or MRI)[10]	X[11]			Every 8 weeks	Every 12 weeks	X
Quality of Life Questionnaires		X		X	X	X
Adverse Events						
Concomitant Medications	Document new or worsening AEs from time of first dose through 28 days after study treatment discontinuation. AE information will be collected at study visits and may also be collected via any other forms of communication or by subject report. Certain AEs and SAEs that are ongoing 28 days after study discontinuation are to be followed until resolution or determination by the investigator that the event is stable or irreversible.					
Follow up						X[12]