



STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Gemcitabine and Nab-paclitaxel combined with Momelotinib in Subjects with Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma Preceded by a Dose-finding, Lead-in Phase
Name of Test Drug:	Momelotinib
Study Number:	GS-US-370-1296
Protocol Version:	Amendment 3
Protocol Date:	16 July 2015
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	10 July 2017
Analysis Plan Author	PPD PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

TABLE OF CONTENTS	2
LIST OF IN-TEXT TABLES	3
LIST OF ABBREVIATIONS.....	4
1. INTRODUCTION	6
1.1. Study Objectives	6
1.2. Study Design	6
1.3. Sample Size and Power	8
2. PLANNED ANALYSES	9
2.1. Data Monitoring Committee	9
2.2. Interim Analyses	9
2.3. Final Analysis	9
3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS	10
3.1. Analysis Sets	10
3.1.1. All Enrolled Analysis Set	10
3.1.2. Safety Analysis Set.....	10
3.1.3. DLT-Evaluable Analysis Set.....	10
3.1.4. Pharmacokinetic Analysis Set	10
3.2. Subject Grouping	11
3.3. Strata and Covariates.....	11
3.4. Examination of Subject Subsets	11
3.5. Multiple Comparisons	11
3.6. Missing Data and Outliers.....	11
3.6.1. Missing Data	11
3.6.2. Outliers	11
3.7. Data Handling Conventions and Transformations	11
3.8. Analysis Visit Windows.....	13
3.8.1. Definition of Study Day	13
3.8.2. Analysis Windows.....	13
3.8.3. Selection of Data in the Event of Multiple Records in a Window	13
4. SUBJECT DISPOSITION	15
4.1. Subject Enrollment and Disposition.....	15
4.2. Extent of Exposure	15
4.2.1. Duration of Exposure to Study Drug.....	16
4.2.2. Adherence to Study Drug	16
4.3. Protocol Deviations	17
4.4. Changes from Protocol-Specified Analysis.....	18
5. BASELINE DATA	19
5.1. Demographics	19
5.2. Other Baseline Characteristics	19
5.3. Medical History.....	19
5.3.1. Pancreatic Cancer Disease History.....	19
5.4. Post-Treatment Anticancer Therapy	20
5.5. Prior and Current Cancer-Related Surgeries and Procedures.....	20
6. EFFICACY ANALYSES	21

6.1.	Definition and Analysis of Efficacy Endpoints.....	21
6.1.1.	Overall Survival	21
6.1.2.	Progression-Free Survival	21
6.1.3.	Overall Response Rate	22
6.1.4.	ECOG Performance Status	22
6.1.5.	Change in Tumor Size	23
6.1.6.	Duration of Response (DOR)	23
6.1.7.	Patient-Reported Outcomes Assessments (PRO)	24
6.2.	Changes from Protocol-Specified Efficacy Analysis	24
7.	SAFETY ANALYSES	25
7.1.	Adverse Events and Deaths.....	25
7.1.1.	Adverse Event Dictionary	25
7.1.2.	Adverse Event Severity	25
7.1.3.	Relationship of Adverse Events to Study Drug.....	25
7.1.4.	Serious Adverse Events.....	26
7.1.5.	Treatment-Emergent Adverse Events.....	26
7.1.6.	Summaries of Adverse Events and Deaths.....	26
7.1.7.	Additional Analysis of Adverse Events	28
7.2.	Clinical Laboratory Evaluations.....	28
7.2.1.	Summaries of Numeric Laboratory Results	29
7.2.2.	Graded Laboratory Values	29
7.2.3.	Shifts Relative to the Baseline Value	30
7.3.	Vital Signs.....	30
7.4.	Prior and Concomitant Medications	30
7.4.1.	Prior Medications	31
7.4.2.	Concomitant Medications.....	31
7.5.	Electrocardiogram Results	31
7.6.	Other Safety Measures	32
7.7.	Changes From Protocol-Specified Safety Analyses	32
8.	PHARMACOKINETIC ANALYSES	33
8.1.	PK Sample Collection	33
8.2.	PK Analyses Related to Intensive PK Sampling.....	33
8.2.1.	Estimation of Pharmacokinetic Parameters.....	33
8.2.2.	Pharmacokinetic Parameters	33
8.3.	Changes From Protocol-Specified Pharmacokinetic/Pharmacodynamic Analyses.....	35
9.	REFERENCES	36
10.	SOFTWARE	37
11.	SAP REVISION.....	38
12.	APPENDIX: CATARACT AE	39

LIST OF IN-TEXT TABLES

Table 1-1.	Dose Escalation Scheme.....	7
Table 8-1.	Study Treatments and Associated Analytes	34

LIST OF ABBREVIATIONS

AE	Adverse event
AEOI	Adverse event of interest
ATC	Anatomical therapeutic chemical
BLQ	Below the lower limit of quantitation
BOR	Best overall response
CA 19-9	Cancer antigen 19-9
CEA	Carcinoembryonic antigen
CI	Confidence interval
CR	Complete response
CRP	C-reactive protein
CSR	Clinical study report
CT	Computed tomography/computed axial tomography scan
DLT	Dose limiting toxicity
DMC	Data monitoring committee
DOR	Duration of response
eCRF	Electronic case report form
ECOG PS	Eastern Cooperative Oncology Group performance status
EOT	End of treatment
EQ-5D	EuroQoL 5 Dimension Descriptive System questionnaire
FACT-Hep	The Functional Assessment of Cancer Therapy – Hepatobiliary questionnaire
ID	Identification
LLOQ	Lower limit of quantitation
MMB	momelotinib
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
ND	No disease
NE	Not evaluable
NN	Non-CR/Non-PD
PFS	Progression-free survival
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
pSTAT3	phospho-signal transducer and activator of transcription 3
RECIST	Response Evaluation Criteria In Solid Tumor
SAE	Serious adverse event

SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
StD	Standard deviation
TEAE	Treatment-emergent AE
TFLs	Tables, figures, and listings
TTR	Time to response

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-370-1296. This SAP is based on the study protocol amendment 3 dated 16 July 2015 and the electronic case report form (eCRF). The SAP will be finalized before the database finalization. Any changes made after the finalization of the SAP will be documented in CSR.

Since the randomized treatment phase of the study was not initiated, this SAP describes the planned statistical analysis for the lead-in phase of this study (hereinafter referred to as “study”) only.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the safety, pharmacokinetics (PK), and define the maximum tolerated dose (MTD) of momelotinib (MMB) combined with nab-paclitaxel/gemcitabine (nab-P+G) in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma.

The secondary objectives of this study are as follows:

- To evaluate the efficacy of MMB combined with nab-P+G in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma.

The exploratory objective of this study is as follows:

PPD

1.2. Study Design

This is an open-label, non-randomized, dose-finding study to define the MTD of MMB in combination with nab-P+G in pancreatic adenocarcinoma patients.

There will be a screening period of up to 21 days to assess subject eligibility including confirmation of previously untreated metastatic pancreatic ductal adenocarcinoma computed tomography (CT) or magnetic resonance imaging (MRI) scans of the tumor will be required within 21 days of first dose of investigational product (MMB).

The end of this trial is defined as the date of the last study contact of the last study subject.

Dose escalation is shown in Table 1-1.

Table 1-1. Dose Escalation Scheme

Dose Level	MMB	G	nab-P
-2	100 mg once daily	800 mg/m ²	100 mg/m ²
-1	100 mg once daily	1000 mg/m ²	100 mg/m ²
1*	100 mg once daily	1000 mg/m ²	125 mg/m ²
2	150mg once daily	1000 mg/m ²	125 mg/m ²
3	200 mg once daily	1000 mg/m ²	125 mg/m ²
4	150 mg twice daily	1000 mg/m ²	125 mg/m ²
5	200 mg twice daily	1000 mg/m ²	125 mg/m ²

*Starting dose

G: gemcitabine; MMB: momelotinib; nab-P: nab-paclitaxel

Three subjects will initially enroll into Dose Level 1. If no DLT occurs in all 3 subjects within the first 28 days (Cycle 1) of treatment, 3 additional subjects will enroll into Dose Level 2.

If 1 DLT occurs in any dose level, that dose level will be expanded to enroll 3 additional subjects. If a second DLT occurs within the same dose level after cohort expansion to 6 subjects, the MTD of nab-P+G combined with MMB has been exceeded. Dose escalation will continue from Dose Level 2 to 3 to 4 to 5 if no DLT occurs in 3 evaluable subjects or < 2 DLTs occur in 6 evaluable subjects within each dose level.

If ≥ 2 DLTs occur in Dose Level 1, Dose Level -1 will open to enroll 3 additional subjects. If no DLT occurs in 3 evaluable subjects or < 2 DLTs occur in 6 evaluable subjects of Dose Level -1, then Dose Level -1 will be the MTD of nab-P+G combined with MMB. If ≥ 2 DLTs occur in Dose Level -1, Dose Level -2 will open to enroll 3 additional subjects. If no DLT occurs in 3 evaluable subjects or < 2 DLTs occur in 6 evaluable subjects of Dose Level -2, then Dose Level -2 will be the MTD of nab-P+G combined with MMB. If ≥ 2 DLTs occur at Dose Level -2, the study will discontinue permanently.

If ≥ 2 DLTs occur in Dose Level 2, 3, 4, or 5, then Dose Level 1, 2, 3, or 4 will be the MTD of nab-P+G combined with MMB, respectively.

Please refer to the study protocol Appendix 5 for a flow diagram of dose escalation.

Dose limiting toxicities are based on CTCAE Version 4.03. Dose limiting toxicities refer to toxicities experienced during the first 28 days of treatment (Cycle 1) that have been judged to be clinically significant and related to study treatment. A DLT is defined as:

- Grade 4 neutropenia lasting > 5 days. Subjects who develop Grade 4 neutropenia during the first 28 days of treatment must have a repeat assessment of their neutrophil count 5 days after the onset of Grade 4 neutropenia to assess for this DLT.

- Grade ≥ 3 neutropenia with fever (temperature ≥ 100.5 °F)
- Grade 4 thrombocytopenia
- Grade 3 or higher non-hematologic toxicity, excluding:
 - Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy
 - Grade 3 diarrhea with maximum duration of 48 hours on adequate medical therapy
 - Alopecia
- A treatment-emergent AE that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk
- Any treatment delay > 4 weeks that is due to study treatment-related adverse effects

Patient-reported outcomes (PRO), clinical, laboratory, and disease assessments will be completed at regular study visits as defined in the study protocol Appendix 2. CT or MRI scans will be performed approximately every 8 weeks to evaluate response to treatment by RECIST v1.1 criteria {Eisenhauer 2009}

1.3. Sample Size and Power

The sample size of the study will be determined based on the number of dose levels evaluated and the emerging MMB-related toxicities. The study will consist of up to 30 subjects.

2. PLANNED ANALYSES

2.1. Data Monitoring Committee

This study has a data monitoring committee (DMC) to review the progress and safety of the study. The committee will convene and review the safety data from subjects in the lead-in phase before initiation of the randomized treatment phase.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency

2.2. Interim Analyses

No formal interim efficacy analysis, with the possibility of early termination for efficacy or futility, is planned.

2.3. Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved, and the database has been cleaned and finalized, the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage and 95% CI of the percentage of subjects in each category will be presented; for continuous variables, the number of subjects [n], mean, 95% CI of the mean, standard deviation [StD] or standard error [SE], median, first quartile [Q1], third quartile [Q3], minimum, and maximum will be presented.

Data collected in the study will be presented in by-subject listings for all enrolled subjects, regardless of whether or not they received study drug. All by subject listings will be presented by dose level, then by subject identification (ID) number in ascending order, unless otherwise specified.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, will be provided by dose level.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening. This is the primary analysis set for efficacy analyses.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of MMB. This is the primary analysis set for safety analyses.

3.1.3. DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set is defined as all subjects in the Safety Analysis Set who complete all treatment and safety procedures through Day 28, inclusive, or experienced a DLT prior to Day 29. During the DLT assessment window, if a subject who fails to receive more than 75% of MMB planned dose for reasons other than DLT, a replacement subject will be enrolled at the same dose level as the replaced subject. Subjects who are replaced but received at least 1 dose of study drug will be included in the Safety Analysis Set.

3.1.4. Pharmacokinetic Analysis Set

The PK Analysis Set includes all subjects who have been administered at least 1 dose of MMB and have at least 1 nonmissing postdose concentration value for the corresponding analyte in serum or plasma.

3.2. Subject Grouping

For analysis based on the defined analysis sets, subjects will be grouped according to the actual dose level received.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule in enrolling subjects. No covariates will be included in efficacy and safety analyses.

3.4. Examination of Subject Subsets

There are no prespecified subject subsets for efficacy and safety analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of partial dates of birth, continuous data less than the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ), and PK data below the LLOQ (BLQ) are described in Section 3.7; missing or incomplete dates for metastatic pancreatic cancer diagnosis are described in Section 5.3.1; for missing or incomplete dates for AE onset was described in Section 7.1.5.2; and missing and incomplete dates for prior and concomitant medications are described in Section 7.4.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set sorted by dose level, subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within subject. Subjects will be listed according the actual treatment received.

Age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings.

If a subject was not dosed with study drug at all, the date the informed consent was signed will be used instead of the first dose date of study. For some countries, only birth year is collected on the CRF. In those cases, “01 January” will be used for the unknown birth day and month for the purpose of age calculation, unless age is captured on the CRF.

Data that are continuous in nature but are less than the LLOQ or above the ULOQ will be imputed as follows:

- A value that is 1 unit less than the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of “< x” (where x is considered the limit of quantitation). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception to this rule is any value reported as < 1. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used for calculation of summary statistics.
- A value that is 1 unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of “> x” (where x is considered the limit of quantitation). Values with decimal points will follow the same logic as above.
- The limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of “≤ x” or “≥ x” (where x is considered the limit of quantitation).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Natural logarithm transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are BLQ will be presented as “BLQ” in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LLOQ at postbaseline time points, where LLOQ is corrected for the dilution factor (ie, reported LLOQ/dilution factor) for determination of summary and order statistics.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as “BLQ.”
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as “BLQ.”
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as “BLQ.”

- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as “BLQ.”
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as “BLQ.”

Pharmacokinetic parameters that are BLQ will be imputed as one-half LLOQ before log transformation or statistical model fitting.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day is the day relative to the date of the first dose of MMB. Study Day 1 will be defined as the day of first dose of MMB administration.

Study day will be calculated from the date of first dose of MMB administration and derived as follows:

- For postdose study days: Assessment Date – First Dosing + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

3.8.2. Analysis Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dose of study drug may be included in the calculation of baseline value, if applicable.

For subjects who prematurely discontinue from the study, early termination data will be assigned to what would have been the next scheduled visit where the respective data were scheduled to be collected.

3.8.3. Selection of Data in the Event of Multiple Records in a Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple nonmissing numeric observations exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, average (arithmetic or geometric mean, as appropriate) will be used for the baseline value.

- For postbaseline visits:
 - The record closest to the nominal day for that visit will be selected.
 - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
 - If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

If multiple valid nonmissing categorical observations exist in a window, records will be selected as follows:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings).
- For postbaseline visits, if there are multiple records with the same time or no time recorded on the same day, the most conservative value within the window will be selected (eg, abnormal will be selected over normal for safety ECG findings).

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by dose level for each investigator, and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects in each dose level.

Listings of all enrolled subjects will be generated to describe subject number, enrollment date, first treatment date, dose level assignment, actual dose level allocation, exposure of MMB, and the reason for discontinuing study treatment.

A summary of subject disposition will be provided by dose level cohort and overall. This summary will present the number of subjects screened, the number of subjects enrolled, and the number of subjects in each of the categories listed below.

- In the All Enrolled Analysis Set
- In the Safety Analysis Set
- In the DLT-Evaluable Analysis Set
- Had any DLT
- Included in the PK Analysis Set
- Discontinuation of MMB with reasons for discontinuation
- Discontinuation of gemcitabine with reasons for discontinuation
- Discontinuation of nab-paclitaxel with reasons for discontinuation
- Did not complete the study with reasons for discontinuation of study

For the status and reasons of study discontinuation, the number and percentage of subjects in each dose level will be provided. The denominator for the percentage calculation will be the total number of subjects in the All Enrolled Analysis Set corresponding to that dose level.

4.2. Extent of Exposure

Extent of exposure to study drug (MMB, gemcitabine, or nab-paclitaxel) will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dosing date is missing, the latest study drug end date, clinical visit date, laboratory sample collection date, or vital signs assessment date that occurred during the on-treatment period will be used.

The total duration of exposure to study drug will be summarized using descriptive statistics (number of subjects [n], mean, StD, median, Q1, Q3, minimum, and maximum). The number of cycles subjects were exposed to study drug will also be summarized using descriptive statistics, as well as the number and percentage of subjects exposed to a given cycle category (≥ 1 , ≥ 2 cycles etc.). The number of subjects who have dose modification or interruption, and the reason, will be summarized as well. Summaries will be provided by dose level for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The total dose (mg) and average daily dose for MMB will be summarized using descriptive statistics (n, mean, StD, median, Q1, Q3, minimum, and maximum).

The presumed total number of doses administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Amount of Study Drug Administered (mg)} = \sum (\text{Daily Dose in mg})$$

The average daily dose in mg will be calculated using the following formula:

$$\text{Average Daily Dose (mg)} = \frac{\text{Total Amount of Study Drug Administered (mg)}}{\text{Total Number of Days on Study Drug}}$$

Where Total Number of Days on Study Drug = Last Dosing Date – First Dosing Date + 1

The total dose (mg/m^2) and average dose by visit for gemcitabine and nab-paclitaxil will be summarized using descriptive statistics (n, mean, StD, median, Q1, Q3, minimum, and maximum).

The presumed total dose administered to a subject will be determined by the data collected on the infusion exposure CRF using the following formula:

$$\text{Total Amount of Study Drug Administered (mg}/\text{m}^2) = \sum \text{Dose at each visit in mg}/\text{m}^2$$

The average dose by visit in mg/m^2 will be calculated using the following formular:

$$\text{Average Dose by Visit (mg/m}^2\text{)} = \frac{\text{Total Amount of Study Drug Administered (mg/m}^2\text{)}}{\text{Total Number of Visits}}$$

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period based on the study drug regimen. Investigator-prescribed interruption, reductions and escalations as specified in the protocol will be taken into account.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}} \right) \times 100$$

Descriptive statistics for the level of on-treatment adherence (n, mean, StD, median, Q1, Q3, minimum, and maximum) with the number and percentage of subjects belonging to adherence categories ($< 75\%$, $\geq 75\%$, $>100\%$) will be provided by the dose level for the Safety Analysis Set. No formal statistical testing is planned.

Discontinuation reasons will be summarized as part of analysis.

A separate by-subject listing of MMB study drug administration and drug accountability will be provided by subject ID number (in ascending order) and visit (in chronological order). A separate by-subject listing of gemcitabine and nab-paclitaxel study drug administration will be provided similarly to MMB.

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on all enrolled subjects. A by-subject listing will be provided for those subjects who violated at least 1 inclusion or exclusion criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of inclusion/exclusion criteria) will be summarized by treatment group for the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

4.4. Changes from Protocol-Specified Analysis

Summary for timing of prescribed dose modification and interruption are not provided.

5. BASELINE DATA

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by dose level cohort and overall using descriptive statistics (n, mean, StD, median, Q1, Q3, minimum, and maximum) for age, and using the numbers and percentages of subjects for sex, race, and ethnicity. Age is calculated in years as specified in Section 3.7. The summary of demographic data will be provided for the All Enrolled Analysis Set.

A by-subject demographic listing, which includes the date the informed consent was signed, will be provided by dose level cohort and subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include body weight (in kg), height (in cm), body mass index (BMI; in kg/m²), body surface area (BSA; in m²), and ECOG performance. These baseline characteristics will be summarized by dose level cohort and overall using descriptive statistics (n, mean, StD, median, Q1, Q3, minimum, and maximum) for continuous variables and using the numbers and percentages of subjects for categorical variables. The summary of baseline characteristics will be provided for the All Enrolled Analysis Set.

A by-subject listing of other baseline characteristics will be provided by dose level cohort and subject ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

General medical history data will not be coded, but will be listed only. A by-subject listing of general medical history will be provided by subject ID number in ascending order.

5.3.1. Pancreatic Cancer Disease History

A summary of disease-specific medical history will be provided for the All Enrolled Analysis Set. Time since metastatic pancreatic cancer diagnosis (months) will be calculated by (first dosing date of MMB – date of metastatic pancreatic cancer diagnosis) / 30.4375. Time since metastatic pancreatic cancer diagnosis will be summarized using summary statistics for a continuous variable. No inferential statistics will be generated.

A by-subject listing of disease-specific medical history will be provided by subject ID number in ascending order.

All partial dates of diagnosis will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- A partial date will not be imputed if the year is missing.

5.4. Post-Treatment Anticancer Therapy

The details of post-treatment anticancer therapy will be listed, including line of therapy, type of regimen, and regimen start/stop date.

5.5. Prior and Current Cancer-Related Surgeries and Procedures

A listing of prior and current cancer-related surgeries and procedures will be provided.

6. EFFICACY ANALYSES

6.1. Definition and Analysis of Efficacy Endpoints

6.1.1. Overall Survival

Overall survival (OS) is defined as the time interval from the first dose of MMB to death from any cause. Subjects who are lost to follow-up or survived until the end of study will be censored at the last date that they were known to be alive. OS analysis will be conducted for subjects in the All Enrolled Analysis Set.

Medians (Q1, Q3) of OS with 95% CIs and the percentage of subjects who are alive at 6 months and 12 months from Study Day 1 will be derived using Kaplan-Meier (KM) method and provided by dose level cohort. A plot of the KM curves for OS will be provided by dose level cohort. A listing will be provided for the information of subject OS, including treatment start date, date of death or censor date, and cause of death.

6.1.2. Progression-Free Survival

Progression-free survival (PFS) is defined as the time interval from the first dose of MMB to the earlier of the first documentation of definitive disease progression (based on RECIST v1.1) or death from any cause. All scans, whether scheduled or unscheduled, will be considered. PFS analysis will be conducted for subjects in the All Enrolled Analysis Set.

Data from surviving, nonprogressing subjects will be censored at the earliest of the time of initiation of anticancer therapy other than the study treatment or the last time that lack of definitive disease progression was objectively documented while on study. Data from subjects who have disease progression or death after at least 2 consecutive missing tumor assessments or after the initiation of anticancer therapy other than the study treatment will be censored at the last time prior to the missing assessments that lack of disease progression was objectively documented or at the time of initiation of anticancer therapy other than the study treatment, whichever is earlier. If a subject does not have a baseline tumor assessment, then the PFS time will be censored at Study Day 1, regardless of whether or not definitive disease progression or death has been observed.

When the start date of new anticancer therapy is incomplete or missing, the following imputation rules will be applied. The imputed date or last visit date for a subject, whichever is later, will be used as the start date of the new anticancer therapy for PFS analysis.

- If day is missing but the month and year are available, then the imputed day will be the first day of the month;
- If day and month are missing but year is available, then the imputed day and month will be 01Jan;
- If day, month and year are all missing, then the imputed date will be the last visit date for the subject.

PFS rates at 3, 6, 9, and 12 months and median (Q1, Q3) PFS times with 95% CIs will be derived using KM methods and provided by dose level cohort. Kaplan-Meier curves will also be provided. A listing will be provided for the information of subject PFS, including treatment start date, and date of PD or censor date.

6.1.3. Overall Response Rate

Best overall response (BOR) is defined as the best response recorded during the follow up period after first dose prior to the time of initiation of anti-cancer therapy other than the study treatment. Overall response rate (ORR) is defined as the proportion of subjects who achieve a best overall response during MMB therapy of complete response (CR) or partial response (PR) based on RECIST v1.1.

Per RECIST criteria (version 1.1), BOR could be assessed as CR, PR, Stable Disease (SD), or Progressive Disease (PD) for subjects with measurable target lesions at baseline; or as CR, NN (Non CR/Non PD), PD for subjects without measurable target lesion identified at baseline; or as no disease (ND) or PD for subjects with no disease identified at baseline. The response of Not Evaluable (NE) will be recorded for subjects who withdraw before the scheduled imaging is performed due to toxicity, clinical deterioration, death or other reasons, or subjects with poor images, or subjects with the minimum criteria for SD or NN duration (7 weeks from baseline assessment) not met or without baseline tumor assessment.

Based on the investigator assessments, the following will be performed for the All Enrolled Analysis Set by dose level cohort and overall:

- Best overall response will be summarized using the number and the percentage of subjects in each category (e.g. Complete Response [CR], Partial Response [PR], Stable Disease [SD] or Progressive Disease [PD]).
- Overall response rates will be presented with corresponding 2-sided 95% exact confidence intervals (CIs) based on Clopper-Pearson method {Clopper 1934}. Subjects who do not have sufficient baseline or on-study tumor assessments to characterize response will be counted as nonresponders and included in the denominator only.

A listing will be provided for the information of subjects' overall response, including scan date and response at each visit, BOR, and duration of response. A histogram will also be provided for the subjects' BOR.

6.1.4. ECOG Performance Status

The ECOG performance status score has a range from 0 (Fully active; able to carry on all pre-disease performance without restriction) to 5 (Dead). The baseline status will be the last score prior to the start of MMB therapy. The worst post-baseline performance status will be the highest score following the start of MMB therapy.

Shift table will be provided showing the change of ECOG performance status from baseline to the worst post-baseline performance status for subjects in the All Enrolled Analysis Set with baseline and at least one post-baseline measurement of performance status.

A listing of ECOG performance status will be provided.

6.1.5. Change in Tumor Size

Tumor size based on the sum of the diameters of target lesions is collected in the eCRF through an MRI/CT scan every 8 weeks post-baseline. Change from baseline and the percent change from baseline will be determined for each post baseline assessment. The best change from baseline and the best percent change from baseline are defined as the largest decrease or the largest percentage decrease in tumor size while the subject was on-treatment prior to the time of initiation of anticancer treatment other than the study treatment. If a subject only experienced tumor size increase, then the best change from baseline is the smallest increase

- Change from baseline = Post-baseline assessment – baseline assessment
- The percent (%) change from baseline = $([\text{Post-baseline assessment} - \text{baseline assessment}] / \text{baseline assessment}) \times 100$
- The best change from baseline = the minimum of change from baseline over time
- The best percent (%) change from baseline = the minimum of % change from baseline

Change in tumor size will be analyzed for subjects in the All Enrolled Analysis Set who have assessments at baseline and at least 1 post-baseline time point. Baseline and the best percent (%) change from baseline will be calculated and summarized.

Descriptive statistics (n, mean, StD, standard errors, median, Q1, Q3, minimum, and maximum) will be presented by dose level cohort. Waterfall plots will be provided for the best percent (%) change from baseline by dose level cohort. A listing of target lesion will be provided.

6.1.6. Duration of Response (DOR)

DOR will be evaluated using investigator assessments based on subset of subjects in All Enrolled Analysis Set who achieve a response and maintain the response. DOR will be summarized using Kaplan-Meier methods (median, Q1, Q3, and corresponding 95% CI).

For the DOR analysis, data will be censored on the date of the last tumor assessment for subjects

- who do not have disease progression or die on study, or
- who start new anti-tumor therapy prior to documented disease progression, or
- who have ≥ 2 consecutive missing tumor assessments before disease progression or death.

6.1.7. Patient-Reported Outcomes Assessments (PRO)

PROs include FACT-Hep and EQ-5D. The FACT-Hep is a 45-item self-report questionnaire to assess the quality of life of pancreatic patients across four general measures (physical, social/family, emotional, and functional), as well as an 18-item disease-specific hepatobiliary cancer subscale. The EQ-5D is a self-report questionnaire used to assess a subject's general health quality of life consisting of five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression).

Data from FACT-Hep and EQ-5D will be scored, processed, and standardized according to their user manuals. Data will be analyzed using appropriate methods specified in the user manuals to account for incomplete questionnaires. The minimum and maximum postbaseline and change from baseline in subscales and overall scores of FACT-Hep, and the minimum and maximum postbaseline in dimensions of EQ-5D will be summarized descriptively by dose level cohort for subjects in the All Enrolled Analysis Set. By subject listings will be provided for FACT-Hep and EQ-5D.

Time to HRQoL worsening is defined as the interval from first dose of MMB to a minimum of 8-point reduction in FACT-Hep total score or death from any cause, whichever is earlier. The median (Q1, Q3) time to HRQoL worsening with 95% CIs will be derived using KM methods and provided by dose level cohort. Kaplan-Meier curves will be provided. A listing of time to HRQoL worsening will also be provided.

6.2. Changes from Protocol-Specified Efficacy Analysis

Analysis and summary are provided for change in tumor size, duration of response, time to FACT-Hep worsening, change in FACT-Hep, EQ-5D, and ECOG performance status. These endpoints were specified in the protocol for the randomized phase (which was not initiated) rather than the lead-in phase.

7. SAFETY ANALYSES

All safety data collected on or after the date that MMB was first administered up to the date of last dose of MMB, gemcitabine or nab-paclitaxel whichever is later, plus 30 days will be summarized by dose level according to the treatment received. Data for the pretreatment and treatment-free follow-up periods will be included in data listings.

In general, categorical and ordinal data will be summarized using count and percentage. Continuous data will be summarized using mean, StD, median, quartiles, minimum, and maximum.

7.1. Adverse Events and Deaths

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product; the event does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The focus of AE summarization will be on treatment-emergent AEs (TEAEs), defined in Section 7.1.5.1, using the Safety Analysis Set. All AEs will be listed.

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be attached to the clinical database.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE Version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentations.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected “Related” on the AE eCRF to the question of “Related to Study Treatment”. Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationships to study drug will be considered related to study drug for summary purpose. However, by-subject data listings will show the relationship as missing from that captured on the CRF.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug.
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and AE stop date is not prior to the first dosing date of study drug, the month and year (or year alone if month is missing too) of onset determine whether an AE is treatment emergent. The AE is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

A brief high-level summary of TEAEs will be provided by dose level cohort and by the number and percentage of subjects who had the following: any AE by severity and overall; any treatment-related AE by severity and overall; any SAE; any treatment-related SAE; AEs that are Grade ≥ 3 in severity; any AEs leading to premature discontinuation of study drug; any AEs leading to study drug interruption and/or dose modification; and any AE that led to premature discontinuation of study. All deaths (including those that are treatment emergent and those that are not treatment emergent) observed during the study will also be summarized and included in this table.

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT, by dose level cohort and overall using the Safety Analysis Set as follows:

- All TEAEs
- All TEAEs by grade
- All TEAEs with Grade 3 or above
- All MMB-related TEAEs by grade
- All gemcitabine-related TEAEs by grade
- All nab-Paclitaxel-related TEAEs by grade
- All treatment-emergent SAEs
- All MMB-related treatment-emergent SAEs
- All gemcitabine-related treatment-emergent SAEs
- All nab-paclitaxel-related treatment-emergent SAEs
- All TEAEs leading to premature MMB discontinuation
- All TEAEs leading to temporary MMB interruption and/or dose modification
- All TEAEs leading to death

Multiple events will be counted once only per subject in each summary. For data presentation, SOC will be sorted by decreasing total frequency, and PT within SOC will be sorted in the same manner. For summaries by severity grade, the most severe event will be selected.

In addition to the by-treatment summaries, data listings will be provided for the following:

- All AEs (with a variable indicating whether the event is treatment-emergent)
- All MMB-related AEs
- All gemcitabine-related AEs
- All nab-paclitaxel-related AEs
- SAEs
- Deaths

- AEs leading to MMB interruption and/or dose modification
- AEs leading to MMB discontinuation
- AEs leading to death

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Treatment-Emergent Adverse Events of Interest

Additional analyses on AEs of interest (AEOI) will be performed.

The following AEOI will be summarized similarly to TEAE by dose level cohort:

- Peripheral neuropathy standardized MedDRA queries (SMQ) (narrow term only)
- Peripheral neuropathy SMQ (narrow term only) leading to discontinuation of study drug
- Cataract (AEOI, defined as AEs listed in Section 12, Appendix: Cataract AE)

The number and percentage of subjects who experienced any of the above events will be summarized for each dose level cohort by AEOI category and PT.

7.1.7.2. Dose Limiting Toxicity

A listing of the DLT AEs will be provided by dose level cohort including cohort number with assigned dose, subject identification, DLT term from investigator as well as CTCAE term and associated severity grade, if available.

A summary of DLT will be presented by SOC and PT.

7.2. Clinical Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of MMB plus 30 days. The analysis will be based on values reported in conventional units. When values are below the LLOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately; all laboratory data will be listed. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be provided by treatment group for the following laboratory test:

- Cancer antigen 19-9 (CA19-9)
- Carcinoembryonic antigen (CEA)
- C-reactive protein (CRP)

The summary will be provided as follows:

- Baseline values
- Post baseline maximum
- Change from baseline to post-baseline maximum
- Post baseline minimum
- Change from baseline to post-baseline minimum

Unscheduled visits will be included for the baseline and post-baseline maximum/minimum calculations.

A by-subject listing will be provided for all laboratory tests including the results and the toxicity grade if applicable. In addition, a by-subject listing for thiamine level will be provided number.

7.2.2. Graded Laboratory Values

CTCAE Version 4.03 will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline up to and including the date of last dose of MMB plus 30 days. If the relevant baseline laboratory data are missing, then any abnormality of at least Grade 1 will be considered treatment emergent.

Summary (number and percentage of subjects) of laboratory abnormalities will be provided by dose level cohort (subjects categorized according to most severe abnormality grade). Only the maximum post-baseline abnormality grade observed for a subject will be counted.

In the summary of laboratory abnormalities, the denominator is the number of subjects with non-missing post-baseline values up to 30 days after last dosing date.

7.2.3. Shifts Relative to the Baseline Value

Shift tables will be presented for gradable laboratory test, showing change in CTCAE severity grade from baseline to the worst post-baseline grade.

7.3. Vital Signs

Descriptive statistics will be provided by dose level cohort for vital signs (including pulse, systolic blood pressure, diastolic blood pressure, body temperature) as follows:

- Baseline value
- Postbaseline maximum value
- Change from baseline to postbaseline maximum value
- Postbaseline minimum value
- Change from baseline to postbaseline minimum value
- Vital signs values and change from baseline at pre-dose, 2 hours postdose, 4 hours postdose timepoints on Cycle 1 Day 1

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of MMB. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Vital signs measured at unscheduled visits will be included for the baseline and postbaseline maximum and minimum value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary. The medications will be categorized as prior, concomitant, or both using the following definitions:

- Prior medications: any medications taken and stopped prior to or on the date of first study drug administration
- Concomitant medications: any medications taken after the date of first study drug administration and up to 30 days after the last dosing date of study drug

7.4.1. Prior Medications

For the purposes of analysis, any medications taken and stopped prior to or on the first dosing date of MMB will be considered prior medications. If a partial stop date is entered and the month and year (if day is missing) or year (if day and month are missing) of the stop date are before the first study drug dosing date, the medication will be considered a prior medication.

No formal statistical testing is planned.

7.4.2. Concomitant Medications

Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and Level 4 and preferred name using the number and percentage of subjects for each dose level cohort. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. Drugs with the same frequency will be ordered alphabetically.

For the purposes of analysis, any medications started prior to or on the first dosing date of study drug and continued to take after the first dosing date, or started after the first dosing date but no later than last dosing date of study drug will be considered concomitant medications. Therefore, medications with a stop date that is on or prior to the date of first dosing date of study drug or a start date that is after the last dosing date of study drug will be excluded from the concomitant medication summary.

If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by dose level cohort, subject ID number, and administration date in chronological order.

7.5. Electrocardiogram Results

Electrocardiogram (ECG) data will be listed only. No summary table will be provided for ECG data.

7.6. Other Safety Measures

A data listing will be provided for subjects experiencing pregnancy during the study.

7.7. Changes From Protocol-Specified Safety Analyses

Laboratory parameters will be summarized for CA 19-9, CEA, and CRP, by maximum and minimum postbaseline values (and changes from baseline to maximum and minimum postbaseline values) rather than every test by values and changes from baseline at each visit, as specified in the protocol. Summary table and listing will not be provided for laboratory abnormalities with Grade 3 or higher. Shift tables will not be presented for nonCTCAE-graded laboratory parameters. There are no other planned changes from the protocol-specified safety analyses.

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

Intensive PK samples will be collected from subjects on C1D15 (pre-MMB dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-MMB dose); 24 hours post-MMB dose sampling will not be applicable in the twice-daily dose level.

8.2. PK Analyses Related to Intensive PK Sampling

Steady-state PK over a 24 hour dosing interval will be determined in subjects in the PK Analysis Set. Concentrations of MMB and the major metabolite GS-644603 in plasma will be determined using validated bioanalytical assays.

8.2.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic parameters will be estimated using Phoenix WinNonlin[®] software using standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for MMB dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{τ} , λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.2.2. Pharmacokinetic Parameters

Pharmacokinetic parameters will be generated for all subjects in the PK Analysis Set. The analytes presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Study Treatments and Associated Analytes

Analyte	Parameters	
	Primary	Secondary
Momelotinib, GS-644603	C_{max} , AUC_{tau}	AUC_{last} , C_{tau} , T_{max} , C_{last} , T_{last} , V_z/F (momelotinib only), λ_z , $T_{1/2}$, CL_{ss}/F (momelotinib only)

Individual subject concentration data and individual subject PK parameters for MMB and GS-644603 will be listed and summarized using descriptive statistics by MMB dose level. Summary statistics (n, mean, StD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters by treatment. Moreover, the geometric mean, 90% CI, and the mean and StD of the natural log-transformed values will be presented for individual subject PK parameter data.

Metabolite to parent ratios will be calculated for AUC_{tau} , C_{max} , and C_{tau} , when available, and summarized similarly to the PK parameters for MMB and GS-644603.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as specified in Section 3.7.

Individual PK parameter data listings and summaries will include all subjects for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of subjects with nonmissing data for that PK parameter.

The following tables will be provided for each analyte by treatment:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics
- Summary statistics for Metabolite to Parent Ratio on PK Parameters

The following figures may be provided for each analyte by treatment:

- Mean (\pm StD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Individual, mean, and median postdose concentration values that are \leq LLOQ will not be displayed in the figures and remaining points connected.

The following listings will be provided:

- PK sampling details by subject including deviations in scheduled and actual draw times and procedures
- Individual data for determination of plasma half-life and corresponding correlation coefficient for each analyte

8.3. Changes From Protocol-Specified Pharmacokinetic/Pharmacodynamic Analyses

The protocol-specified MMB metabolite, GS-642112, was not assessed since the levels of this metabolite were expected to be lower than 10%, based on data from previous clinical studies.

9. REFERENCES

Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Dec. Biometrika* 1934;26 (4):pp. 404-13.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). *Eur J Cancer* 2009;45 (2):228-47.

10. SOFTWARE

SAS[®] Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

WinNonlin[®] (Pharsight Corporation, Mountain View, CA) is to be used for all PK analyses.

11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

12. APPENDIX: CATARACT AE

MEDDRA Term Name*	MEDDRA Code	MEDDRA Level
Atopic cataract	10069649	PT
Cataract	10007739	PT
Cataract congenital	10007747	PT
Cataract cortical	10007748	PT
Cataract diabetic	10007749	PT
Cataract nuclear	10007759	PT
Cataract operation	10063797	PT
Cataract subcapsular	10007764	PT
Cataract traumatic	10007766	PT
Lens discolouration	10070549	PT
Lenticular opacities	10024214	PT
Radiation cataract	10037756	PT
Toxic cataract	10044135	PT
Bioptic eye surgery	10078599	PT
Eye opacity	10078394	PT
Cornea verticillata	10077604	PT

*: MEDDRA Version 20.0