16.1.9 DOCUMENTATION OF STATISTICAL METHODS

The document(s) presented below are enclosed.

Statistical Analysis Plan	21 JUN 2021

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	INCB 54828-MA-TA-208 / NCT04003623
Study Protocol Title:	A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumors Harboring Activating FGFR Mutations or Translocations (FIGHT-208)
Date:	21 June 2021
Version:	Final Version 1.0

SIGNATURE PAGE

Author:

[redacted], PhD [redacted] Date

[redacted]

Approval:

[redacted] Date

[redacted]

DocuSigned by:
[redacted] 18-Aug-2021 | 16:26 EDT

Incyte
[redacted]

DocuSigned by:
[redacted] 18-Aug-2021 | 13:14 PDT
258042053E34462...

Date

[redacted]

Incyte
[redacted]

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Event
DCR	Disease Control Rate
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
[redacted]	[redacted]
eCRF	Electronic Case Report Form
FGFR	Fibroblast Growth Factor Receptor
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term
QD	Once Daily
[redacted]	[redacted]
QTcB	QT interval by Bazette
QTcF	QT interval by Fredericia
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria for Solid Tumor
SD	Stable Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
WHO	World Health Organization

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Incyte Protocol INCB 54828-MA-TA-208 (Amendment 1, 14 June 2019).

3.1 Study Objectives

3.1.1 Primary Objective(s)

To determine the efficacy of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancies with an activating FGFR mutation or translocation.

3.1.2 Secondary Objective(s)

- To determine other clinical efficacy measurements of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancies with an activating FGFR mutation and/or translocation.
- To determine the safety and tolerability of pemigatinib.

3.2 Overall Study Design and Plan

This is an open-label, monotherapy study of pemigatinib in participants with advanced/metastatic or surgically unresectable solid tumor malignancies harboring an activating FGFR mutation or translocation. This study consists of 2 cohorts; Cohort A will enroll participants with FGFR translocations, fusions, and rearrangements, and Cohort B will enroll participants with FGFR mutations. This study will enroll approximately 50 participants. Participants will receive pemigatinib 13.5 mg QD continuously as long as they are receiving benefit and have not met any criteria for study withdrawal. Participants with local laboratory data documenting a gain-of-function FGFR1, FGFR2, or FGFR3 mutation gene rearrangement, or other mutation identified in a CLIA-certified laboratory are eligible. Confirmatory testing through the central genomics laboratory (Tempus, Chicago, IL) will be performed for all participants; however, results from the central genomics laboratory are not required before enrollment. Centralized genomic testing results will allow participants to be assigned to 1 of the following cohorts:

- Cohort A: FGFR1-3 in-frame fusions or FGFR2 intron 17 rearrangements

- Cohort B: Known/predicted activating point mutations in FGFR1-3 (excluding kinase domain)

Note that there is no difference in the treatment regimen between the cohorts.

The sponsor may choose to cap enrollment of any one tumor type and/or FGFR alteration in order to allow representation of multiple tumor types and avoid analysis being influenced by any 1 tumor type or due to lack of response in 1 or more tumor subtypes.

A fresh biopsy at baseline (or archival tissue that was collected less than 12 months from date of screening) will be mandatory for participants whose tumors were not previously profiled at the reference lab. On-treatment and end of study biopsies are encouraged for participants with safely accessible lesions. Treatment will start on Day 1. Participants will undergo regular safety assessments during treatment as well as regular efficacy assessments. Participants will be allowed to continue administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

All data collection will be performed as indicated in the schedule of assessments (Table 1 and Table 2, see below).

Note that, due to COVID-19 pandemic, only one subject was enrolled in the study. The study is closed for lack of enrollment in 2021. Corresponding subject information will be listed for an abbreviated report. No summaries as specified in this analysis plan will be implemented.

Table 1 Schedule of Activities

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up		Survival	Notes
		Cycle 1			Cycles 2+		Safety	Disease		
	Days -35 to -1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)		(EOT + 30-35 d)	Every 9 Weeks (± 7 d)	Every 12 Weeks	
Administrative procedures										
Informed consent	X									Section Protocol section 8.1.1
Contact IRT	X	X			X	X				
Inclusion/exclusion criteria	X									
Prior treatments, procedures, surgery for disease	X									
General and disease medical history	X									
Prior/concomitant medications	X	X	X	X	X	X	X			
Dispense/administer pemigatinib		X			X*					*Assess for up-titration.
Collect study drug and review diary cards			X	X	X	X				Study drug collected only at Cycles 2+ and EOT.
Safety assessments										
Slit lamp, visual acuity, fundoscopy with digital imaging (eye)	X				X*	X				*Once every 3 cycles starting at Cycle 3.
Optical coherence tomography	X*				X*	X*				*Only if clinically indicated.
AE assessments	X	X	X	X	X	X	X			
Physical examination	X	X	X	X	X	X	X			Height at screening only.
Vital signs/body weight	X	X	X	X	X	X	X			Weight on Day 1 of each cycle.
12-lead ECG	X	X			X	X	X			
Efficacy assessments										
CT or MRI	X				X*	X**		X		*Once every 3 cycles starting at the end of Cycle 3. Participants achieving PR or CR will have a confirmatory CT or MRI ≥ 4 weeks (per RECIST v1.1). **Perform at EOT if not done within 1 month prior to EOT.
ECOG	X	X			X	X	X			
[redacted]										
Survival									X	

Table 2 Schedule of Laboratory Assessments

Procedure	Screening	Treatment					Follow-Up		Survival	Notes
		Cycle 1			Cycles 2+		Safety	Disease		
	Days -35 to -1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	EOT	(EOT + 30-35 d)	Every 9 Weeks (± 7 d)	Every 12 Weeks	
Clinical laboratory assessments										
Blood chemistries	X	X*	X	X	X**	X	X			*May be performed within 3 days of first dose (cannot be same as screening results). **Hyperphosphatemia in Cycle 1 requires Day 8 testing of serum phosphate in Cycle 2+.
Hematology	X	X*			X	X				*May be performed within 3 days of first dose (cannot be same as screening results).
Endocrine (PTH only)	X				X*	X				*Every 3 cycles on Day 1 starting with Cycle 3.
HBV/HCV testing	X									
Urinalysis	X					X				
Pregnancy testing	X*	X			X	X*				*Serum
[redacted]										
Genomic testing										
Tumor tissue sampling	X*				X**	X***				*Mandatory tissue at baseline; archival tissue allowed if less than 12 months from date of screening. **Optional on-treatment biopsies (preferably Cycle 2 between Days 7-14). ***Optional biopsy at time of progression.
Blood or Saliva	X									Tumor/normal matched sample.

Note: Screening laboratory assessments must be performed within 14 days of Cycle 1 Day 1. If performed more than 14 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study drug administration on Cycle 1 Day 1.

4 DETERMINATION OF SAMPLE SIZE

Overall, the study plans to enroll approximately 50 participants. Assuming overall response rate (ORR) is 30%, 50 participants will provide at least 80% power to test the null hypothesis of ORR ≤ 15% using a normal-approximate z test at 1-sided significance level of 0.05.

When a tumor subtype j within each cohort reaches 10 participants (or more), a statistical evaluation for ORR (p_j) within the subtype will be conducted. The tumor subtype j may be discontinued from further enrollment if the posterior probability $P(p_j < 0.15|n_j, N_j,\alpha, \beta) > 0.3$ where n_j is the number of responders in jth subtype, N_j is the number of participants with jth tumor subtype, α and β are parameters of the prior distribution and are set to be $\alpha = 1.7625$ and $\beta = 9.9875$ (Beta distribution with mean = 0.15, variance = 0.01). Tumor subtypes with at least 10 patients and $P(p_j < 0.15|n_j, N_j,\alpha, \beta) \leq 0.3$ may continue to enroll participants. Any tumor subtype j with at least 10 participants and $P(p_j > 0.30|n_j, N_j,\alpha, \beta) > 0.5$ may enroll up to 30 additional participants as an expansion cohort of the tumor subtype. These participants will not be counted towards the 50 participants planned for the study. At the end of the study, $P(p_j < 0.15|n_j, N_j,\alpha, \beta)$ and $P(p_j > 0.\ 30|n_j, N_j,\alpha, \beta)$ will be evaluated for all tumor subtypes within each cohort (see Protocol Table 14 and Table 15). A cohort of at least 25 participants will provide > 0.8 probability of observing 6 responders if underlying response rate is 0.3. The initial calculation of these posterior probabilities of each tumor subtype will begin when 10 participants have completed the assessment for primary response.

These rules based on posterior probabilities are provided as guidance for recruiting participants and discontinuing recruitment due to lack of response. The decision to continue recruiting to a tumor subtype or discontinue recruitment will be made based on the degree of responses observed (e.g., number of CRs), other relevant clinical parameters, and medical assessments.

In addition to the aforementioned process, other methods including but not limited to hierarchical Bayesian models may be used to decide if a tumor subtype in each cohort will discontinue enrollment or continue to enroll subjects.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

ORR: defined as the proportion of participants in each cohort who achieve a complete response (CR), or partial response (PR) based on RECIST v1.1 or RANO

5.2 Secondary Endpoints

Efficacy Endpoints

- Progression free survival (PFS): defined as the time from first dose until progressive

disease (PD) (per RECIST v1.1 or RANO) or death (whichever is first) in each cohort

- Duration of response (DOR): defined as the time from the date of first assessment of CR or PR until the date of the first PD (per RECIST v1.1 or RANO) or death (whichever is first) in each cohort
- Disease control rate (DCR): defined as the proportion of participants who achieved best overall response of CR, PR, or stable disease (SD) per RECIST v1.1 or RANO
- Overall survival (OS): defined as the time from first dose of study drug to death of any cause in each cohort

Safety and tolerability: Occurrences of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs) according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) v5.0, physical exam changes, vital sign changes, laboratory evaluations, and Electrocardiogram (ECG) values in each cohort

6 STATISTICAL METHODS

6.1 Analysis Population

Efficacy Evaluable

The efficacy evaluable population includes all enrolled participants who received at least 1 dose of study drug. The efficacy evaluable population will be used for the summary of participant disposition, demographics, and disease characteristics, and analyses of all efficacy data.

Safety

The safety population includes all enrolled participants who received at least 1 dose of study drug. All safety analyses will be conducted using the safety population.

Per Protocol

The per protocol population includes all efficacy evaluable population participants who are sufficiently compliant with the protocol.

6.2 General Statistical Consideration

In general, summaries will be provided by tumor type within each cohort. No multiple testing adjustment is planned, i.e., each tumor type per cohort is separately evaluated. For subject disposition, subject demographic and disease characteristics, prior and concomitant therapy, study drug exposure, and safety and tolerability endpoints, subjects from all tumor types and cohorts will be combined and summarized as well.

For continuous variables, descriptive statistics (mean, standard deviation [Std Dev], median, minimum [Min], and maximum [Max]) will be displayed; for discrete variables, number and percentage of subjects will be used.

For change-from-baseline calculations, the last measurement prior to the first dose of any study drug will be used as the baseline value.

In general, for summary statistics, the mean and median will be displayed to one decimal place greater than the original values; the standard deviation will be displayed to two decimal places greater than the original values.

All tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Version 9.4 or higher.

6.3 Subject Disposition

The following hierarchy of subject status will be summarized. The number and percentage of subjects in each category will be presented.

- Subjects who have been enrolled (i.e., signed informed consent)
- Subjects who have been treated for at least one dose of pemigatinib
- Subjects who have early discontinuation of treatment and reasons for early discontinuation
- Subjects who completed safety follow-up phase
- Subjects who are followed for vitals contacts (i.e., survival follow-up)
- Subjects end of study status.

Summaries will be provided for all subjects enrolled.

6.4 Demographic and Disease Characteristics

Demographic and disease characteristics will be summarized using descriptive statistics. Variables to be summarized are listed but not limited to as below. Summaries will be provided per each tumor type per cohort as well as all combined for Efficacy evaluable population.

- Age, gender, ethnicity, race, and geographic region
- Primary tumor type
- Time from initial diagnosis of tumor to first dose day (in months); [1 month=30.4375 days]
- TNM classification
- Current stage (Locally advanced, Metastatic)
- Time from most recent progression/recurrence to first dose day (in months)
- Prior lines of antineoplastic medication therapy
- Prior antineoplastic radiotherapy (yes/no)
- Prior antineoplastic surgery (yes/no)
- Prior loco-regional therapy (yes/no)
- Eastern Cooperative Oncology Group (ECOG) performance status

6.5 Medical History

Number and percentage of subjects with relevant and/or current medical history/conditions will be summarized by categories of conditions. For ongoing conditions, grade of condition (i.e., 1-4) will also be summarized. Medical history/current medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be provided based on the Efficacy evaluable population for each tumor type within each cohort as well as combined cross both cohorts.

6.6 Prior and Concomitant Cancer and non-Cancer Therapy

6.6.1 Prior Cancer Therapy

The number of cancer therapy regimens that subjects received prior to enrollment will be summarized by frequency counts. The best response to the most recent line of therapy will be provided.

Similarly, the prior radiotherapy will be summarized for the location of therapy, reason for treatment, and with the best response to the most recent therapy. Loco-regional therapy will be summarized by the type of procedure and the best response to the most recent therapy.

These summaries will be performed on the Efficacy evaluable population for each tumor type within each cohort as well as combined cross both cohorts.

6.6.2 Post Treatment Cancer Therapy

Post-treatment discontinuation cancer therapy will be listed.

6.6.3 Other Prior/Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications include medications that were stopped before the first dose of study drug. Concomitant medications include medications that (1) started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's final dose. All medications will be presented in subject data listings.

The number and percentage of subjects taking prior medications or concomitant medications will be summarized by anatomical therapeutic chemical (ATC) and preferred term (PT) for the Safety population. If a subject takes more than one medication in the same ATC class, the subject will be counted only once within that classification. The same subject may contribute to two or more preferred terms within the same ATC classification.

These summaries will be performed on the Safety population for each tumor type within each cohort as well as combined cross both cohorts.

6.7 Study Drug Exposure and Compliance

All subjects start pemigatinib at 13.5 mg/day and allow to titrate to 18.0 mg/day; also are allowed 2 levels down-titrate before discontinuation.

The extent of exposure (defined as Last Dose Date – First Dose Date + 1) will be summarized. In addition, the number and percentage of subjects with dose reduction will be provided by the number of levels reduced (i.e., 1 or 2 dose level reductions). The average daily dose (in mg, prescribed and actual) will be summarized. Study drug intensity (or compliance) defined as the percentage of actual daily dose out of prescribed daily dose will also be summarized.

These analyses will be based on the Safety population by tumor type within each cohort, as well as combined cohorts.

6.8 Efficacy Analyses

The efficacy analysis is based on disease response assessments. Assessment of disease response will be performed by investigators using RECIST v1.1 or RANO (for Brain tumor only). Responses for each disease evaluation assessment will be recorded in eCRFs.

Tumor response is determined by the investigator at each time point when tumor imaging is performed. All response-related endpoints (ORR, DCR, DOR, and PFS) will be based on RECIST v1.1 or RANO and derived programmatically using the investigator's assessments of tumor response at each time point. The date of response is based on the image dates. In

the event that there are images taken on different days, the latest date among all images taken will be used for the response date if the overall response is non-progressive disease. If the overall response is PD, then the earliest date of all images taken will be used for the progression date.

6.8.1 Best Overall Response (BOR)

Overall response will be evaluated using RECIST v1.1 for subjects with solid tumors other than brain tumor and RANO criteria for subjects with brain tumor. A subject's BOR is the most favorable response recorded any time after the start of study drug until the date when any new anticancer therapy is initiated. A BOR of either complete response (CR) or partial response (PR) requires confirmation of the assessment at least 4 weeks later. A BOR of stable disease (SD) requires the assessment to be recorded no less than 8 weeks after the start of study drug.

As a result, BOR can be any of the following: CR, PR, SD, PD, or not evaluable.

Table 3 below describes the derivation of BOR from overall response assessments at each visit. Note that BOR categories referenced in this table can be based on overall response evaluated by either RECIST v1.1 or RANO. The number and percentage of subjects in each BOR category will be summarized.

Table 3 Best Overall Response When Confirmation of Complete Response and Partial Response is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration was met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration was met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration was met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration was met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration was met, otherwise, NE

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
NE	NE	NE

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.

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease (requires a minimum duration of 8 weeks from the start of treatment.)

6.8.2 Objective Response Rate (ORR)

The number and percentage of subjects with BORs of either CR or PR, taking into account any requirement for confirmation, will be calculated. The rates will be presented along with two-sided 90% exact confidence intervals. The 90% CIs will be derived using the Clopper-Pearson (Hollander, 1973) exact binomial confidence interval method.

The analysis of ORR will be performed for the Efficacy evaluable population as well as the Per-protocol population.

6.8.3 Disease Control Rate (DCR)

The number and percentage of subjects with a confirmed CR or PR, or an SD will be summarized. To be counted in the calculation of DCR, the CR or PR must be confirmed by a second assessment at least 4 weeks later; otherwise, the SD must be observed at least 6 months from the start of study drug. The rates will be presented along with two-sided 90% exact confidence intervals; 90% confidence intervals (CIs) will be derived using the Clopper-Pearson method. Analyses will be performed for the Efficacy evaluable population.

6.8.4 Time to Response (TTR)

Time to response, defined as the time from the first dose of study drug to the first assessment of PR or CR, will be summarized descriptively for responders (i.e., subjects with a confirmed CR or PR) based on the Efficacy evaluable population.

6.8.5 Duration of Response (DOR)

Duration of response will be calculated from the first date of confirmed CR/PR to the date of death or the date of first documented tumor progression, whichever is earlier, using RECIST v1.1 or RANO. Subjects who remain alive without evidence of disease progression will be censored on the date of their last tumor assessment. Subjects who start a new anticancer therapy without a prior PD will be censored on the date of their last tumor assessment prior to initiating the new anticancer therapy. Response duration will only be evaluated in subjects who have an objective response of CR or PR.

The median DOR, along with its two-sided 95% CI (Brookmeyer, 1982), will be estimated using the Kaplan-Meier (KM) method.

6.8.6 Progression-Free Survival (PFS)

PFS will be calculated as the number of days from the first dose of study drug to the date of death or PD (regardless of relationship), whichever is earlier. Subjects who remain alive and do not progress will be censored on the last tumor assessment date. Subjects who start subsequent therapy without a prior reported progression will be censored on the date of last tumor assessment prior to initiation of subsequent anticancer therapy. Subjects who have no post-baseline tumor assessments and do not die will be censored on Day 1.

The median PFS time, along with its two-sided 95% CI, will be estimated using the KM method. In addition, two-sided 95% CIs for the PFS rate will be constructed at pre-specified time intervals (such as 3 months, 6 months, …, etc.), using the log-log transformation methodology of Kalbfleisch and Prentice (Kalbfleisch, 1980) where the estimated variance of log (- log($\hat{S}(t)$) is:

$$\tau^2(t) = \sigma^2[\hat{S}(t)\log(\hat{S}(t))]^2$$

The 100 x (1-α)% CI for S(t) is given by:

$$\left[\hat{S}(t)\right]^{\exp(z_{\alpha/2}\tau(t))} \le S(t) \le \left[\hat{S}(t)\right]^{\exp(-z_{\alpha/2}\tau(t))}$$

Above analyses will be performed for the Efficacy evaluable population.

6.8.7 Overall Survival (OS)

Overall survival is defined as the time from the first dose of study drug to the date of death due to any cause. For subjects who do not die, the OS time will be censored on the date when the subject was last known to be alive. The date "last known to be alive" will be defined as the latest date of contact with the subject based on the following (subjective to additional collection dates): non-imputed AE start and stop dates, visit/collection dates (including unscheduled visits) of serum/urine pregnancy tests, safety laboratory collection (e.g., hematology, serum chemistry, coagulation profiles, serology sample, and urinalysis), vital signs, physical exams, ECG assessments, [redacted] tumor biopsy or tumor assessments, concomitant medication/post treatment cancer therapy, and extended survival follow-up contact dates where the subject's status is "alive". The analysis methodology for OS will be similar to that used for PFS.

[redacted]

6.10 Safety Analyses

6.10.1 Adverse Events

All subjects will be assessed regularly for the potential occurrence of adverse events (AEs) from the date of informed consent to 30-35 days after the last dose of study drug or until the start of new anticancer therapy, whichever occurs first. The treatment-emergent adverse event (TEAE) is defined as any event with start date at or after the first dose of pemigatinib.

A subject with several occurrences of the same AE will be counted once and classified by the most severe occurrence. AEs with missing severity ratings will be classified as having unknown severity.

Any AE with an eCRF description of related will be considered related. A subject with several occurrences of the same AE will be counted once and classified as related if at least one of them is classified as related. An AE with a missing relationship to study drug will be assumed to be missing.

An overview of adverse events for the Safety population will be provided, summarizing the incidence of the following:

- Any TEAEs, related TEAEs
- Any Grade ≥3 TEAEs; related Grade ≥3 TEAEs
- Any serious TEAEs; related serious TEAEs
- Any discontinuation of study drug due to TEAEs
- Any Grade 5 TEAEs; related Grade 5 TEAEs

TEAE summaries by SOC and PT will be provided for the following:

- TEAEs (overall and any treatment-related)
- Grade ≥3 TEAEs (overall and any treatment-related)
- Serious TEAEs (overall and any Serious treatment-related)
- TEAEs leading to discontinuation of study drug (TEAEs leading to treatment discontinuation)
- Related TEAEs leading to discontinuation of study drug
- TE Fatal AEs (overall and any treatment-related)

In addition, a summary will be provided for the number and percentage of subjects with TEAEs by the maximum NCI CTCAE grade. For this summary, subjects with multiple adverse events will be counted only once by the highest NCI CTCAE grade within an SOC and preferred term.

6.10.2 Laboratory Evaluation

For chemistry, coagulation, endocrine, serology, and hematology parameters, laboratory measurements (including actual values collected at baseline, last value post baseline, and their changes from baseline) will be summarized. In addition, the maximum and minimum post-baseline values with their changes from baseline will be presented. For continuous laboratory tests, overtime plot of mean evaluations will be provided.

Shift tables from baseline to the worst post-baseline values will be provided for chemistry parameters and hematology parameters that have NCI-CTCAE toxicity grades. Both scheduled and unscheduled post baseline values during the treatment period will be considered. Additionally, the number and percentage of subjects with Grade ≥ 3 will be presented for each CTCAE gradable laboratory test. For non-CTCAE gradable laboratory tests, the shift table based on the laboratory normal range will be presented.

All clinical laboratory data will be listed by subject. Values outside the normal ranges will be flagged and toxicity grades will be displayed for relevant parameters.

6.10.3 Vital Signs and Weight Measurement

Vital signs measurements include heart rate, respiratory rate, temperature, systolic blood pressure, and diastolic blood pressure. Vital sign measurements and weight measurement at baseline, changes from baseline to the measurement at each cycle, and the last visit value post baseline with its change from baseline will be summarized. Only scheduled visit values will be included in this summary.

In addition, the maximum and minimum post-baseline values and their changes from baseline will be summarized.

6.10.4 Electrocardiogram

ECG measurements include heart rate, PR interval, RR interval, QRS interval, QT interval, QTcF and QTcB intervals. ECG measurements at baseline, changes from baseline to the measurements at each visit, and the last visit value post baseline with its change from baseline will be summarized. In addition, the maximum and minimum post-baseline values will be summarized.

The number and percentage of subjects with elevated QTcF or QTcB values (≥ 450 msec, > 480 msec, and > 500 msec) at baseline and any time post baseline will be presented. In addition, the number and percentage of subjects with QTcF or QTcB values that increase by > 30 msec and > 60 msec from baseline to any time post baseline will be presented.

A shift table from baseline to the worst post-baseline values during the treatment period will be provided for QTcF and QTcB intervals. The following categories will be used: < 450 msec, ≥ 450 and ≤ 480 msec, > 480 and ≤ 500 msec, and > 500 msec.

6.10.5 ECOG Performance Status

A frequency table will present the number and percentage of subjects classified by their highest (worst) grade for ECOG performance status observed during the study.

6.10.6 Ophthalmic examinations

Ophthalmic examinations will also be summarized for the Safety population. Abnormalities discovered via optical coherence tomography will be summarized as a shift table for the worst cases and/or listed.

7 INTERIM ANALYSES

No formal interim analysis is planned.

8 CHANGES IN THE PLANNED ANALYSES

Study is terminated early due to lack of enrollment. A patient profile or subject listings will be provided.

9 MOCK TABLES, LISTINGS, AND GRAPHS

Not applicable.

10 REFERENCES

1. Hollander M, Wolfe DA. Nonparametric statistical methods. John Wiley & Sons, Inc. 1973.

2. Brookmeyer R, Crowley J (1982): A confidence interval for the median survival time. Biometrics, 38: 29-41.

3. Kalbfleisch JD, Prentice RL (1980): The statistical analysis of failure time data. John Wiley & Sons, Inc.