Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS201922-0001
Title	An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-803/M4344 as a Single Agent and in Combination with Cytoxic Chemotherapy in Participants with Advanced Solid Tumors
Trial Phase	I
Investigational Medicinal Product(s)	M4344
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Integrated Analysis Plan Reviewers	**Function** — **Name** PPD — PPD PPD, Merck PPD, Merck PPD, Merck Medical Responsible, Merck PPD, Merck PPD, Merck PPD, Merck PPD, Merck PPD, Merck

Approval Page

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An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-803/M4344 as a Single Agent and in Combination with Cytoxic Chemotherapy in Participants with Advanced Solid Tumors

Merck responsible	Date
PPD	Via ELDORADO approval process
	Via ELDORADO approval process

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
AUC	Area Under the Concentration-time Curve
BID	Twice daily
BIW	Twice weekly
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
CI	Confidence Interval
CR	Complete Response
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DCR	Disease Control Rate
DEM	Dose Escalation Meeting
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GeoCV	Geometric Coefficient of Variation
GeoMean	Geometric Mean
HLT	Higher Level Term
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
CCI [redacted]	
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification

Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MDSC	Myeloid Derived Suppressor Cells
mFAS	Modified Full Analyis Set
Min	Minimum
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not Evaluable
OR	Objective Response
ORR	Objective Response Rate
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
CCI [redacted]	
PK	Pharmacokinetics
PR	Partial Response
PT	**Preferred Term**
Q1	25th Percentile
Q3	75th Percentile
QD	Once Daily
QTcF	Fridericia's Correction of QT
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCR	Screening Analysis Set
SD	Stable Disease
SDTM	Study Data Tabulation Model
SMQ	Standardized MedDRA Queries
StdDev	Standard Deviation
SOC	System Organ Class

TEAE	Treatment Emergent Adverse Event
Treg	Regulatory T Cells
ULN	Upper Limit of Normal
WHO	World Health Organization
WHO-DD	World Health Organization-Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	24Aug2018	PPD	First version.

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the final analysis of data collected for protocol MS201922-0001. Only analyses for Parts A, A2, and B1 are covered in this IAP. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed with results included in the CSR, but not identified in this prospective IAP, will be clearly identified in the CSR.

The IAP is based upon Section 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with International Conference on Harmonization (ICH) E9.

5 Objectives and Endpoints

Part A:

	Objective	Endpoint	IAP Section
Primary Objectives	To evaluate the safety and tolerability of multiple ascending doses of single-agent M4344 administered twice-weekly (BIW) in participants with advanced solid tumors	Safety parameters, including adverse events (AEs), clinical laboratory values (serum chemistry and hematology), vital signs and electrocardiogram (ECG) assessments	15.2, 15.4, 15.5, 15.6
	To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of single agent M4344 administered BIW in participants with advanced solid tumors	MTD and/or RP2D of single-agent M4344 administered BIW	15.1
Secondary Objectives	To evaluate pharmacokinetics (PK) of single-agent M4344 when administered BIW in participants with advanced solid tumors	PK parameter estimates of single-agent M4344 administered BIW, derived from plasma concentration-time data	16
	To assess potential antitumor activity of single-agent M4344 when administered BIW in participants with advanced solid tumors.	Best Overall Response Objective response (OR) Disease stabilization Sum of longest diameter Evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1	14.1
CCI [redacted]			

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Part A2:

	Objective	Endpoint	IAP section
Primary Objectives	To evaluate the safety and tolerability of multiple ascending doses of single-agent M4344 administered in a twice daily (BID), once daily dose (QD), or an alternativeschedule in participants with advanced solid tumors	Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs and ECG assessments	15.2, 15.4, 15.5, 15.6
	To determine the MTD and/or RP2D of single-agent M4344 administered in a BID or QD dose schedule in participants with advanced solid tumors	MTD and/or RP2D of single-agent M4344 administered with a twice daily or once daily dose schedule	15.1
Secondary Objectives	To evaluate PK of single-agent M4344 when administered in a BID or QD dose schedule in participants with advanced solid tumors	PK parameter estimates of single-agent M4344 administered with a twice daily or once daily dose schedule, derived from plasma concentration-time data	16
	To assess potential antitumor activity of single-agent M4344 when administered in a BID or QD dose schedule in participants with advanced solid tumors.	Best Overall Response Objective response (OR) Disease stabilization Sum of longest diameter Evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1	14.1

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Part B1:

	Objective	Endpoint	IAP section
Primary Objectives	To evaluate the safety and tolerability of multiple ascending doses of M4344 when administered in combination with carboplatin in participants with advanced solid tumors	Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs and ECG assessments	15.2, 15.4, 15.5, 15.6
	To determine the MTD and/or RP2D of M4344 administered in combination with carboplatin in participants with advanced solid tumors.	MTD and/or RP2D of M4344 administered in combination with carboplatin	15.1
Secondary Objectives	To evaluate the PK profile of M4344 when administered in combination with carboplatin in participants with advanced solid tumors	PK parameter estimates of M4344 administered in combination with carboplatin derived from plasma concentration-time data	16.1
	To evaluate potential antitumor activity after administering M4344 in combination with carboplatin in participants with advanced solid tumors.	Best Overall Response Objective response (OR) Disease stabilization Sum of longest diameter Evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1	14.1
CCI [redacted]			

6 Overview of Planned Analyses

Dose Escalation Meetings (DEMs) will determine the next dose level to be explored based on the available safety data on previous cohort(s). Prior to each DEM a data snapshot will have been taken from the clinical database as described in the Statistical Analysis Plan for DEM. Planned data displays for these meetings are described in a separate document, the Statistical Analysis Plan for DEM. There are no interim analyses currently planned for Parts A, A2, and B1 of this study, but interim analyses may be conducted for the purpose of data review and regulatory updates.

6.1 Final Analysis

All final, planned analyses identified in the Clinical Trial Protocol and in this IAP will be performed only after the last subject has completed the study with all trial data in-house, database locked for each study part (Part A2 has a separate database from Parts A and B1), and data released for statistical analyses.

A data review meeting will be held prior to each database lock. In addition, no database can be locked until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

Only analyses of Parts A, A2, and B1 of the trial are covered in this IAP. Analyses on the other parts of the trial will be described in a separate document.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Important protocol deviations include

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion

All important protocol deviations will be documented in the Clinical Trial Management System (CTMS) and in the Study Data Tabulation Model (SDTM) datasets, whether identified through site monitoring, medical review or data management programming.

8.2 Definition of Analysis Sets and Subgroups

Screening Analysis Set (SCR)

The screening analysis set includes all subjects who signed the informed consent form.

Safety Analysis Set (SAF)

The SAF will include all enrolled subjects who received at least 1 dose of study drug (either M4344 or carboplatin (Part B1 only)) with the actual amount > 0 mg. Analyses performed on the SAF will consider subjects' planned dose group.

Dose Limiting Toxicity (DLT) Evaluable Set

The DLT evaluable set includes all enrolled subjects who received at least one dose of M4344 and either:

- Experienced a DLT before the end of Cycle 1 (21 days after start of treatment) or
- Received the following minimum required doses of study drug(s) in Cycle 1 (21 days from start of treatment):
    - Part A: at least 80% (5 out of 6) of scheduled M4344 doses through the end of Cycle 1
    - Part B1: carboplatin dose on Day 1 and M4344 dose on Days 2 and 9
    - Part A2: at least 80% (34 out of 42 for BID regimen or 17 out of 21 for QD regimen) of scheduled M4344 doses through the end of Cycle 1.

Subjects who are withdrawn before they meet one of these criteria will be excluded from the determination of the MTD (and will be replaced), and thus will be excluded from the DLT evaluable set.

Full Analysis Set (FAS)

The FAS is defined as all enrolled subjects who satisfy all of the following criteria:

- received at least 1 dose of study drug with the actual amount > 0 mg
- have a baseline scan with a measurable target lesion (sum of diameters of all target lesions > 0 mm)
- have at least 1 disease assessment on treatment with a measureable target lesion (sum of diameters of all target lesions >= 0 mm); or subjects who have discontinued the study due to either progressive disease or death.

Modified Full Analysis Set (mFAS)

The mFAS is defined as all enrolled subjects who satisfy all of the following criteria:

- received at least 1 dose of study drug with the actual amount > 0 mg
- have a baseline scan with a measurable target lesion (sum of diameters of all target lesions >= 0 mm)

Pharmacokinetic Analysis Set (PAS)

The PAS will include all enrolled subjects who receive at least one dose of M4344 with the actual amount > 0 mg and provide at least one measurable post-dose concentration. Subjects will be analyzed according to the actual treatment they received. All PK analyses will be based on this analysis set.

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Table 1 Summary of Analysis and Associated Analysis Set

Analyses	SCR	DLT	SAF	FAS/mFAS	PAS	CCI	CC I
Disposition	✓						
Baseline Assessments			✓				
Past and Concomitant Therapies			✓				
Compliance and Exposure			✓				
Efficacy				✓			

Analyses	SCR	DLT	SAF	FAS/mFAS	PAS	CCI	CC
Safety: DLTs and MTD/RP2D (primary endpoint)		✓					
Other Safety and Tolerability			✓				
Pharmacokinetic Analysis					✓		
CCI							

9 General Specifications for Data Analyses

Unless otherwise indicated, summary tables will be presented by study part, dose group and overall based on the analysis set of interest; listings will be presented using the same analysis sets as corresponding tables.

Pooling of centers:

Data will be pooled across centers.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using descriptive statistics, i.e.

number of subjects (N), number of subjects with non-missing values,

arithmetic mean (Mean), standard deviation (StdDev),

median, 25th Percentile - 75th Percentile (Q1-Q3),

minimum (Min), and maximum (Max).

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of subjects still present in the trial at that visit, unless otherwise specified.

Definition of baseline:

The last non-missing measurement prior to the first administration of study treatment (either M4344 or carboplatin (Part B1 only)) will serve as the baseline measurement.

Definition of duration:

Duration will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of treatment start + 1) (if not otherwise specified).

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event (e.g. time since last dose date will be calculated as the event date – the date of last dose).

Unscheduled visits:

Assessments from unscheduled visits will be used for the derivation of baseline values and worst on-treatment values. However, descriptive statistics by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits per protocol.

Conversion factors:

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Handling of missing data:

Unless otherwise specified, missing data will not be replaced.

In all subject data listings, imputed values will be presented and flagged as such.

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd" (not done). For example, if n=1, the measure of variability (StdDev) cannot be computed and will be presented as "nd".

Treatment day

Treatment day is defined relative to the start of a treatment. Treatment Day 1 is the day of the first administration of trial drug (M4344 or carboplatin as applicable to the study part). The day before Treatment Day 1 is defined as Treatment Day -1. (No Treatment Day 0 is defined.)

On-treatment period

The on-treatment period is defined as the date of the first dose of a trial drug (M4344 or carboplatin as applicable) until the minimum of the following: date of last dose of study treatment + 30 days and the date of death.

Definiton of Missing category

If not otherwise specified the following categories will be summarized under the missing category:

- missing
- unknown

SAS version:

All analyses will be performed using SAS® Software version 9.4 or higher.

Presentation of PK Concentration Data

PK concentration data will be descriptively summarized by part, treatment and day using: number of non-missing observations, Mean, StdDev, coefficient of variation (CV%), Min, Median and Max.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

- Min, Mean, Median and Max: 3 significant digits
- StdDev: 4 significant digits
- CV%: 1 decimal place

Presentation of PK Parameter Data

PK parameter data will be descriptively summarized by part, treatment and day using: number of non-missing observations, Mean, StdDev, CV%, Min, Median, Max, geometric mean (GeoMean), geometric coefficient of variation (GeoCV) and the 95% CI for the GeoMean (lower 95% CI for GeoMean, upper 95% CI for GeoMean).

PK parameter C_{max} will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

- Min, Mean, Median, Max, GeoMean and 95% CI: 3 significant digits
- StdDev: 4 significant digits
- CV% and GeoCV%: 1 decimal place

Non-compartmental computation of pharmacokinetic parameters will be performed using the computer program Phoenix® WinNonlin® version 6.4 or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).

10 Trial Subjects

The subsections below include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Subjects and Discontinuations

Analysis set: SCR

The disposition table will include the following information:

- Number of subjects screened (overall column only)
- Number and percentage of subjects who discontinued from the trial prior to treatment (overall column only)
- Number and percentage of subjects who took at least one dose of M4344 (SAF subjects)
- Number and percentage of subjects who took at least one dose of carboplatin (SAF subjects) (Part B1 only)
- Number and percentage of SAF subjects who completed M4344 overall and by completion reason (progressive disease or death)
- Number and percentage of SAF subjects who completed carboplatin overall and by completion reason (progressive disease or death) (Part B1 only)
- Number and percentage of SAF subjects who discontinued the M4344, overall and by reason for discontinuation
- Number and percentage of SAF subjects who discontinued the carboplatin, overall and by reason for discontinuation (Part B1 only)
- Number and percentage of SAF subjects that completed Long-Term Follow-Up and their status (alive, dead, or lost to follow-up) at Long-Term Follow-Up (Parts A and B1 only)
    - For subjects that are alive at Long-Term Follow-Up, their status post Safety Follow-Up will be summarized (alive without disease progression, progressed, started new anti-cancer therapy, withdrew consent).
- Number and percentage of SAF subjects who completed the trial
- Number and percentage of SAF subjects who discontinued the trial, overall and by discontinuation reason

Separate summary tables of analysis populations as well as subject enrollment for each region, country, and site will be provided.

All relevant subject disposition data will be presented in data listings including reasons for exclusion from analysis sets.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

Analysis set: SAF

The following summary tables and listings of important protocol deviations will be provided (separately for pre-/post inclusion deviations):

- Frequency table per reason of important protocol deviations
- Listing of important protocol deviations

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

Not applicable since no Per-Protocol population was defined for any parts of this study.

11 Demographics and Other Baseline Characteristics

Analysis set: SAF

11.1 Demographics

Demographic characteristics will be summarized by using the following information from the "Demography" eCRF pages.

Demographic characteristics

- Sex: male, female
- Race: white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected, other
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, not collected
- Ethnicity (Part A2): Japanese, Not Japanese
- Age (years): summary statistics
- Age categories :
    - < 65 years, ≥ 65 years
    - 65-74 years, 75-84 years, ≥85 years
- Pooled Region:
    - North America
    - Europe
- BSA at Baseline: summary statistics

Specifications for computation:

Age (years):

- (date of given informed consent - date of birth + 1) / 365.25
- In case of missing day for at least one date, but month and year available for both dates:

  For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
- In case of missing month for at least one date, but year available for both dates:

  For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used
- BSA (m^2) = ([height (cm) x weight (kg)] / 3600)$^{1/2}$

Site codes will be used for the determination of the subject's geographic region.

All relevant demographic data will be presented in data listings.

11.2 Medical History

Analysis set: SAF

The medical history will be summarized from the "Medical History" eCRF page, using the latest version of Medical Dictionary for Regulatory Activities (MedDRA), preferred term (PT) as event category and MedDRA system organ class (SOC) body term as Body System category.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

A supportive listing of medical history data by subject will include all the relevant data fields as collected on the "Medical History" eCRF pages.

11.3 Prior Anti-cancer Treatments and Procedures

Analysis set: SAF

The prior anticancer treatments and procedures are collected from the "Prior Anti-cancer Therapy" (Parts A and B1), "Prior Anti-cancer Drug Therapy Details" (Part A2), "Prior Radiotherapy" (Parts A and B1), "Prior Anti-cancer Radiotherapy Details" (Part A2), and "Prior Cancer Surgery" (Parts A and B1) eCRF pages.
The summary of prior anti-cancer treatments and procedures will include the following:

- Number of subjects with at least one prior anti-cancer therapy
- Type of therapy: chemotherapy, hormonal therapy, immunotherapy, investigational therapy, or other
- Regimen number of prior anti-cancer therapy: neoadjuvant, adjuvant, regimen 1 to regimen 10, or unknown
- Best response to regimen from prior anti-cancer therapy: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE), or unknown
- Time elapsed since most recent anti-cancer therapy (months): summary statistics
- Duration of most recent anti-cancer therapy (months): summary statistics

Summary of prior radiotherapy will include the following variables:

- Number of subjects with at least one prior radiotherapy

- Location: brain, breast, lung, pleura, head and neck, esophagus, spinal cord, vertebrae, lymph nodes, bone, or other

The following listings of prior anti-cancer therapies will also be provided:

- Listings of prior anti-cancer therapies
- Listing of prior radiotherapies
- Listing of prior cancer surgeries (Parts A and B1 only)

These will include subject identifier and all the relevant data collected on the corresponding eCRF pages.

11.4 Other Baseline Characteristics

Analysis sets: SAF

Information on other baseline characteristics are collected from the "Vital Signs," "WHO Performance Status" (Parts A and B1), "ECOG Performance Status" (Part A2), "Primary Malignancy" (Parts A and B1), and "Disease History" (Part A2) eCRF pages. Disease characteristics collected at the pre-treatment evaluation visit will be summarized. Summary statistics will be presented for the following:

- Height at Baseline (cm): summary statistics
- Weight at Baseline (kg): summary statistics
- Body mass index (BMI) at baseline (kg/m^2): summary statistics
- Eastern Cooperative Oncology Group (ECOG) performance status: 0, 1, 2, 3, 4
- Summary of primary malignancy including the following:
    - Number of subjects with at least one primary malignancy
    - Primary malignancy: non-small cell lung cancer, small cell lung cancer, breast cancer, ovarian cancer, colorectal cancer, prostate cancer, or other
    - Histopathological grade of primary malignancy: G1/Well differentiated, G2/Moderately differentiated, G3/Poorly or undifferentiated, GX/Grade cannot be assessed, or other
    - TNM staging at diagnosis: T, N, M and associated sub-categories
    - Stage at diagnosis: IA, IB, IIA, IIB, III, IIIA, IIIB, IV, or other
    - Time elapsed since time of primary malignancy (months): summary statistics

Specifications for computation:

- BMI (kg/m^2) = weight(kg)/[height(m)]^2

Baseline characteristics with respect to vital signs, physical examinations, and hematology/biochemistry will be part of Section 15 (Safety Evaluation).

All relevant baseline characteristics data will also be presented in data listings.

12 Previous or Concomitant Medications/Procedures

Analysis sets: SAF

12.1 Previous Medications

Previous medications are medications, other than trial medications and pre-medications for trial drug, which started before first administration of trial drug (M4344 or carboplatin, as applicable), regardless of when dosing of the medication ended.

Previous medications will be summarized from the "Prior and Concomitant Medications" eCRF page. Anatomical Therapeutic Chemical (ATC)-2nd level and preferred term will be tabulated as given from the latest version of World Health Organization-Drug Dictionary (WHO-DD). In case multiple ATCs are assigned to a drug, all ATC-2nd level will be used for reporting. In case the date values will not allow to unequivocally allocate a medication to previous medication, the medication will be considered as previous medication.

All reported previous medications will be listed.

12.2 Concomitant Medications

Concomitant treatments are medications, other than trial medications, which are taken by subjects any time on-trial (on or after the first day of trial drug treatment for each subject) or within 30 days after last dose of trial drug.

Concomitant treatment will be summarized from the "Prior and Concomitant Medications" eCRF page. ATC-2nd level and preferred term will be tabulated as given from the WHO-DD current version. In case multiple ATCs are assigned to a drug, all ATC-2nd level will be used for reporting. In case the date values will not allow unequivocal allocation of a medication as a concomitant medication, the medication will be considered a concomitant medication.

Medications that started before the first dose of a trial drug (M4344 or carboplatin, as applicable) and continued after the first dose of a trial drug will be summarized as previous medications and separately as concomitant medications.

All relevant concomitant medication data will be listed.

12.3 Concurrent Procedures

All **concurrent procedures**, which were undertaken any time during the trial, will be summarized according to the eCRF page "Non-Pharmacological Treatment or Procedures" (Parts A and B1) or "Concomitant Procedures" (Part A2).

Concurrent procedures will be derived in the same way as concomitant medications. In case the date values will not allow unequivocal allocation of a procedure as a concurrent procedure, the procedure will be considered a concurrent procedure.

All concurrent procedure data will be listed, including flags for procedures that took place prior to, on or after the date of first dose of a trial drug (M4344 or carboplatin, as applicable), or within 30 days after the last dose of a trial drug (M4344 or carboplatin, whichever was taken last).

13 Treatment Compliance and Exposure

Analysis set: SAF

Dosing information is collected from the "Study Drug Administration: VX-803 – Clinic Dose" (Parts A and B1), "Study Drug Administration Home Dose: VX-803" (Parts A and B1), "Study Drug Administration: Carboplatin" (part B1 only), "End of Dosing" (Parts A and B1), "M4344 Time of Administration" (Parts A2), and "M4344 Administration Details" (Part A2) eCRF pages.

- Part A: M4344 is taken twice a week (on treatment days 1, 4, 8, 11, 15, and 18) of a 21-day treatment cycle.
- Part A2: M4344 is taken twice a day every day of a 21-day treatment cycle. Once daily dosing and additional cohorts with a planned drug holiday may also be explored.
- Part B1:
    - Carboplatin is administered by infusion on treatment day 1 of a 21-day treatment cycle
    - M4344 is taken on treatment days 2 and 9 of a 21-day treatment cycle. An additional cohort with one additional dose on day 5 may be explored.

Total number of administrations of M4344

Total number of administrations is calculated as the sum of administrations that a subject received across cycles where actual dose received is > 0 mg or the eCRF field for "Did the subject take the dose of VX-803?" on the "Study Drug Administration Home Dose: VX-803" is marked as "Yes" or if the eCRF field for "Was VX-803 administered?" on the "Study Drug Administration: VX-803 – Clinic Dose" is marked as "Yes."

Total number of infusions of carboplatin (part B1 only)

Total number of infusions is calculated as the sum of the actual number of infusions that a subject received across cycles, regardless of infusion delays, interruptions, or any other deviations from the protocol required schedules. An infusion is regarded to be administered if either the actual dose received is > 0 mg or the duration of the infusion is > 0 minutes.

Total cumulative dose

Total cumulative dose for a study drug is the sum of the actual dose amount that a subject receives across cycles.

- M4344: The total cumulative dose (mg) is the sum of the actual dose amount across all cycles. The individual actual dose (mg) is taken from the "Dose level administered (mg)" field from the "Study Drug Administration: VX-803 – Clinic Dose" and "Study Drug Administration Home Dose: VX-803 Part A" (Parts A and A2) or "Study Drug Administration Home Dose: VX-803 Part B/C" (Part B1) at each dosing day.

- Carboplatin: The total cumulative dose (mg) is the sum of the actual dose amount taken from "Scheduled dose to be administered in mg" if "Was entire dose administered?" is answered as "Yes" on the "Study Drug Administration: Carboplatin" eCRF page. If "Was entire dose administered?" is answered as "No" then the result from "If no, actual volume given (mL)" will be used

Total planned dose

For each study drug, total planned dose (mg) is calculated based on the initial planned dose as follows:

Initial planned dose on the first dosing day (mg/administration) × number of planned administrations/cycle × treatment duration (weeks) / 3 (weeks/cycle)

For each study drug the values for initial planned dose (mg/administration) and number of planned administrations/cycle are according to the planned dose level/schedule treatment group. The treatment duration is derived for each study drug at subject level, as defined below.

Duration of therapy

Treatment duration will be calculated differently based on the dosing days and frequency as follows:

Part A: During each 21 day cycle, M4344 is taken twice a week on treatment days 1, 4, 8, 11, 15, and 18. Duration of M4344 therapy is calculated as follows:

$$\text{Duration of M4344 (weeks)} = \left(\frac{date\ of\ last\ dose - date\ of\ first\ dose + 4}{7}\right)$$

Part A2: During each 21 day cycle, M4344 is taken twice a day, every day of the treatment cycle. Duration is calculated as follows:

$$\text{Duration of M4344 (weeks)} = \left(\frac{date\ of\ last\ dose - date\ of\ first\ dose + 1}{7}\right)$$

Part B1: During each 21 day cycle carboplatin is administered by intravenous infusion on treatment day 1 and M4344 is taken on treatment days 2 and 9. Duration of M4344 and carboplatin is calculated as follows:

$$\text{Duration of M4344 (weeks)} = \left(\frac{date\ of\ last\ dose - date\ of\ first\ dose + 14}{7}\right)$$

$$\text{Duration of Carboplatin (weeks)} = \left(\frac{date\ of\ last\ dose - date\ of\ first\ dose + 21}{7}\right)$$

Dose intensity

- M4344

$$\text{Dose intensity (mg/3 week)} = \left(\frac{\textit{Total Cumulative dose of M4344 (mg)}}{\textit{(duration (in weeks)/3)}}\right)$$

- Carboplatin

$$\text{Dose intensity (mg/3 week)} = \left(\frac{\textit{Total Cumulative dose of carboplatin (mg)}}{\textit{(duration (in weeks)/3)}}\right)$$

Relative dose intensity

The relative dose intensity (%) is calculated based on 3-week cycles for each study drug by dividing the dose intensity by the planned 3-weekly cumulative dose of the appropriate study drug.

The following summary tables will be provided:

- Duration of therapy (weeks) and by subgroups of ≤ 3 weeks, > 3 – 6 weeks, > 6 – 9 weeks, > 9 -12 weeks, > 12 weeks
- Total number of administrations
- Total number of infusions (for carboplatin in Part B1)
- Total cumulative doses (mg)
- Dose intensity (mg/3 week)
- Relative dose intensity (%) and by subgroups of < 60%, ≥ 60% - < 80%, ≥ 80% - < 90%, ≥ 90% - ≤110%, >110%

Dose reductions

Dose reduction is defined as less than 90% dose compliance *at a single dose*. Dose compliance is calculated, *for each dose received*, as the percentage of actual non-zero dose (mg) received with respect to the initial planned dose on Cycle 1 Day 1.

Minimum dose compliance will be derived for each subject (across all of the subject's non-zero doses received) as follows:

$$\text{Minimum dose compliance (\%)} = \left(\frac{\textit{100 x actual non–zero minimum dose amount (mg)}}{\textit{initial planned dose (mg)}}\right)$$

The minimum doses of the trial drugs will be derived per subject and categorized according to a < 50%, ≥ 50% - < 70%, ≥ 70% - < 90%, ≥ 90% level of the planned dose. Subjects with minimum dose compliance ≥ 90% are considered to have no dose reductions.

Therapy Delays

Therapy delays will be derived for M4344 and carboplatin in Parts A and B1 based on study drug administration date. Delays will be grouped into the following categories based on the deviation to the planned treatment administration day (relative to the previous treatment administration date):

- No delay (including 1-2 day delays)
- 3-8 day delay
- 9-15 day delay
- >= 16 day delay

All relevant trial drug exposure data will be presented in data listings, including dose reduction or delay reasons.

14 Efficacy Analyses

Analysis set: FAS

14.1 Analysis of Objective Response (Secondary Endpoint)

Best overall response (BOR) is defined as the best response per RECIST 1.1 across all time points until end of treatment or determination of PD using the Investigator reported overall response per time point and excluding assessments after further anticancer therapy. Clinical deterioration will not be considered as documented disease progression.

In the case of multiple dates of scans within the same tumor assessment, the earliest scan date will be used as the date of tumor assessment. The order to obtain the BOR is the following: CR, PR, SD, PD, NE. If a subject is missing the baseline tumor assessment and/or has no on-treatment tumor assessments, BOR will be NE.

When SD is believed to be the best response, it must also meet the protocol-specified minimum 6 weeks from the start of a trial drug. If the minimum time is not met, the subject's BOR depends on the subsequent assessments. For example, a subject who has SD at the first assessment, PD at the second assessment, and does not meet the minimum duration for SD, will have a best overall response of PD. The same subject lost to follow-up after the first SD assessment would be considered NE for BOR.

The confirmed BOR will also be analyzed. In this case, CR and PR need to be confirmed at a subsequent assessment, at least 4 weeks after initial overall response assessment of CR/PR. Table 2 summarizes the derivation rules described by Eisenhauer, et al (2009) for the BOR when confirmation from subsequent assessment is needed.

Table 2 BOR when confirmation of CR/PR is required

Overall response first time point	Overall response subsequent time point[a]	Confirmed BOR
CR	CR	CR
CR	PR	SD, if minimum criteria for SD duration met at first time point. Otherwise PD
CR	SD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD.
CR	PD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD.
CR	NE	SD, if minimum criteria for SD duration met at first time point. Otherwise NE.
PR	CR	PR
PR	PR	PR
PR	SD	SD, if minimum criteria for SD duration met at subsequent time point. Otherwise NE
PR	PD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD.
PR	NE	SD, if minimum criteria for SD duration met at first time point. Otherwise NE.
NE	NE	NE

[a] Subsequent time point is not necessarily the direct subsequent scan (e.g. PR-SD-PR will have PR as confirmed BOR).

Both confirmed and unconfirmed BOR will be summarized by tabulating the number and percentage of subjects with CR, PR, SD, PD, or NE as BOR.

A swimmer plot displaying key radiological milestones will be produced by dose group and study part. For each subject, the time from treatment start until end of follow-up will be represented (from treatment start to last date known to be alive or date of death). In addition, following information will be displayed: time to confirmed BOR (CR, PR or SD), time to progression, and status at the end of the follow-up (alive or dead).

Objective response rate (ORR) is defined as the proportion of subjects having achieved a BOR of PR or CR (summarizes as objective response [OR]) according to RECIST version 1.1. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

ORR will be summarized by visit along with the 2-sided 90% confidence interval (CI) using the Clopper-Pearson (1) method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

Disease control rate (DCR) is defined as the proportion of subjects having achieved a BOR of CR, PR, or SD according to RECIST version 1.1.

The DCR will be summarized by visit along with the 2-sided 90% CI using the Clopper-Pearson (1) method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

Tumor shrinkage will be summarized as the percent change in target lesions (sum of diameters of all target lesions for non-nodal lesion and short axis for nodal lesion) per time point from baseline. The tumor response will be based on the investigator assessment and derived as follows:

(Sum of target lesions at Week XX – sum of target lesions at baseline) / sum of target lesions at baseline x 100%

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of a subsequent anti-cancer therapy, derived as follows:

Minimum of ((sum of target lesions at Week XX – sum of target lesions at baseline) / sum of target lesions at baseline) x 100%

The percent change from baseline in target lesions per time point as well as other relevant information will be presented in a data listing.

A waterfall plot of maximum percent reduction from baseline in the sum of diameters of target lesions for each subject with measurable disease at baseline and at least one valid post-baseline assessment will be provided. The waterfall plot will show the bar for the subject with the largest positive change on the left, and the bar for the subject with the largest negative change on the right.

The listing of tumor assessments (including e.g. lesion number, description and location, type of lesion, imaging date, assessment method, diameter (mm), sum of diameter of target lesions (mm), BOR (confirmed and unconfirmed) will be provided by subject as recorded from the "Imaging Scan Disease Assessment - Target Lesions" (Parts A and B1), "Imaging Scan Disease Assessment - Non-Target Lesions", "Imaging Scan Disease Assessment - New Lesions" (Parts A and B1), "Imaging Scan – Overall Response Assessment" (Parts A and B1), "Sum of Diameters (Accoring to RECIST 1.1)" (Part A2), "Tumor Assessment – Target Lesions" (Part A2), "Tumor Assessment – Non-Target Lesions" (Part A2), and "Tumor Assessment – New Lesions" (Part A2) eCRF pages.

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as AEs, laboratory tests and vital signs.

15.1 Maximum Tolerated Dose (Primary Endpoint)

Analysis set: DLT analysis set

The maximum tolerated dose (MTD) is defined as the highest dose for a given schedule at which there is no more than 1 DLT in 6 participants. The DLT information will be based on the "Adverse Events" eCRF page where "Dose-limiting toxicity?" = Yes.

A summary table of DLTs during the first cycle of study treatment will be provided including the following information:

- Number of subjects with no DLT
- Number of subjects with one or more DLTs

A listing of DLTs will also be provided.

15.2 Adverse Events

Analysis set: SAF

Treatment emergent adverse events (TEAEs) are defined as those events with onset dates occurring within the on-treatment period as defined in Section 9.

All analyses described in Section 15.2 will be based on TEAEs if not otherwise specified.

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of trial treatment then the onset date will be replaced by the minimum of start of trial treatment and AE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the later case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off outcome of AE is ongoing at cut-off.

AEs will be summarized and presented based on the information collected from the "Adverse Events" eCRF page. Pretreatment AEs are defined as AEs that were reported or worsened after signature of the informed consent form up to the start of the trial drug (M4344 or carboplatin, as applicable).

- Related adverse events: adverse events with relationship to study treatment reported by the investigator and those of unknown relationship (i.e. missing data for relationship).
    - M4344: "Relationship to VX-803" (Parts A and B1) or "Relationship with M4344" (Part A2) = "Related", "Possibly Related", or missing
    - Carboplatin: "Relationship to carboplatin" = "Related", "Possibly Related", or missing
- Serious adverse events (SAEs): serious adverse events (serious adverse events = "Yes").
- AEs leading to permanent treatment discontinuation
    - M4344: "VX-803 Action Taken" (Parts A and B1) or "Action(s) taken with M4344" (Part A2) = "DrugWithdrawn"

- Carboplatin: "Carboplatin Action Taken" = "Drug Withdrawn"

- AEs leading to temporary treatment discontinuation
  - M4344: "VX-803 Action Taken" (Parts A and B1) or "Action(s) taken with M4344" (Part A2) = "Drug Interrupted"
  - Carboplatin: "Carboplatin Action Taken" = "Drug Interrupted"

15.2.1 All Adverse Events

AEs will be summarized by worst severity (according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0) per subject, using MedDRA preferred term as event category and MedDRA primary system organ class (SOC) body term as Body System category.

If an AE is reported for a given subject more than once during treatment, the worst severity and the worst relationship to trial treatment will be tabulated. In case a subject had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

The following overall frequency tables will be prepared by dose group and overall. In addition the tables will be provided by PT and primary SOC in alphabetical order:

- Any TEAE
- Any trial drug related TEAEs*
- Any serious TEAEs
- Any non-serious TEAEs
- Any trial treatment related serious TEAEs*
- Any TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Any trial drug related TEAE by NCI-CTCAE severity grade (≥3, ≥4)*
- Any TEAEs leading to death (TEAEs with Grade 5 or outcome "fatal" if grade 5 not applicable)
- Any trial drug related TEAEs leading to death (TEAEs with Grade 5 or outcome "fatal" if grade 5 not applicable)*

Tables annotated by * will be summarized as follows:

- Parts A and A2 with a summary for M4344
- Part B1: summaries for M4344, carboplatin, and M4344/carboplatin

The listing for all AEs (whether treatment-emergent or not) will include all the data fields as collected on the "Adverse Events" eCRF page.

Clinical trial.gov and EudraCT -requirements

Summary tables for non- serious adverse events excluding SAEs applying frequency threshold of 5% will be provided by study part. The non-serious AEs are not restricted to non-serious TEAEs.

15.2.2 Adverse Events Leading to Treatment Discontinuation

The following overall frequency tables based on AE actions will be prepared. In addition, summaries in terms of PT and primary SOC will be provided.

Temporary discontinuation

- Any TEAEs leading to temporary discontinuation of M4344 (Parts A, A2, and B1)
- Any TEAEs leading to temporary discontinuation of carboplatin (Part B1)
- Any TEAEs leading to temporary discontinuation of at least one trial drug (Part B1)
- Any TEAEs leading to temporary discontinuation of both trial drugs (Part B1)
- Any trial drug related TEAEs leading to temporary discontinuation of M4344 (Parts A, A2, B1)
- Any trial drug related TEAEs leading to temporary discontinuation of carboplatin (Part B1)

Permanent discontinuation

- Any TEAEs leading to permanent discontinuation of M4344 (Parts A, A2, and B1)
- Any TEAEs leading to permanent discontinuation of carboplatin (Part B1)
- Any TEAEs leading to permanent discontinuation of at least one trial drug (Part B1)
- Any TEAEs leading to permanent discontinuation of both trial drugs (Part B1)
- Any trial drug related TEAEs leading to permanent discontinuation of M4344 (Parts A, A2, B1)
- Any trial drug related TEAEs leading to permanent discontinuation of carboplatin (Part B1)

Dose reduction

- Any TEAEs leading to dose reduction of M4344 (Parts A, A2, and B1)
- Any TEAEs leading to dose reduction of carboplatin (Part B1)
- Any TEAEs leading to dose reduction of at least one trial drug (Part B1)
- Any TEAEs leading to dose reduction of both trial drugs (Part B1)
- Any trial drug related TEAEs leading to dose reduction of M4344 (Parts A, A2, B1)
- Any trial drug related TEAEs leading to dose reduction of carboplatin (Part B1)

15.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.3.1 Deaths

All deaths, deaths within 30 days after last dose of trial drug, and deaths within 60 days after first dose of trial drug will be tabulated based on information from the "End of Dosing" (Parts A and B1), "M4344 Administration Details" (Part A2), "Long-Term Follow-Up" (Parts A and B1), and "Death" (Part A2) eCRFs.

- Number of Deaths
- Number of Deaths within 30 days after last dose
- Number of Deaths within 60 days after first dose

In addition, data relevant to subject deaths will be provided in an individual subject data listing together with selected dosing information (date of first / last administration of applicable trial drug). The death listing will also include the following:

- AEs with fatal outcome (list preferred terms of AEs with outcome=fatal),
- Flag for death within 30 days of last trial treatment (for each drug)
- Flag for death within 60 days of first trial treatment (for each drug)

15.3.2 Serious Adverse Events

Please refer to Section 15.2.1 for serious adverse event (SAE) related outputs. The listings of SAEs will also be provided with relevant information such as AE SOC/PT, start/stop date, toxicity grade, relationship to trial drug, action taken with study treatment, and outcome.

15.3.3 Other Significant Adverse Event

Safety summaries will be performed for special adverse event categories on "Blood bilirubin increased", "ALT/AST increased", and "Nausea/Vomiting". Special aadverse event categories will be summarized by category and PT. The given terms constitutes of pooled MedDRA PTs.

Categories are defined as follows:

- Blood bilirubin increased : Bilirubin conjugated abnormal, Bilirubin conjugated increased, Bilirubin urine present, Bilirubinuria, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, CSF bilirubin positive, Hyperbilirubinaemia and Urine bilirubin increased

- ALT/AST increased: Standardised MedDRA Queries (SMQ) – Narrow scope – Drug related hepatic disorders – comprehensive search

- Nausea/Vomiting: Higher Level Term (HLT) of Nausea and vomiting symptoms

15.4 Clinical Laboratory Evaluation

Analysis set: SAF

All statistical analyses of laboratory values will be performed using SI units.

Laboratory results will be classified according to the latest version of NCI-CTC as provided by the central or local laboratory. Additional laboratory results that are not part of NCI-CTC will be presented according to the categories: below normal limits, within normal limits and above normal limits (according to the laboratory normal ranges). For a complete list of laboratory tests to be analyzed, please refer to Appendix I.

The worst on-treatment grade will be summarized considering only subjects with on-treatment laboratory samples: Laboratory tests by NCI-CTC grade (0, 1, 2, 3, 4, any).

Quantitative data will be examined for trends using descriptive statistics (mean, StdDev, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline to each visit over time. The changes computed will be the differences from baseline. Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, and High). The number of subjects with clinical laboratory values below, within, or above normal ranges at baseline compared to endpoint will be tabulated for each test by treatment. Shift tables of baseline versus endpoint (as well as the worst value at any on-treatment visit) will be presented. Abnormalities classified according to NCI-CTCAE toxicity grading will be described using the worst grade.

NCI-CTC grades available:

- Number and percentage of subjects with any, NCI-CTC grade 0, 1, 2, 3, 4, 3 or 4 laboratory abnormalities under treatment – (worst case)
- Shifts in toxicity grading from baseline NCI-CTC grade to worst on-treatment NCI-CTC grade

The highest NCI-CTC grade during the on-treatment period is considered as the worst grade for the summary.

NCI-CTC grades not available:

Number of subjects with shifts from baseline normality to post-baseline normality based on worst on-treatment value

The normality categories will be produced based on the normal range for all hematology and blood chemistry parameters as follows:

- Baseline: Low/Normal/High/Missing/Overall
- Worst on-treatment: Low/Normal/High/Missing/Overall

Normal category includes low values for high parameters and high values for low parameters.

Subjects without post baseline laboratory samples will be excluded from analyses with respect to values after the baseline.

The following figures and tables will be provided for each test mentioned above:

- Boxplots of laboratory values at baseline and by on-treatment time point
- Boxplots of the absolute change from baseline by on-treatment time point
- A plot of peak on-treatment alanine aminotransferase (ALT) versus peak on-treatment total bilirubin, both relative to the upper limit of normal (ULN) will be provided. This eDISH plot (evaluation of drug-induced serious hepatotoxitiy) will have reference lines at 3×ULN for ALT and at 2×ULN for total bilirubin.

Boxplots for laboratory parameters where toxicity grades are defined based on the ratio of the parameter values and the ULN will not be displayed using the unit of measurement but instead using the ratio of the measured value over ULN. This comprises alkaline phosphatase (ALP), ALT, aspartate aminotransferase (AST), bilirubin, creatinine, and lactate dehydrogenase (LDH).

Coagulation parameters

Coagulation parameters are only assessed at the screening visit, so these will be listed.

Urinalysis

All urinalysis and microscopic analysis will be presented in listings only.

For all tests not mentioned above but present in the clinical data, a listing with the number of subjects with at least one result for the respective test will be provided. This listing will include data from scheduled and unscheduled time points.

Individual subject laboratory values that are outside the normal range will be included in a separate data listing along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will be flagged.

- Listing of laboratory values by category (hematology, serum chemistry, urinalysis, and coagulation)
- Listing of abnormal laboratory values

In addition, a listing displaying parameters with at least one value with grade ≥ 3 will be provided. For each subject, only parameters where at least one value has grade ≥ 3 will be displayed (all visits for the corresponding parameter will be displayed in the listing).

15.5 Vital Signs

Analysis set: SAF

Vital sign values and their changes from baseline will be summarized for each scheduled visit on treatment.

The changes of vital sign measurements from baseline to most extreme post-baseline on-treatment change after start of first dose of trial drug will be presented. The categorization of maximum changes is grouped as follows:

Vital Sign Baseline Category	Change from Baseline Category
Body temperature increase	< 1°C , 1-<2°C , 2-<3°C, ≥ 3 °C
Heart rate increase from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Heart rate decrease from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
SBP increase from baseline <140 mmHg; ≥ 140 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from baseline <140 mmHg; ≥ 140 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP increase from baseline <90 mmHg; ≥ 90 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP decrease from baseline <90 mmHg; ≥ 90 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
Respiration rate increase from baseline <20 bpm ; ≥ 20 bpm	≤5 bpm, >5 – 10 bpm, >10 bpm
Respiration rate decrease from baseline <20 bpm ; ≥ 20 bpm	≤5 bpm, >5 – 10 bpm, >10 bpm

The following summaries will be prepared for vital sign parameters as grouped above considering only subjects with on-treatment values:

- Maximal Shifts (changes in categories)
- Listing of highest change per subject

An additional subject data listing will present all changes from baseline reported in the highest categories.

15.6 Other Safety or Tolerability Evaluations

Analysis set: SAF

ECG

Descriptive statistics of observed values and changes from baseline at each scheduled visit will be provided for ECG measures of PR interval, QRS interval, QT interval, QTc interval (derived using Fridericia's correction method), and HR.

The Fridericia's Correction (QTcF) is derived as follows:

Fridericia's Correction (QTcF) $QTc_f = \frac{QT}{\sqrt[3]{RR}}$

where: RR = RR-interval measured in seconds.

Shifts from normal baseline values to abnormal on-treatment results will be summarized. Listings of 12-lead ECG data will also be provided with all relevant information such as visit, date/time of assessment, measurement, and results.

- Shifts from baseline to worst on-treatment value
- Listing of ECG results

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Population: PK Analysis Set

Non-compartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® version 6.4, or higher (Pharsight Corporation, a Certara Company, Princeton, New Jersey). Phoenix® WinNonlin® or the statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary North Carolina), Windows version 9.2 or higher may be used to produce tables, listings and figures, where appropriate.

Pharmacokinetic parameters will be calculated using standard non-compartmental methods and the actual administered dose and actual sampling times.

For each subject with PK data, PK parameters will be calculated for M4344 and summarized by dose and day according the following groups:

- M4344 alone in Part A
- M4344 alone in Part A2 BID
- M4344 alone in Part A2 QD if applicable
- M4344 in combination after carboplatin in Part B1

The following PK parameters will be evaluated for each of the groups:

C_{max}	Maximum observed concentration
C_{max}/Dose	The Dose normalized maximum observed concentration. Normalized using the actual dose, and the formula C_{max} /Dose.
C_{trough}	The concentration observed immediately before next dosing.
AUC_{0-t}	Area under the concentration-time curve (AUC) from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification.

AUC_{0-t}/Dose	The Dose normalized AUC_{0-t}. Normalized using the actual dose, and the formula AUC_{0-t} /Dose.
t_{max}	Time to reach the maximum observed concentration C_{max}
t_{last}	Time of last measurable conentration
$AUC_{0-\tau}$	Area under the concentration-time curve (AUC) over a dosing interval.
$AUC_{0-\tau}$ /Dose	The Dose normalized $AUC_{0-\tau}$.
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last} , as estimated using the linear regression from λ_z determination. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\lambda_z$
$AUC_{0-\infty}$/Dose	The Dose normalized $AUC_{0-\infty}$. Normalized using actual dose, and the formula $AUC_{0-\infty}$ /Dose.
AUC_{extra}	Percentage of $AUC_{0-\infty}$ obtained by extrapolation (AUC_{extra}), calculated by $(1 - [AUC_{0-t}/AUC_{0-\infty}])\times 100$.
λ_z	Terminal first order elimination rate constant
$t_{½}$	Apparent terminal half-life, $t_{½} = \ln 2/\lambda_z$
V_z/F	Apparent predicted volume of distribution during the terminal phase. $V_z = Dose/(AUC_{0-\infty}*\lambda_z)$
$R_{acc(Cmax)}$	Accumulation ratio for C_{max}, calculated as $C_{max\ D8}/C_{max\ D1}$. (Parts A and A2)
$R_{acc(AUC0-\infty)}$	Accumulation ratio for $AUC_{0-\infty}$, calculated as $AUC_{0-\infty\ D8}/AUC_{0-\infty\ D1}$. (Part A)
$R_{acc(AUC0-t)}$	Accumulation ratio for AUC_{0-t}, calculated as AUC_{0-tD8}/AUC_{0-tD1}. (Part A)
$R_{acc(AUC0-\tau)}$	Accumulation ratio for $AUC_{0-\tau}$, calculated as $AUC_{0-\tau D8}/AUC_{0-\tau D1}$. (Part A2)
$R_{acc(AUC)}$	Accumulation ratio for AUC, calculated as $AUC_{0-\tau D8}/AUC_{0-\infty\ D1}$. (Part A2)
CL/F	The apparent total body clearance. $CL/F = Dose/ AUC_{0-\infty}$.
CLss/F	The apparent total body clearance at steady state. $CLss/f = Dose/ AUC_{0-\tau}$. (Part A2)
Ae_{0-24}	The cumulative amount excreted from time zero (= dosing time) to the end of the current collection interval after dosing. Amount_Recovered = Σ(Concentration * Volume).
Ae_{0-24}%	The cumulative percentage of dose excreted from time zero (= dosing time) to the end of the current collection interval after dosing. Percent_Recovered = 100*Amount_Recovered/Dose.
CL_R	The renal clearance of drug: $CL_R = Ae_{0-24}/AUC_{0-24}$.

Additional parameters may be calculated in order to further characterize the PK of M4344 and/or its metabolites.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression to determine λ_z
- Number of data points included in the log-linear regression analysis to determine λ_z
- Goodness of fit statistic (Rsq) for calculation of λ_z

The calculation of the AUC will be performed using the mixed log-linear trapezoidal method. The actual time of blood sampling (14 significant digits or the SAS format Best12) will be used for PK parameter calculation. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. For AUC_{0-24}, if the actual sampling time at time 24 hours is not equal to the scheduled observation time, AUC_{0-24} will be calculated based on estimated concentration at the scheduled time and not the concentration at the actual observation time. Otherwise, there will be no further imputation of missing data.

Predose samples will be considered as if they had been taken simultaneously with the administration, and will be assigned a time of 0 hours. The same applies to the relevant pre-dose sample (i.e. trough sample) for assessment of multiple dose pharmacokinetics. Concentrations below the lower limit of quantification (LLOQ), will be taken as zero.

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin best fit methodology will be used as standard. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any concentrations <LLOQ which occur after the last quantifiable data point should not be used.

AUC_{extra} should be less than 20%, the coefficient of correlation (R^2) should be $\geq$0.8000 and the observation period over which the regression line is estimated should be at least twofold the resulting $t_{1/2}$ itself. If these criteria are not met, then the rate constants and all derived parameters (e.g. λz, $t_{1/2}$, $AUC_{0-\infty}$ AUC_{extra}, Vz/F, CL/F, CLss/F) will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags will be included in the study specific SDTM.

The following Listings, Tables and Figures will be provided:

Tables/Listings

- Individual plasma M4344 and metabolite concentrations and summary statistics by analyte, group, dose group, and day

- Individual cumulative urine M4344 and metabolite amounts and summary statistics by analyte, group and dose group
- Individual urine M4344 and metabolite amounts and summary statistics by analyte, sampling interval, group and dose group
- Individual plasma M4344 and metabolite through concentrations and summary statistics by analyte, group, dose group, and day
- Individual plasma and urine M4344 and metabolite Pharmacokinetic parameters and summary statistics by Group, dose group, and day
- Individual diagnostic M4344 and metabolite PK parameters
- Individual Plasma M4344 and metabolite Concentrations, actual Date/Time of sample collection, scheduled time, time deviation (by Group, dose group, and day)
- Individual urine M4344 and metabolite Concentrations, actual Date/Time of start and end of sample collection, scheduled time, urine volume (by Group, dose group, and day)
- The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

Figures

- Individual M4344 and metabolite concentration-time profiles; linear and Semi-Log Scale (overlaid by Day)
- Individual M4344 and metabolite concentration-time profiles by Group, dose group, and day; linear and Semi-Log Scale
- Median M4344 and metabolite concentration-time profiles by Group, dose group, and day; linear and Semi-Log Scale (n>= 3)
- Median M4344 and metabolite concentration-time profiles; linear and Semi-Log Scale (overlaid by day) (n>= 3) by group and dose group
- Boxplots for M4344 and metabolite PK parameters (e.g. $AUC_{0-\infty}$/Dose, AUC_{0-t}/Dose, C_{max}/Dose)-vs dose by Group and day
- Boxplots for M4344 and metabolite PK parameters (e.g. $AUC_{0-\infty}$/Dose, AUC_{0-t}/Dose, C_{max}/Dose)-vs day by group.
- Scatterplots for M4344 and metabolite PK parameters (e.g. $AUC_{0-\infty}$/Dose, AUC_{0-t}/Dose, C_{max}/Dose)-versus dose by day and Group, (overlaid with medians)
- Observed Log Racc(C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) vs dose for Part A. with reference line at Racc=1

All descriptive summaries of PK data will be performed using the PK Analysis Set.

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[redacted]

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17 References

1. Clopper, C. J., & Pearson, E. S. (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika, 26, 404–413.

18 Appendices

Appendix I Safety Laboratory Test Panels

Serum Chemistry[a]	Hematology[a]	Urinalysis[a,d]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen/Urea[b]	Erythrocytes	Nitrite
Creatinine	Mean corpuscular hemoglobin	Urobilinogen
Sodium	Mean corpuscular hemoglobin concentration	Urine protein
Potassium	Mean corpuscular volume	pH
Calcium	Platelets	Urine blood
Chloride	Leukocytes	Specific gravity
Magnesium	Differential (absolute and/or percent[e]):	Urine ketone
Bicarbonate	Eosinophils	Urine bilirubin
Inorganic phosphate	Basophils	Urine glucose
Total bilirubin	Neutrophils	
Direct bilirubin	Lymphocytes	
Total protein	Monocytes	
Albumin	**Coagulation studies[a,c]**	
Creatine kinase[c]	Activated partial thromboplastin time	
Alkaline phosphatase	Prothrombin time	
Aspartate aminotransferase	Prothrombin time International Normalized Ratio	
Alanine aminotransferase		
Lactate dehydrogenase		
Uric acid[c]		
Thyroid stimulating hormone[c]		

a. Labs will be performed at Screening (Protocol Table 1) and at specified times during the Treatment and Follow-up Period (Protocol Tables 2, 3, 4, and 5)
b. If blood urea nitrogen cannot be collected, urea may be substituted.
c. Creatine kinase, uric acid, thyroid stimulating hormone, and coagulation parameters will only be tested at Screening.
d. If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed and results provided for leukocytes, erythrocytes, crystals, bacteria and casts.
e. Per local laboratory availability.

ELECTRONIC SIGNATURES

Document: ctp-ms201922-0001-iap-main-text-body-v1

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Business Approval	01/17/2019 12:40:06
PPD	Task Completed (Approval eSign): Approved	Business Approval	01/21/2019 10:51:03

Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS201922-0001
Title	An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of M4344 (formerly VX-803) as a Single Agent and in Combination with Cytotoxic Chemotherapy in Participants with Advanced Solid Tumors
Study Phase	I
Investigational Medicinal Product(s)	M4344
Clinical Study Protocol Version	29 January 2020 / Version 8.0

Integrated Analysis Plan Author

Coordinating Author	
PPD , Merck	PPD
Function	**Author(s) / Data Analyst(s)**
PPD	PPD

Integrated Analysis Plan Date and Version	14Apr2021 / Version 1.0

Integrated Analysis Plan Reviewers

Function	Name
PPD , PPD	PPD
PPD , Merck	
PPD , Merck	
Medical Responsible, Merck	
PPD , Merck	

Approval Page

Integrated Analysis Plan: MS201922-0001

An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of M4344 (formerly VX-803) as a Single Agent and in Combination with Cytotoxic Chemotherapy in Participants with Advanced Solid Tumors

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within ELDORADO via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADME	Absorption, Distribution, Metabolism, and Elimination
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COVID-19	2019 Novel Coronavirus Disease
CR	Complete Response
(e)CRF	(electronic) Case Report Form
aCSR	Abbreviated Clinical Study Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
ICH	International Conference on Harmonization
IAP	Integrated Analysis Plan
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
nd	Not Done
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease or Protocol Deviation or Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model

SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	14Apr2021	PPD	N/A: First version

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the analysis of data collected for protocol MS201922-0001 – Part C.

The study was prematurely terminated by the sponsor and an abbreviated study report will be written.

Results after the database lock for the final analysis will be included in the abbreviated Clinical Study Report (aCSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the aCSR but not identified in this prospective IAP will be clearly identified in the aCSR.

The IAP is based on Section 8 (Statistics) of the study protocol and protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol and protocol amendments.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To evaluate the efficacy of M4344 in terms of confirmed objective response.	Objective response according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as assessed by Investigator	Section 14.1
To evaluate the safety and tolerability of M4344	Occurrence of: • treatment-emergent adverse events (TEAEs) and treatment-related TEAEs, as per NCI-CTCAE v5.0 • Laboratory abnormalities • Clinically significant abnormal vital signs • Clinically significant abnormal ECGs	Section 15
Secondary		
To evaluate the duration of response for subjects receiving M4344	Duration of response according to RECIST v1.1, as assessed by Investigator	Section 13
To evaluate the overall survival (OS) for subjects receiving M4344	OS	Section 14.3
To evaluate the progression-free survival (PFS) for subjects receiving M4344	PFS according to RECIST v1.1 as assessed by Investigator	Section 14.4
To evaluate the PK of M4344	No PK parameter estimates of M4344 will be provided.	Section 16.1
CCI [redacted]		

6 Overview of Planned Analyses

Study Part C was to explore potential antitumor efficacy and aimed to confirm the safety and tolerability of single agent M4344. Parts C1-C3 planned to enroll participants whose tumors harbored loss-of-function mutations in one or more of the following genes ARID1A (C1), ATRX and/or DAXX (C2), ATM (C3).

The study Part C was stopped after 13 subjects were enrolled; and therefore, only a final analysis will be conducted. Due to the low number of cohorts and participants, it was decided to reduce the scope of the TLFs. Data will not be summarized per Part. Where appropriate, only listings will be provided. Details are provided in the respective sections.

Statistical analyses will be performed using CDISC SDTM data. These SDTM data contain as clean as possible eCRF data, as well as external data, including laboratory data, biomarker data, and electrocardiogram data. A data review meeting will be held prior to the database lock. In addition, no database can be locked until this IAP has been approved.

6.1 Interim Analyses

No interim analysis will be performed as this study was stopped prematurely.

6.2 Final Analysis

All final, planned analyses identified for Part C in the Clinical Trial Protocol and in this IAP will be performed after the last participant last visit for Part C.

7 Changes to the Planned Analyses in the Clinical Study Protocol

Only analyses of Part C of the trial are covered in this IAP. Analyses on other parts of the trial are described in separate documents.

Due to the premature discontinuation of study Part C and the low number of subjects enrolled, the scope of the statistical analysis is reduced. The table in Section 5 indicates which objectives were not addressed.

8 Analysis Populations and Subgroups

8.1 Definition of Analysis Populations

Screening Analysis Population (SCR)

The Screening analysis population includes all participants who signed the informed consent.

Full Analysis Set (FAS)/ Safety Analysis Set (SAF)

The full analysis set (FAS) will include all participants who received at least one dose of study drug. All analyses will be performed on the FAS/SAF population, or a subset thereof, as specified for a given analysis.

8.2 Subgroup Definition and Parameterization

No subgroup analyses will be performed.

9 General Specifications for Data Analyses

This section describes any general specifications to be used for the analysis. Subsequent sections may include specifications unique to that analysis, which may override the broader instructions given here.

9.1 Analysis groups

There will be 1 treatment group labelled as "M4344 250mg QD – Part C".

9.2 Presentation of Continuous and Qualitative Variables:

Continuous variables will be summarized using descriptive statistics, i.e., number of participants with non-missing values (n), mean, median, standard deviation, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum.

Qualitative variables and rates will be summarized by frequency counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the sample size of the analysis set of interest. Counts of missing observations will be included in the denominator and presented as a separate category.

If confidence intervals are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

Missing statistics, e.g. when they cannot be calculated, will be presented as "nd". For example, if n=1, the standard deviation cannot be computed and will be presented as "nd".

9.3 Pooling of Centers:

In order to provide overall estimates of treatment effects, data will be pooled across sites. The "site" factor will not be considered in statistical models or for subgroup analyses due to the high number of participating sites in contrast to the anticipated small number of participants treated at each site.

9.4 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to the first study treatment administration will be used as the baseline measurement.

If an assessment time is missing, or the study treatment start time is missing, if the assessment is planned to be performed before treatment per protocol and is performed on the same day as the start of treatment, it will be assumed that it was performed prior to treatment start. Unscheduled assessments performed on the day of study treatment are assumed to have been performed after the start of treatment if the time of the assessment or treatment start are otherwise missing.

Absolute and percent changes from baseline are defined as:

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.5 Unscheduled visits

Data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted.

9.6 Study Day

Study Day is defined relative to the date of the first administration of study treatment. Study Day 1 is defined as the day of start of study treatment; the day prior is Study Day -1 (i.e., no Study Day 0 is defined).

9.7 Definition of Duration and 'Time Since' Variables

Durations in days will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of randomization + 1) if not otherwise specified.

The time since an event (e.g., time since first diagnosis) will be calculated as reference date minus date of event.

9.8 Conversion Factors

The following conversion factors will be used to convert days into months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

9.9 Date of Last Contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date prior to or at the data cut-off date among the following:

- All participant assessment dates (blood draws [laboratory, PK], vital signs, performance status, ECG, tumor assessments, quality of life assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.
- AE start and end dates
- Date of follow-up, if participant is known to be alive, as collected on the 'Follow-up' eCRF page

- Study drug start and end dates
- Date of study discontinuation if reason for discontinuation is not "Lost to follow-up"

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status, such as the date a blood sample was processed, will not be used.

9.10 Definition of On-treatment Period

The on-treatment period is defined as the time from the first dose of study treatment day to the last administration day of study treatment + 30 days, the data cutoff day, or death, whichever occurs first.

9.11 Imputation of Missing Data

If performed, details of imputation are specified below. If not otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings, imputed values will be presented, and imputed information will be flagged.

9.11.1 Incomplete Disease History Dates

Incomplete dates for disease history (e.g. initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is the same as the year of the first study treatment, the month and day will be imputed as January 1st.

If the date is completely missing, no imputation will be performed.

9.11.2 Incomplete Adverse Events Dates

Incomplete AE-related dates are imputed for use in determining whether the AE is considered Treatment-Emergent. Incomplete dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015. If the end date or resolution date indicates that the AE has stopped before start of treatment, this date will be used for imputation instead of start of treatment date.

- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if only the day is missing), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date.

In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off this date will be kept.

9.11.3 Incomplete Concomitant Medication and Concurrent Procedure Dates

For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Rules presented in Table 2 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure, based on the stopping rules presented in Table 1.

Table 1 Stopping rules for medication/procedure end dates

End date of medication/procedure			Stopping rule
Day	Month	Year	
UNK	UNK	UNK	After treatment start (ongoing)
UNK	UNK	< Treatment start (year)	Before treatment start
UNK	UNK	>= Treatment start (year)	After treatment start
UNK	< Treatment start (month and year)		Before treatment start
UNK	>= Treatment start (month and year)		After treatment start
< Treatment start (complete date)			Before treatment start
>= Treatment start (complete date)			After treatment start

UNK = Unknown

Table 2 Rules to define previous and/or concomitant medication

Start date of medication/procedure			Stopping rule (see Table 1)	Medication/procedure
Day	Month	Year		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	<= Treatment start (year)	Before treatment start	Previous
UNK	UNK	<= Treatment start (year)	After treatment start	Previous and concomitant

Start date of medication/procedure			Stopping rule (see Table 1)	Medication/procedure
Day	Month	Year		
UNK	UNK	> Treatment start (year) and <= Treatment end + 28 days (year)	After treatment start	Concomitant
UNK	<= Treatment start (month and year)		Before treatment start	Previous
UNK	<= Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and <= Treatment end + 28 days (month and year)		After treatment start	Concomitant
<= Treatment start (date)			Before treatment start	Previous
<= Treatment start (date)			After treatment start	Previous and concomitant
> Treatment start (date) and <= Treatment end + 28 days (date)			After treatment start	Concomitant

UNK = Unknown

9.11.4 Incomplete End Date of Study Treatment Date

- In case the last date of study drug is missing or incomplete the date of last administration of study drug will be taken from the treatment termination eCRF pages.
- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, study treatment should be considered to be ongoing and the cut-off date should be used in the analysis as the last dosing date.
- If the last date of study drug is completely or partially missing and there is either an End of Treatment eCRF page OR a death date available (within the cut-off date) then imputed last dose date is:
  - = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)
  - = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)
  - = min (EOT date, death date), for all other cases

9.11.5 Incomplete Death Date

For the purpose of survival analyses partially missing death dates will be imputed as follows:

If only the day is missing, the death date will be imputed to the maximum of the day after the date of last contact and the 15th day of the month.

Otherwise it will not be imputed.

Imputation of Death Date is used for survival analyses only. In the death listings, non-imputed data will be presented.

9.11.6 Incomplete Tumor Assessment Dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of the complete investigation dates (e.g. X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be imputed as the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

9.11.7 Incomplete Subsequent Anti-Cancer Therapy Dates

Incomplete dates for start date of subsequent anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for some efficacy analyses.

- If only day is missing, it will be imputed as the last day of the month unless the end date of subsequent anti-cancer therapy is before that date. In that case, the incomplete anti-cancer therapy start date will be imputed as the end date of the anti-cancer therapy.
- If both day and month are missing, no imputation will be performed.
- Incomplete subsequent anti-cancer therapy stop dates will not be imputed.

9.12 Analysis software

All analyses will be performed using SAS® Software version 9.4 or higher.

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study treatment/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

The number and percentage of participants in each of the below disposition categories will be presented by analysis group and total, where applicable. Percentages will be presented with respect to the number of treated participants

- Total number of participants screened (i.e. participants who gave informed consent)
- Number of participants who discontinued from the study prior to treatment overall and grouped by the main reason (e.g. failure to meet inclusion or exclusion criteria, withdrawal of consent)
- Number and percentage of treated participants.
- Number and percentage of treated participants who discontinued the study treatment (overall and by primary reason)
- The end of study status will be summarized by:
    - Number and percentage of participants who completed or prematurely discontinued the study, grouped by main reason

Additionally, the number of participants screened, and enrolled in each analysis population will be provided overall, by region, by country within region, and by site.

A listing of pertinent participant disposition information for each participant will be provided.

10.2 Protocol Deviations

Analysis Set: FAS/SAF

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations include:

- Participants enrolled and dosed on the study who did not satisfy enrolment criteria
- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive an excluded concomitant medication
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Deviation from Good Clinical Practice (GCP)
- Any other protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

IPDs will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting, at the latest.

All protocol deviations will be documented in the Clinical Trial Management System (CTMS). All IPDs will be included in SDTM datasets whether identified through site monitoring, medical review or programming.

A listing will be provided for all protocol deviations and the subset of protocol deviations that were attributed to the impact of the COVID-19 pandemic will be identified in this listing.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Analysis Set: FAS/SAF

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Demography eCRF page and the baseline vital signs assessment:

- Sex: Male, Female
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not Collected at this Site
- Ethnic origin: Hispanic or Latino/Not Hispanic or Latino
- Ethnic origin: Japanese or Not Japanese
- Age (years)
- Age categories:
  - < 65 years,
  - ≥ 65 years
    - 65-74
    - 75-84
    - ≥ 85 years
- Pooled Region:
  - North America
  - Europe
- BSA (m^2) at Baseline
- Weight (kg)
- BMI (kg/m^2) at Baseline
- Eastern Cooperative Oncology Group (ECOG) Performance status (0,1,2,3,4)

Specifications for computation:

- Age [years]
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day for at least one date, but month and year available for both dates:
  - For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
  - In case of missing month for at least one date, but year available for both dates:

  For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used

  The integer part of the calculated age, without rounding, will be used for reporting purposes.
- BSA $[m^2] = \sqrt{\frac{height[cm] \times weight[kg]}{3600}}$
- BMI $[kg/m^2] = \frac{weight\,[kg]}{height[cm]^2} \times 10000$
- Site codes will be used for the determination of the participant's geographic region.

11.2 Medical History

Analysis Set: FAS/SAF

Participant medical history will be summarized from the "Medical History" eCRF page, using the most recent MedDRA version available. A listing of medical history data by participant will include all the relevant data fields as collected on the "Medical History" CRF page.

11.3 Other Baseline Characteristics

Analysis Set: FAS/SAF

11.3.1 Disease History

The following information on disease characteristics collected at baseline will be listed:

- Site of primary tumor
- Tumor mutation, i.e. ARID1A, ATX, DRXX, and/or ATM
- Time since initial cancer diagnosis
- Time since date of documented, locally advanced, inoperable or metastatic disease diagnosis
- TNM staging at initial diagnosis

- TNM staging at study entry
- ECOG performance status at baseline

11.3.2 Prior Anti-Cancer Therapy

The prior anti-cancer therapies are collected under the "Prior Anti-Cancer Therapy", "Prior Anti-Cancer Radiotherapy" and "Prior Anti-Cancer Surgery" eCRF pages.

The listings of prior anti-cancer treatments and procedures will be provided as follows. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of prior anti-cancer drug therapies
- Listing of prior anti-cancer radiotherapy
- Listing of prior anti-cancer surgeries.

12 Previous or Concomitant Medications/Procedures

Analysis Set: FAS/SAF

Concomitant medications are medications, other than study treatment, which are taken by participants any time during the On-treatment Period.

Previous medications are medications, other than study treatment and pre-medications for study treatments, which started before the first administration of study treatment.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date. Please refer to Section 9.12.3 for details on the classification of medications with partial start and end dates.

Concomitant and previous medication details captured on the "Prior and Concomitant Medications" eCRF page will be included in a listing, along with a flag to indicate whether the medication was identified as a previous or concomitant medication.

All relevant details of **Concurrent procedures** captured on the CRF page "Non-pharmacological Treatments or Procedures" will be listed.

13 Study Treatment: Compliance and Exposure

Analysis Set: FAS/SAF

All dosing calculations and summaries will be based on "M4344 Administration Details" CRF page. During each 21-day cycle, M4344 is taken once a day, every day of the treatment cycle.

Total number of administrations of M4344

Total number of administrations is calculated as the sum of administrations that a subject received across cycles where actual dose received is > 0 mg.

Total cumulative dose

Total cumulative dose for the study treatment is the sum of the actual dose amounts that a subject receives across all cycles.

Duration of exposure

$$\text{Duration of exposure (weeks)} = \left(\frac{\text{date of last dose-date of first dose+1}}{7}\right)$$

Total planned dose

Total planned dose (mg) is calculated based on the established Part C planned dose as follows:

Planned cumulative dose (mg) = Cohort dose (mg/administration) × duration of exposure (days)

Dose intensity

$$\text{Dose intensity (mg/day)} = \frac{\text{Total cumulative dose of M4344 (mg)}}{\text{Duration of exposure (days)}}$$

Relative dose intensity

The relative dose intensity (%) is calculated by dividing the dose intensity by the planned daily dose of the study drug.

The following will be summarized:

- Duration of therapy (weeks): by summary statistics and counts/percentages of the following categories: ≤ 3 weeks, > 3 – 6 weeks, > 6 – 9 weeks, > 9 -12 weeks, > 12 weeks
- Total number of administrations
- Total cumulative doses (mg)
- Dose intensity (mg/day)
- Relative dose intensity (%): by summary statistics and counts/percentages of the following categories: < 60%, ≥ 60% - < 80%, ≥ 80% - < 90%, ≥ 90% - ≤110%, >110%
- Minimum dose compliance (%): < 50%; ≥ 50% - < 70%; ≥ 70% - < 90%; ≥ 90% relative to initially planned dose

14 Efficacy Analyses

Analysis Set: FAS/SAF

14.1 Primary Endpoint: Best Overall Response and Objective Response

Objective Response (OR) is defined as a confirmed Best Overall Response (BOR) of complete response (CR) or partial response (PR). Requirements for confirmation of responses is detailed below.

BOR will be based on investigator-reported overall responses from the treatment start date until documented disease progression, assessed in accordance to RECIST v1.1 (Eisenhauer et. al.). Only tumor assessments performed before the start of subsequent anti-cancer treatments will be considered in the assessment of BOR. If a tumor assessment was performed on the same day as start of new anti-cancer treatment, it will be assumed that the tumor assessment was performed prior to the start of the new anti-cancer treatment and will be included in the evaluation of BOR. Clinical deterioration will not be considered as documented disease progression, for the sake of BOR evaluation.

Confirmed BOR requires the following:

- Complete response (CR): at least two determinations of CR at least 4 weeks apart (with no PD in between)
- Partial response (PR): at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart (and not qualifying for a CR), with no PD in between
- Stable disease (SD) (applicable only to participant with measurable disease at baseline): at least one SD assessment (or better) at least 6 weeks after treatment start date (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline): at least one non-CR/non-PD assessment (or better) at least 6 weeks after treatment start date (and not qualifying for CR or PR).
- Progressive disease (PD): PD ≤12 weeks after treatment start date (and not qualifying for CR, PR, non-CR/non-PD or SD).
- Not Evaluable (NE): all other cases.

SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the minimum duration for SD definition has been met.

Participants who do not have an on-treatment radiographic tumor assessment due to early progression, who receive anti-tumor treatments other than the study treatments prior to reaching confirmed CR or PR, or who die, progress, or drop out for any reason prior to reaching confirmed CR or PR will be counted as non-responders in the assessment of OR.

Each participant will have an objective response status (0: 'no OR'; 1: 'OR'). The confirmed **Objective Response Rate (ORR)** will be calculated along with the two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the SAS FREQ procedure using the EXACT option).

Disease Control (DC) is defined as a confirmed BOR of CR, PR, SD or Non-CR/non-PD. DC rate (DCR) is the proportion of participants with DC. DCR will be calculated along with the two-sided 95% CI using the Clopper-Pearson method.

In addition, the frequency (number and percentage) of participants with confirmed BOR of CR, PR, SD, PD, non-CR/non-PD, and NE will be tabulated. Participants with BOR of NE will be summarized by reason for having NE status. The following reasons will be used in hierarchical order:

- No baseline assessment
- No post-baseline assessments due to death before first post-baseline assessment
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- Subsequent anticancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after start date)
- PD too late (>12 weeks after start date of treatment)

Special and rare cases where confirmed BOR is NE due to both early SD and late PD will be classified as 'SD too early'.

Participant lesion measurements, tumor assessments, and best overall response, will be included in a listing.

14.2 Duration of Response

Given the small number of subjects and the low likelihood that any will experience an objective response, duration of response will not be analyzed.

14.3 Overall Survival

Overall survival (OS) is defined as the time from treatment start to the date of death due to any cause. OS for participants without death prior to cut-off will be censored at date of last contact. Overall survival in months is calculated as follows:

OS (months) = [date of death or censoring– treatment start date +1]/30.4375

The OS time or censoring time will also be presented in a participant listing.

14.4 Progression-Free Survival

Progression Free Survival (PFS) time is defined as the time from start date to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever

occurs first. The tumor response will be determined according to RECIST 1.1 (Eisenhauer et. al.) and assessed by the investigator. PFS censoring logic is equivalent to DR censoring.

PFS time (in months) = (Date of PD or death – treatment start date + 1)/ 30.4375 (months)

Kaplan-Meier estimates (product-limit estimates) will be presented with a summary of associated statistics including the median OS time with two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley . The estimate of the standard error will be computed using Greenwood's formula.

Unique reasons for censoring will be summarized based on assignment to the categories in Table 3, following the hierarchy shown.

Table 3 PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No baseline assessment
2	No death within 12 weeks of treatment start and no adequate post-baseline tumor assessment, including if death is observed > 12 weeks after treatment start	No post-baseline tumor assessment
3	Start of subsequent anti-cancer therapy before event, including if no event was observed	Start of subsequent anti-cancer therapy
4	Event more than 2*(scheduled time between tumor assessments) [a] weeks after last adequate post-baseline tumor assessment	Event after 2 or more missing assessments
5	No event and end of study reason is "Withdrew consent"	Withdrawal of consent
6	No event and "Lost to follow-up" indicated on any disposition eCRF page	Lost to follow-up: Status collected on eCRF page
7	Censoring date > 2*(scheduled time between tumor assessments) weeks before cut-off date	Lost to follow-up: two or more missing scans preceding data cut date
8	No event and none of the conditions in the above hierarchy are met	Administrative censoring: Ongoing in the study without an event

[a] Per protocol, subjects are to receive tumor scans once every six weeks for the first six cycles (18 weeks), then every 9 weeks thereafter.

The PFS time/censoring time and the reasons for censoring will also be presented in a participant listing.

15 Safety Analyses

Analysis Set: FAS/SAF

15.1 Primary Endpoint: Adverse Events

Treatment-emergent adverse events (TEAE) are those events with onset dates occurring within the on-treatment periods as defined in Section 9.10.

Adverse events related to study treatment are those events with relationship missing, unknown or yes.

Serious adverse events (SAEs) are AEs with the eCRF field "Serious adverse event" marked "Yes"

AEs leading to temporary treatment discontinuation are those with the action "Drug interrupted" selected.

AEs leading to permanent treatment discontinuation are those with "Drug withdrawn" checked as an "Action taken with M4344" on the Adverse Events eCRF page.

AEs leading to death are AEs with NCI-CTCAE toxicity Grade 5 or outcome "fatal".

All analyses described in Section 15.1 will be based on TEAEs if not otherwise specified. Separate listings will be produced for AEs outside the on-treatment period and AEs attributed to the impact of COVID-19.

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest, by primary SOC, in alphabetic order, and PT in decreasing frequency for the Total column.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a given SOC or PT, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 5.0) per participant, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

Incomplete AE-related dates will be handled as specified in Section 9.12.2.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following:
  - TEAEs
  - TEAEs with NCI-CTCAE Grade ≥ 3, by grade
  - Related TEAEs
  - Related TEAEs with NCI-CTCAE Grade ≥ 3, by grade

  - TEAEs leading to temporary treatment discontinuation
  - Related TEAEs leading to temporary treatment discontinuation
  - TEAEs leading to permanent treatment discontinuation
  - Related TEAEs leading to permanent treatment discontinuation
  - Serious TEAEs
  - Non-Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - Related TEAEs leading to death
- TEAEs by SOC, PT and worst CTCAE toxicity grade
- Treatment related TEAEs by SOC, PT and worst CTCAE toxicity grade
- TEAEs leading to permanent discontinuation of M4344 by SOC and PT
- Related TEAEs leading to permanent discontinuation of M4344 by SOC and PT

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Summary tables for non-serious adverse events excluding SAEs will be provided. The non-serious AEs are not restricted to non-serious TEAEs.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

All deaths, deaths within 30 days after last dose of study treatment, deaths within 60 days after first dose, as well as reason for death, will be tabulated based on information from the "Death" eCRFs page.

- Number of deaths
- Number of deaths within 30 days after last dose of study treatment
- Number of deaths within 60 days after first dose of study treatment
- Primary Reason of Death
  - Disease progression
  - Event related to study treatment
  - Event not related to study treatment
    - Subset of subjects who died due to the impact of COVID-19
  - Unknown

In addition, date and cause of death will be provided in individual participant data listing together with selected dosing information (date of first / last administration, number of cycles treated).

This listing will include:

- AEs with fatal outcome (list preferred terms of AEs with outcome=fatal)
- Flag for death within 30 days of last study treatment
- Flag for death within 60 days of first study treatment

15.2.2 Serious Adverse Events

The following overall frequency tables will be prepared for serious adverse events (SAEs):

- Incidence of serious AEs by SOC and PT
- Incidence of related serious AEs by SOC and PT

The listings of SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

15.3 Primary Endpoint: Clinical Laboratory Evaluation

Parameters with NCI-CTCAE grades available:

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0. Some of the toxicity gradings are based on laboratory measurements in conjunction with clinical findings. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria. For example, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier (symptomatic and intervention indicated) and therefore Grade 2 will not be derived. Abnormalities classified according to NCI-CTCAE toxicity grading version will be described using the worst on-treatment grade. For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa.

The laboratory toxicities will be tabulated with counts of participants and percentages during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of participants in the analysis population. Subjects without an on-treatment result or results which are not CTCAE gradable will be counted in the "Missing" category.

- The summary of laboratory parameters by CTCAE grade table will include number and percentage of participants with Grade 1, 2, 3, 4, 3/4, and any grade (1 to 4), laboratory abnormalities during the on-treatment period.
- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

The following parameters are CTCAE-gradable:

Hematology:

Hemoglobin, leukocytes, lymphocytes, neutrophils/absolute neutrophil count, platelet count.

Serum Chemistry:

Albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), total bilirubin, cholesterol, creatinine, creatine kinase, potassium, sodium, magnesium, calcium, glucose, gamma glutamyl transferase (GGT), lipase, phosphates, triglycerides.

Please see the further details of NCI-CTCAE gradable parameters in the Appendix.

For **calcium**, CTCAE grading is based on Corrected Calcium. Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment period will be summarized by treatment group:

- ALT $\geq$ 3×ULN, ALT $\geq$ 5×ULN, ALT $\geq$ 10×ULN, ALT $\geq$ 20×ULN
- AST $\geq$ 3×ULN, AST $\geq$ 5xULN, AST $\geq$ 10×ULN, AST $\geq$ 20×ULN
- (ALT or AST) $\geq$ 3×ULN, (ALT or AST) $\geq$ 5×ULN, (ALT or AST) $\geq$ 10×ULN, (ALT or AST) $\geq$ 20×ULN
- TBILI $\geq$ 2×ULN
- Concurrent ALT $\geq$ 3×ULN and TBILI $\geq$ 2×ULN
- Concurrent AST $\geq$ 3×ULN and TBILI $\geq$ 2×ULN
- Concurrent (ALT or AST) $\geq$ 3×ULN and TBILI $\geq$ 2×ULN
- Concurrent (ALT or AST) $\geq$ 3×ULN and TBILI $\geq$ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) $\geq$ 3×ULN and TBILI $\geq$ 2×ULN and ALP $\leq$ 2×ULN or missing

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency and percentage.

Parameters with NCI-CTCAE grades not available:

Laboratory results that are not part of NCI-CTCAE will be presented according to categories based on comparison to normal reference ranges (i.e. Low, Normal, and High).

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and row percentage) of participants with:

- shifts from baseline normal to at least one result above normal during on-treatment period
- shifts from baseline normal to at least one result below normal during on-treatment period

In this study, these apply to the following parameters:

Hematology:

Hematocrit, Red Blood Cell (RBC), Reticulocytes, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC).

Serum Chemistry:

Chlorine, C-Reactive Protein, Lactate Dehydrogenase (LDH), Total Protein, Total Urea, Uric Acid.

The following figures will be provided:

- An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for the different biomarker cohorts, by graphically displaying peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT =3×ULN and total bilirubin =2×ULN.
- An equivalent eDISH plot of peak serum AST (/ULN) vs peak total bilirubin (/ULN) will also be provided.

Listings of laboratory results will be provided for all hematology and biochemistry parameters. The listings will be sorted by parameter and visit for each participant. Laboratory values that are outside the normal range will be flagged in the data listings, and corresponding normal ranges and CTCAE grades will be provided.

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with at least one post-baseline TBILI ≥ 2×ULN, ALT≥ 3×ULN or AST ≥ 3×ULN will be provided.

Any other laboratory parameter collected will be listed in dedicated listings presenting all relevant information collected on the eCRF or by the central lab:

- Coagulation: [activated partial thromboplastin time (aPTT) and prothrombin time (INR).

- Urinalysis: all urinalysis parameters
- Other parameters: hormone, and immunology parameters
- Pregnancy test

15.4 Primary Endpoint: Vital Signs

Analysis Set: FAS/SAF

Vital sign values and their changes from baseline will be presented in listings only.

15.5 Other Safety or Tolerability Evaluations

15.5.1 Primary Endpoint: Electrocardiogram (ECG) Measurements

Analysis set: FAS/SAF Analysis Set

12-Lead ECG information will come from the "Standard 12-Lead ECG" and measurements from the central ECG assessments.

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as:

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Listings of ECG data will also be provided with all relevant information such as visit, date/time of assessment, measurement, and results.

15.5.2 Time-Matched ECG and PK measures

There will no analyses performed on time-matched ECG and PK parameters.

15.5.3 Eastern Cooperative Oncology Group Performance Status

Analysis set: FAS/SAF Analysis Set

Eastern Cooperative Oncology Group Performance Status (ECOG PS) information will come from the "ECOG Performance Status" eCRF page. Listings of each participant's ECOG PS over time will be provided.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Listing of concentrations will only be provided.

CCI [redacted]

16.3 COVID-19 Impact

Analysis set: SAF

COVID-19 related impact on the planned trial procedures will be based upon the eCRF pages related to disposition ('TTERM', 'STERM', and 'DEATH'), as well as the protocol deviations linked to the COVID-19 pandemic. Data listings will identify:

- Any COVID-19 related protocol deviation
  - Missed visits overall
  - Missed efficacy evaluations
  - Missed dosing visits
- Participants with cause of death related to COVID-19
- Participants with a COVID-19 AE.

17 References

Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. Biometrics 1982;38:29-41. DOI: 10.2307/2530286

Clopper, C. J., & Pearson, E. S. (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika, 26, 404–413

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D.,Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, National Cancer Institute of Canada-Clinical Trials Group, 10 Stuart Street, Queen's University, Kingston, Ontario, Canada. eeisenhauer@ctg.queensu.ca, 2009;45:228-47

18 Appendices

18.1 NCI-CTCAE Gradable and Non-Gradable Safety Laboratory Test Parameters and Direction(s) of Abnormality

NCI-CTCAE v5.0 gradable parameters

Category	Parameter	Name in NCI-CTC	Direction(s) of abnormality
	Serum chemistry		
Electrolytes	Calcium	Hypocalcemia/Hypercalcemia	Low/High
Electrolytes	Potassium	Hypokalemia/Hyperkalemia	Low/High
Electrolytes	Sodium	Hyponatremia/Hypernatremia	Low/High
Enzymes/liver	Alanine Aminotransferase	Alanine Aminotransferase increased	High
Enzymes/liver	Alkaline Phosphatase	Alkaline Phosphatase increased	High
Enzymes/liver	Aspartate Aminotransferase	Aspartate Aminotransferase increased	High
Enzymes/liver	Total bilirubin	Blood bilirubin increased	High
Metabolism	Glucose	Hypoglycemia	Low
Renal/kidney	Creatinine	Creatinine increased	High
	Hematology		
Platelets	Platelets Count	Platelet count decreased	Low
Red blood cells	Hemoglobin	Anemia/Hemoglobin increased	Low/High
White blood cells/differential	White Blood Cell Count	White blood cell decreased/Leukocytosis	Low/High
White blood cells/differential	Absolute Lymphocytes Count	Lymphocyte count decreased/increased	Low/High
White blood cells/differential	Absolute Neutrophils Count	Neutrophil count decreased	Low
White blood cells/differential	Eosinophils	Eosinophilia	High

NCI-CTCAE non-gradable parameters

Category	Parameter (LBTEST)	Direction(s) of abnormality
	Serum chemistry	
Metabolism	Glucose	High
Plasma proteins	Total protein	Low
Renal/kidney	Blood Urea Nitrogen	High
	Hematology	
Red blood cells	Hematocrit	High/Low
Red blood cells	Mean Corpuscular Hemoglobin	High/Low
Red blood cells	Mean Corpuscular Hemoglobin Concentration	High/Low
Red blood cells	Mean Corpuscular Volume	High/Low
Red blood cells	Reticulocytes	High/Low
White blood cells/differential	Basophils	High
White blood cells/differential	Monocytes	High/Low

ELECTRONIC SIGNATURES

Document: ctp-ms201922-0001-iap-part-c-v1

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Technical Approval	26-Apr-2021 16:53
PPD	Task Completed (Approval eSign): Approved	Business Approval	27-Apr-2021 07:17
PPD	Task Completed (Approval eSign): Approved	Technical Approval	27-Apr-2021 09:28
PPD	Task Completed (Approval eSign): Approved	Technical Approval	28-Apr-2021 08:48
PPD	Task Completed (Approval eSign): Approved	Business Approval	29-Apr-2021 14:18