Protocol C3851001

A PHASE 1 STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ESCALATING DOSES OF PF-06939999 (PRMT5 INHIBITOR) IN PARTICIPANTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER, HEAD AND NECK SQUAMOUS CELL CARCINOMA, ESOPHAGEAL CANCER, ENDOMETRIAL CANCER, CERVICAL CANCER AND BLADDER CANCER

Statistical Analysis Plan
(SAP)

Version: 1
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

This is the first version.

2. INTRODUCTION

PF-06939999 is an orally available small molecule inhibitor of protein arginine methyltransferase 5 (PRMT5) that is investigated in participants with advanced or metastatic HNSCC, NSCLC, esophageal, endometrial, cervical and bladder cancer.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3851001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

2.1.1. Primary Objectives

To assess safety and tolerability at increasing dose levels of PF-06939999 in successive cohorts of participants with selected advanced or metastatic solid tumors in order to estimate the Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD) and select the Recommended Phase 2 Dose (RP2D)/schedule.

2.1.2. Secondary Objectives

- *To characterize the single and multiple dose pharmacokinetics (PK) of PF-06939999 following oral administration.*
- *To evaluate preliminary anti-tumor activity.*

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2.2. Study Design

The study is divided into 2 parts, dose escalation (Part 1) followed by dose expansion (Part 2). The Part 2 dose expansion protocol specifics will be covered in a subsequent amendment once the maximum tolerated dose (MTD) is reached in Part 1.

Part 1 (dose escalation) is estimated to enroll approximately 40 participants. Bayesian Logistic Regression Model (BLRM) will be used to determine the MTD. Participants will receive escalating doses of PF-06939999 starting from 0.5 mg once daily (QD) which is one sixth the human equivalent dose of the highest non-severely toxic dose (HNSTD)/no-observed-adverse-effect level (NOAEL) based on body surface area scaling of the dose. Dose limiting toxicities (DLT) will be assessed during Cycle 1 (the first 28 days) to inform dose escalation and determine the MTD. Cohort size will be approximately 3 participants, with at least 1 DLT-evaluable participant per cohort in the first three cohorts and at least 2 DLT evaluable participants per cohort in the remaining cohorts.

PF-06939999 will be administered as a single agent, orally QD for the first cohort then BID in 28 day cycles for all subsequent cohorts on a continuous basis until disease progression, participant refusal or unacceptable toxicity. The estimated length of treatment is approximately 2 years. Any additional treatment with PF-06939999 beyond 2 years shall be discussed and approved by the Sponsor.

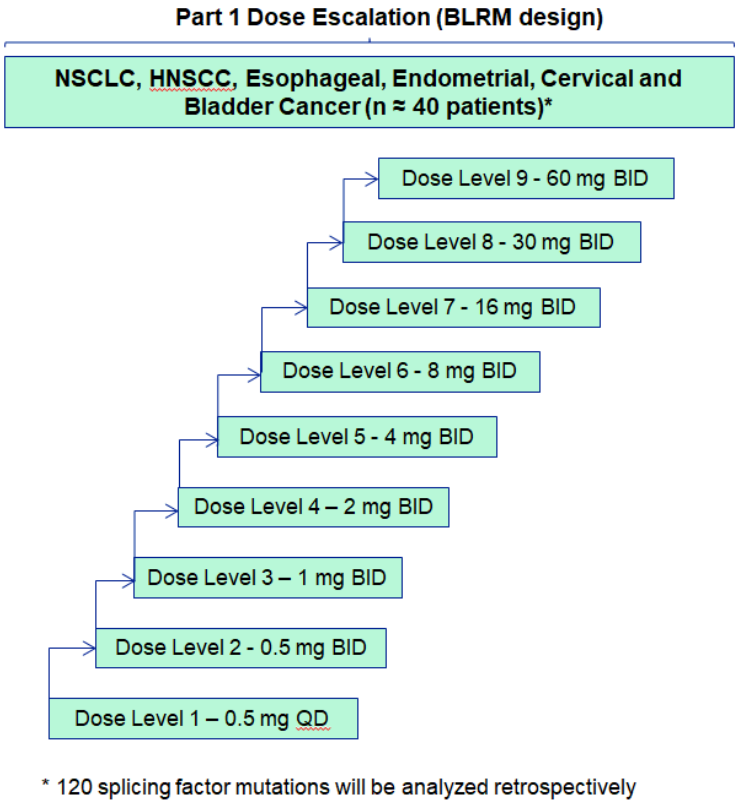
***Number of Participants**: According to stopping criteria for dose escalation, approximately 15–50 participants will be enrolled in the Part 1 dose escalation portion of the study, however the total number of participants will depend on the number of dose levels needed to determine the MTD and number of participants evaluable for DLT at each dose level. It is envisioned that overall sample size for Part 1 will be approximately 40 participants.*

***Intervention Groups and Duration**: Part 1 is estimated to enroll approximately 40 participants. On average the total duration of study participation for each participant is anticipated to be approximately 2 years, with 28 days of screening, length of treatment of approximately 22 months and a follow-up period of 28 days after the last dose. Participants will receive PF-06939999 at the dose level of their enrollment cohort QD for the first cohort then BID for all subsequent cohorts on a continuous basis. Other dosing regimen, eg, once daily or intermittent dosing, may also be considered in the study if supported by emerging clinical data.*

***Data Monitoring Committee:** No.*

Study Schema

Figure 1. Part 1 Dose Escalation (BLRM design)



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- Dose Limiting Toxicities (DLTs).

Participants who discontinue treatment before completing Cycle 1 or receive less than 75% of the planed doses for reasons other than treatment-related toxicity (eg, missed appointments, misplaced investigational product supplies, development of coexisting medical condition rendering the participant unable to swallow medication, development of rapidly progressing disease) might be replaced.

For the purpose of dose escalation, the DLT observation period will be first cycle of treatment (within 28 days of first dose) in each participant including day 29 labs. Significant adverse events considered to be related to the investigational product or treatment under investigation that occur after the DLT observation period will be reviewed in context of all safety data available. That review may result in re-evaluation of the dosing level or regimen.

Hematologic Dose-Limiting Toxicities:

Any Grade 4 hematologic AE is a DLT with the following clarifications:

1. *Grade 4 neutropenia regardless of intervention is a DLT.*

2. *Febrile neutropenia (defined as absolute neutrophil count <1000/mm3 with a single temperature of >38.5°C [101.3°F] or a temperature of ≥38°C [100.4°F] sustained for more than 1 hour) is a DLT.*

3. *Grade 3 neutropenia with infection is a DLT.*

4. *Grade 3 thrombocytopenia with ≥Grade 2 clinically significant bleeding (defined as hospitalization or urgent medical intervention for atypical bleeding sites) is a DLT.*

5. *Grade 3 anemia requiring blood transfusion is a DLT.*

Non Hematologic Dose-Limiting Toxicities:

Any Grade ≥3 non-hematologic adverse events (AEs) is a DLTs with the following clarifications:

1. *Grade 3 nausea/vomiting or diarrhea lasting ≥4 days after treatment with adequate antiemetics or other supportive care is a DLT.*

2. *Confirmed drug induced liver injury (DILI) meeting Hy's law criteria is a DLT.*

3. *For participants with Grade 2 hepatic transaminase or alkaline phosphatase levels at baseline as a result of liver metastasis or bone metastasis, a hepatic transaminase or alkaline phosphatase level >10 times the upper limit of normal will be considered a DLT.*

4. *Clinically important or persistent toxicities that are not included in the above criteria may be considered a DLT following review by Pfizer and the investigators. All DLTs need to represent a clinically significant shift from baseline.*

Any toxicity causing greater than 2 weeks of dose delay is a DLT. Note: Participants deriving clinical benefit from study treatment who experience a DLT may continue on study at a reduced dose following recovery of the AE to Grade 1 or baseline, only after discussion between the Investigator and Sponsor.

Any dose reduction due to an adverse event (per protocol) during the first cycle will be qualified as participant experiencing DLT.

The following AEs will not be adjudicated as DLTs:

- *Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.*

- *Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE version 5.0]), timing, seriousness, and relationship to study therapy. Detailed description is available in Section 3.5.1.*

- *Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.*

3.2. Secondary Endpoint(s)

- *Pharmacokinetic parameters of PF-06939999: Single Dose (SD) - Cmax, Tmax, AUClast, and as data permit, t1/2, AUCinf, CL/F, and Vz/F.*

- *Pharmacokinetic parameters of PF-06939999: Multiple Dose (MD) - Css,max, Tss,max, AUCss,τ , and as data permit, CL/F, Vss/F, and Rac (AUCss,τ,/AUCsd,τ,).*

- *Tumor response: Objective response rate (ORR) and duration of response (DoR), as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST Appendix 4) version 1.1.*

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3.4. Baseline Variables

Baseline characteristics will be collected according to Schedule of Activities as specified in the protocol. No baseline variable will be used for stratification or as covariates in the statistical analysis. Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration in the first cycle.

Laboratory baseline will be the last predose measurement of before the first dose of any component of the study treatment.

Baseline for ECG is defined as Cycle 1 Day 1 predose. ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations.

3.5. Safety Endpoints

3.5.1. Adverse Events

Severity of adverse events (AEs) will be graded according to CTCAE version 5.0.

The definitions of an AE and an SAE can be found in Appendix 3 of the protocol.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue PF-06939999 (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow up information in an expedited fashion.

3.5.2. Laboratory Data

Oral temperature, pulse rate, and blood pressure (BP) will be assessed.

Further details of the laboratory tests can be found in Appendix 2 of the protocol.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior releasing the database and classifications will be documented per standard operating procedures.

Table 1: Analysis Sets

Population	Description
Full analysis set	*The full analysis set includes all enrolled participants.*
Per protocol analysis set (Evaluable for MTD)	*The per protocol analysis set includes all enrolled participants who had at least one dose of study treatment and either experienced DLT or do not have major treatment deviations during the DLT observation period.*
Safety set	*The safety analysis set includes all enrolled participants who receive at least one dose of study treatment*
Modified Intent to Treat (mITT)	*The modified intent to treat (mITT) is the analysis population that will follow the ITT principle and include participants receiving at least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment, disease progression, or death before the first tumor assessment. The mITT population may be used for interim analysis and*

Population	Description
	conference presentations when the study is still ongoing.
PK analysis	*The PK parameter analysis population is defined as all enrolled participants treated who do not have protocol deviations influencing PK assessment, and have sufficient information to estimate at least 1 of the PK parameters of interest.* *The PK concentration population is defined as all enrolled participants who are treated and have at least 1 analyte concentration.*
Response Evaluable	*The response evaluable population will include all participants who received at least one dose of study treatment and had baseline disease assessment or measurable disease at baseline, if applicable and at least one post baseline disease assessment.*
CCI*/Biomarker*	*The* CCI */Biomarker analysis population is defined as all enrolled participants with at least 1 of the PD/Biomarkers evaluated at pre and/or post dose.*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There will be no hypothesis testing in this study.

5.2. General Methods

The data are summarized by cohort defined by the initial dose of the study drug. DLT rates at the study dose levels will be presented via mean and medians and a Bayesian credible interval based on the posterior density from the full probability model and will be used for the dose escalation decision meetings.

5.2.1. Analyses for Continuous Data

Continuous data will be summarized with the mean, median, minimum, maximum, coefficient of variation and standard deviation. Missing values will be excluded from the analysis.

5.2.2. Analyses for Categorical Data

Categorical data will be summarized by number of unique patient incidence. Missing data will be excluded from the analysis.

5.2.3. Analyses for Binary endpoints

Binary data will be summarized using number of unique patient incidence, and Wilson's confidence interval for binomial proportions will be presented if warranted.

Binary endpoints in this study include ORR, complete response (CR), partial response (PR) based on RECIST 1.1. Descriptive statistics along with the corresponding 2-sided 95% confidence intervals using an exact method will be provided for these endpoints if the sample size per cohort permits.

5.2.4. Analyses for time-to-event data

The time-to-event data will be presented for individual patient and by cohort when applicable.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

5.3.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of onset cannot be prior to day one date). In this case, the date resulting in 0 time duration will be used. Pfizer standards are also used if both month and day are missing (Jan 1 unless negative time duration). This excludes the pharmacokinetic, ECG, and pharmacodynamic analyses, which will only use the actual date collected or if date not available deem the data missing.

5.3.2. Efficacy Analysis

For the time-to-event endpoints, the missing data handling method will be censoring. Censoring rules for time-to-event endpoints are detailed in Appendix 2.

5.3.3. Pharmacokinetics

5.3.3.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

5.3.3.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

5.3.4. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.5. QTc

For the QTc analyses, no values will be imputed for missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Dose Limiting Toxicities (DLTs)

- Analysis set: Per protocol analysis set. Dose limiting toxicities (DLT) will be assessed during Cycle 1 (the first 28 days) to inform dose escalation and determine the MTD.

- Analysis methodology:

Statistical Methods:

Bayesian adaptive approach: The dose escalation in the Part 1 of the study will be guided by a Bayesian analysis of Cycle 1 dose limiting toxicity (DLT) data for PF-06939999. Toxicity is modelled using two-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose.

Assessment of participant risk: After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-06939999 will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	*[0, 0.16]*
Targeted dosing:	*[0.16, 0.33]*
Overdosing:	*[0.33, 1]*

The escalation with overdose control (EWOC) principle: Dosing decisions are guided by the escalation with overdose control principal (Rogatko 2007). A dose may only be used for newly enrolled participants if the risk of over-dosing at that dose is less than 25%.

Prior distributions: Weakly informative prior distributions based on pre-clinical/expert opinion information will be chosen for the logistic parameters.

Stopping criteria:

The maximum number of participants in dose escalation part of the trial was set to 50. The trial will be stopped when the following criteria are met:

- *At least 6 participants have been treated at the recommended MTD/RP2D.*
- *The dose $\tilde{d}$ satisfies one of the following conditions:*
  - *The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$.*
  - *A minimum of 15 participants have been treated in the trial.*

In case of change of the dosing regimen, DLT data accumulated during the dose escalation with the original regimen might be used to form a prior for further BLRM analysis. Details about derivation of this prior using Meta-Analytic-Predictive (MAP) approach can be found in Technical supplement to Appendix 9 of the protocol.

- Intercurrent events and missing data: Each cohort will have at least one DLT-evaluable patient for first 3 dose levels and and at least two DLT-evaluable patient for all other dose levels. Missing values will not be imputed.

6.1.2. Adverse Events

- Analysis set: Safety analysis set.
- Analysis methodology: characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE version 5.0]) timing, seriousness, and relationship to study therapy. Further description is given in Section 6.4.1. The treatment emergent adverse events will be defined according to Pfizer's standard definition.
- Intercurrent events and missing data: intermediate missing values will not be imputed.

6.1.3. Laboratory abnormalities

- Analysis set: safety analysis set.

- Analysis methodology: Presented as tables and characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done. Shift tables or figures may be created for select laboratory abnormalities. Results meeting the Hy's Law as defined in the protocol may also be presented as tables or listings.

- Intercurrent events and missing data: intermediate missing values will not be imputed.

6.2. Secondary Endpoint(s)

6.2.1. Pharmacokinetic Analysis

Plasma concentrations of PF-06939999 will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose, cycle, day and nominal time.

Individual participant plasma concentration-time data within a dose interval after Cycle 1 Day 1 and Cycle 1 Day 15 will be analyzed using noncompartmental methods to determine single- and multiple- dose PK parameters.

Single-dose PK parameters to be estimated will include the maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), and area under the plasma concentration versus time curve (AUC) from time 0 to the last sampling time point within the dose inveral (AUClast), and if data permit, AUC from time 0 extrapolated to infinity (AUCinf), terminal elimination half life (t1/2), apparent oral plasma clearance (CL/F), and apparent volume of distribution (Vz/F).

Multiple-dose PK parameters to be estimated will include steady state Cmax (Cmax,ss), Tmax, AUC within one dose interval (AUCtau,ss), minimum plasma concentration (Cmin,ss), steady-state CL/F (CLss/F), and if data permit, apparent volume of distribution (Vss/F), t1/2, and accumulation ratio (Rac).

The single dose and steady state (ie, multiple dose) PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose level, cycle and day.

Dose normalized AUCinf (AUCtau at steady state), AUClast and Cmax will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual participant values and the geometric means for each dose.

Pharmacokinetic/Pharmacodynamic (PK/PD) Correlation

PK and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-0639999 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

6.2.2. Tumor Response

- Overall Response Rate (ORR).
- ORR as assessed using RECIST version 1.1. ORR is defined as the proportion of patients who achieved completed response (CR) or partial response (PR) per RECIST 1.1.
- Duration of Response (DOR).
- Duration of response is defined as the time from start date (which is the date of first documentation of PR or CR) to date of first documentation of objective progression or death. DOR is only applicable to those patients with an objective response.
- Analysis set: Response Evaluable.
- Intercurrent events and missing data: Data after study drug discontinuation and rescue will be excluded; intermediate missing values will not be imputed.

6.3. Baseline and Other Summaries and Analyses

6.3.1. Baseline Summaries

Baseline characteristics such as demographics, prior medication, medical history, ECOG performance status, and primary diagnosis will be tabulated and listed. For ECOG performance status a shift table (worst post-baseline vs baseline) may be produced. The Safety Analysis Set will be used.

6.3.2. Study Conduct and Participant Disposition

An accounting of the study patients will be tabulated. The subject evaluation groups will be listed. The Full Analysis Set will be used.

Subject discontinuation from treatment and study will be tabulated and listed separately with their reason for discontinuation. The Safety Analysis Set will be used.

6.3.3. Study Treatment Exposure

The safety analysis set will be used.

Dose modifications are described in the protocol. The following will be summarized by subject for overall and each dose level:

- Number of subjects per dose level;

- Median and range of number of cycles started per subject;
- Number (%) of subjects starting a cycle (1, 2, 3…);
- Number (%) of dose interruptions (include both known and unknown dates);
- Number (%) of subjects with dose reductions;
- Number (%) of each reason (drug related AE vs AE vs. Other) dose interruptions and dose reductions;
- Time on treatment (median, range).

The following will be summarized by cycle received for overall and each dose level:

- Total number of cycles started;
- Number of cycles started per subject (median, range);
- Number of cycles before 1st reduction (median, range);
- Number of cycles before 1st interruption (median, range).

The following will be summarized for cumulative dose by dose level and cycle:

- Summary statistics (mean, median, standard deviation and range) of cumulative dose and cumulative percent of administered dose (compared to planned dose) by cycle and overall.

Listings by subject (ordered by dose level): start date and stop date of each dosing period within each cycle (including records with 0 mg), administered total daily dose for each period, any missed doses with unknown dates (Y/N), number of missed doses with unknown dates, reason for any dosing changes.

Listings by subject and each cycle (ordered by dose level): cycle length, total planned dose, administered total dose, percentage of planned dose, dose reduction (yes/no), and dose interruption (yes/no).

6.3.4. Concomitant Medications and Nondrug Treatments

Prior, concomitant, and further therapies (drug and non-drug treatments) will be coded by the World Health Organization (WHO) medical dictionary. Listings of prior, concomitant, and further therapies will be provided separately.

6.4. Safety Summaries and Analyses

All safety analyses will be performed on the safety population.

Summaries and analyses of safety parameters will include all participants in the safety analysis set.

AEs, ECGs, BP, PR, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

6.4.1. Adverse Events

AEs will graded by the investigator according to the CTCAE version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event data will be reported in tables and listings. Summaries of adverse event by mapped terms, appropriate thesaurus level, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of adverse events leading to death and premature withdrawal from study treatment. The number and percentage of participants who experienced any AE, SAE, treatment related AE, treatment related SAE, and AEs leading to treatment discontinuation, dose interruption and dose reduction will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Listings of DLTs and deaths will be provided.

6.4.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic and biomarker measurements.

6.4.3. Vital Signs

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

7. ELECTROCARDIOGRAMS

The analysis of ECG results will be based on participants in the safety analysis set with baseline and on-treatment ECG data and will follow the ICH E14 guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.

For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

QT intervals will be corrected for heart rate (HR) (QTc) using standard correction factors (ie, Fridericia's (default correction), Bazett's, and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT, HR, RR interval, PR interval (PR), QRS, QTcF (and other correction factors, eg, QTcB as appropriate), and dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor depending on HR (default QTcF) will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point.

Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction methods will be used) using maximum absolute QTc results. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %).

If more than one ECG is collected at a nominal time post dose (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. *The mean of the replicate measurements (eg, triplicate ECGs obtained) will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTc value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the clinical study report (CSR) in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTc value and the average of the predose triplicate values on Day 1.*

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Table 2: Safety QTc Assessment

Degree of Prolongation	***Mild (msec)***	***Moderate (msec)***	***Severe (msec)***
Absolute value	*>450-480*	*>480-500*	*>500*
Increase from baseline		*30-60*	*>60*

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

Categorical data analysis will follow Appendix 3.

7.1. Physical Examination

Participants will have a physical examination to include weight, vital signs, assessment of ECOG performance status and height; height will be measured at screening only.

Findings should be recorded in the source documents, and any change from baseline considered by the investigation to be clinically significant should be recorded as an adverse event in the CRF.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9. REFERENCES

10. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Tumor response: Objective response rate (ORR) and duration of response (DoR), as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST Appendix 4) version 1.1	Summary	Response Evaluable	Separately for observed data.	N/A

Appendix 2. Time to Event Data Analysis Censoring Rules

Table 3. Progression Free Survival and Duration of Response

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	First dosing date in Cycle 1	Censored
No on-study assessments	First dosing date in Cycle 1	Censored
Alive, on treatment2 and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation2	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment prior to discontinuation[2]	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation[2]	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation[2]	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments	Date of last objective tumor assessment prior to the event	Censored

1. For date of censorship, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.
2. or within 28 days of discontinuation of treatment.

Table 4. Time to Progression

Situation	Date of Progression/Censoring1	Outcome
Inadequate baseline assessment	First dosing date in Cycle 1	Censored
No on-study assessments	First dosing date in Cycle 1	Censored
Alive, on treatment2 and no Progression	Date of last objective tumor assessment	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation2	Date of first objective tumor assessment showing objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment prior to discontinuation2	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment prior to discontinuation	Censored
New anticancer treatment <28 days after discontinuation of treatment without progression	Date of last objective tumor assessment prior to new anticancer treatment	Censored
Death prior to first planned tumor assessment	Start date (C1D1)	Censored
Death without objective progression prior to treatment discontinuation2	Date of last objective tumor assessment prior to death	Censored
Progression after 2 or more missed tumor assessments	Date of last objective tumor assessment prior to the event	Censored

1. For censoring date, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.
2. or within 28 days of discontinuation of treatment.

DOSD and DOR

Censoring rules for DOSD and DOR will be the same as for PFS.

Appendix 3. Categorical Classes for ECG and Vital Signs

Categories for QTcB and QTcF

QTcB/QTcF (ms)	max. ≤450	450<max. ≤480	480<max.≤500	max. >500
QTcB/QTcF (ms) increase from baseline	max. <30	30≤max. <60	max. ≥60	

Categories for PR and QRS

PR (ms)	max ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max ≥200	
QRS (ms) increase from baseline	Baseline >100 and max. ≥25% increase	Baseline ≤100 and max. ≥50% increase

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfil these criteria are to be listed in the study report.

Appendix 4. RECIST 1.1 Tumor Assessment Criteria

Adapted from E.A. Eisenhauer, P. Therasseb, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below:

Measurable Lesions

Lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-measurable Lesions

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥ 10 but < 15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Special Considerations Regarding Specific Lesions

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary lesions:

If a measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥ 15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the

axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- **Complete Response (CR):** disappearance of all target lesions.
- **Partial Response (PR): at** least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.
- **Stable Disease (SD):** neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the CRF.

Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Response in non-target lesions is defined as follows:

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Cytology, histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg, taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For patients having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg, not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of FDG-PET is sometimes reasonable to complement a CT scan assessment of a PD (particularly for possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up

- No FDG-PET at baseline and a positive FDG-PET at follow- up: if the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Determination of Overall Response by the RECIST 1.1 Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in the following table.

Table 5. Response Evaluation Criteria in Solid Tumors by RECIST 1.1

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease,			
PD = progressive disease, and NE = inevaluable.			

Best Overall Response

The best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as the following table.

Table 6. Best Overall Response When Confirmation of CR and PR Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.