Integrated Analysis Plan

Study Number:	MS201512_0010
Clinical Study Protocol Title:	A First-in-human, Phase I, Open-label Study of the ATM inhibitor M4076 in Participants with Advanced Solid Tumors
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Merck Compound:	M4076
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Approval Page

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A First-in-human, Phase I, Open-label Study of the ATM inhibitor M4076 in Participants with Advanced Solid Tumors.

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within Veeva Vault (BREEZE) 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

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical classification
ATM	Ataxia-telangiectasia Mutated
AUC	Area under the curve
BLRM	Bayesian 2-parameter Logistic Regression Model
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CMH	Cochran-Mantel-Haenszel
CALCIO	Corrected Calcium and Ionized Calcium
CR	Complete Response
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DL	Dose Level
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of response
ECG	Electrocardiogram

ECOG	Eastern Co-operative Oncology Group
eDISH	Drug-Induced Serious Hepatotoxicity
FAS	Full Analysis Set
FU	Follow-up
GCP	Good Clinical Practice
γ-H2AX	Gamma Histone Family Member X
HR	Hazard Ratio
HRQoL	Health-related quality of life
IAP	Integrated Analysis Plan
ICE	Intercurrent Event
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
ICD-O	International Classification of Diseases for Oncology
IPD	Important Protocol Deviation
IRC	Independent Review Committee
ITT	Intention To Treat
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
LLN	Lower Limit of Normal
LLOQ	The lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
MTD	Maximum Tolerated Dose
NA	Not Applicable
nd	Not done
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
p-ATM	Phosphorylated Ataxia-Telangiectasia Mutated
Pd	Pharmacodynamics

PD	Progressive Disease or Protocol Deviation or Pharmacodynamics
PFS	Progression Free Survival
PT	Preferred Term
PGx	Pharmacogenetics/Pharmacogenomics
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PR	Partial Response
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RDE	Recommended Dose for Expansion
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCR	Screening analysis set
SMC	Safety Monitoring Committee
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cell Count
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	09 November 2021	PPD	Initial Version
2.0	19 December 2022	PPD	Only final analysis will be performed. DLTs will be presented only by DLT analysis set. Non-relevant analyses removed: • Table on baseline tumor assessment • ECOG shift table • Subsequence anti-cancer therapy • Prior Anti-cancer Therapy by ATC and PT

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for all the analyses of data collected for protocol MS201512_0010 including Part 1A (dose escalation) and Part 1B (preliminary food effect cohort).

Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR) or in separate reports. 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 CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based on Section 9 (Statistical considerations) of the protocol amendment version 4.0 dated 27 October 2022 and is prepared in compliance with International Conference on Harmonization (ICH E9). It describes analyses planned in the protocol and protocol amendments. Details of the Safety Monitoring Committee (SMC) analyses for regular review of the participants' safety are provided in appendix.

5 Objectives and Estimands

Objectives and Estimands: M4076 Monotherapy Dose Escalation (Part 1A) and Preliminary Food Effect Assessment (Part 1B)

Objectives	Estimands Attributes	IAP section
Primary		
To determine dose-toxicity relationship and MTD (if reached) of M4076 monotherapy in participants with advanced solid tumors.	**Endpoints**: • Occurrence of Dose Limiting Toxicities (DLTs). • Occurrence of adverse events (AEs) and treatment-related AEs. • Occurrence of clinically significant changes in vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings. **Strategy for handling intercurrent events:** For DLTs: • Discontinuation of treatment (> 20% planned treatment missed during DLT period) to prevent a DLT: composite strategy (to be considered a DLT). • Discontinuation treatment administrations not due to DLT or preventing a DLT (> 20% of planned treatment missed during DLT period): participant not considered in DLT analysis. **For other endpoints:** All available data from participants in safety analysis set will be used. **Population:** Patients with advanced solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary:** • DLT probability as estimated using BLRM and credibility interval (only applicable for DLTs). • Standard summary statistics.	Section 15.1 Section 15.2, 15.3 Section 15.4, 15.5, 15.6
Secondary		
To determine the recommended dose for expansion (RDE) of M4076 monotherapy in participants with advanced solid tumors.	**Endpoints:** • In addition to safety and tolerability, changes from baseline for the following Pd biomarkers may be considered for determining the RDE: ATM pathway readouts such as, but not limited to, p-ATM, γ-H2AX and p-CHK2 in blood and tumor. • In addition, pharmacokinetic (PK) data will be used to support determination of the RDE.	Section 15 Section 16.1
To characterize the PK profile of M4076 monotherapy in participants with advanced solid tumors.	**Endpoints:** • PK parameters of M4076 in plasma after single dose and multiple doses. • Urine PK parameters (e.g., renal clearance) will be characterized in Part 1B if data permits.	Section 16.1

Objectives	Estimands Attributes	IAP section
To evaluate preliminary clinical activity parameters of M4076 monotherapy in participants with advanced solid tumors.	**Endpoints:** • Objective response (OR) according to RECIST 1.1 assessed by Investigator. • Duration of response (DoR) according to RECIST 1.1 assessed by Investigator. • Progression Free Survival (PFS) according to RECIST 1.1 assessed by Investigator.	Section 14
To assess the effect of food on the PK of M4076 administered as a single dose under fed/fasting conditions in a cohort of participants with advanced solid tumors at the RDE from Part 1A.	**Endpoints:** Fed/fasted ratio of M4076 plasma PK parameters: $AUC_{0-tlast}$, $AUC_{0-\infty}$ and, C_{max} when administered as a single dose with or without food.	Section 16.1
To assess changes in pharmacodynamic markers of M4076 activity in tumor and blood during M4076 monotherapy.	**Endpoints:** Absolute and relative changes over time from baseline of ATM pathway readouts, such as, but not limited to p-ATM, p-CHK2 and γ-H2AX.	Section 16.2
CCI [redacted]		

6 Overview of Planned Analyses

The following analyses are planned for this trial:

- Safety Monitoring Committee (SMC) analyses (See IAP for SMC in Appendix 18.3)
- Final analysis for dose escalation and food effect cohort (Part 1A and Part 1B)

Statistical analyses (except for SMCs) will be performed on the basis of CDISC SDTM data. These SDTM data contain as clean as possible eCRF data as well as external data for central laboratory biomarker data, tumor assessment results by Investigator and DLT decisions from SMC.

Statistical analyses for SMCs will be performed on the basis of eCRF/external data.

A data review meeting will be held prior to any database lock. In addition, no database can be locked until this IAP has been approved (except for emergency).

All planned analyses identified in the Clinical Study Protocol and in this IAP will be performed.

6.1 Analyses for SMC meetings

Details of analyses for SMC meetings will be specified in a separate IAP, provided in Appendix 18.2.

6.2 Primary Analysis for dose escalation and food effect cohort (Part 1A and Part 1B)

The cutoff for the primary analysis of the safety, available PK, available Pd and preliminary antitumor activity data from Part 1A and Part 1B will be triggered when all participants have reached either the first on-treatment tumor assessment, or experienced death or premature withdrawal for any reason, whichever comes first.

All trial data up to the primary analysis cutoff date will need to be in-house, all data queries resolved, and the database locked for primary analysis.

This analysis will be the main analysis. All planned analyses as specified in the TLF table of contents for primary analysis will be performed.

6.3 Final Analysis for dose escalation and food effect cohort (Part 1A and Part 1B)

Final analyses to report further efficacy and safety data will be performed once the End of Study has been reached. Please refer to the study protocol for details on when participants are considered to have completed the study.

All planned analyses as specified in the TLF table of contents for final analysis will be performed.

7 Changes to the Planned Analyses in the Clinical Study Protocol

There are no changes to the planned analyses in the clinical study protocol.

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Screening Analysis Set (SCR)

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

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

The analysis set will include all screened participants, who received at least one dose of any study intervention. Analyses will consider participants as treated.

Participants will be classified according to the dose actually received. See Section 9 for details on determination of actual dose level. The Full Analysis Set (FAS) and the Safety Analysis Set (SAF) are identical. In outputs this analysis set will be denoted by 'FAS/SAF'. Analyses of safety and efficacy will be based on this analysis set.

Dose Limiting Toxicity Analysis Set (DLT)

The DLT Set will include all participants who received at least one dose of study intervention and meet at least one of the following criteria:

- Experienced at least one DLT during the DLT period, regardless of the administered number of doses of study intervention/completion in the DLT period
- Received at least 80% of the planned cumulative dose during the DLT period of each study intervention and completed the DLT period
- Additionally, participants who did not receive 80% of the planned total dose of study intervention, but at least 80% dosing of a different dose cohort and finished the DLT period are eligible for the DLT analysis set to be analyzed in the highest dose cohort for which they received 80% of dosing.

The final decision on evaluability for dose escalation analysis will be made by the SMC (e.g. considering relevant deviations from dosing schedule).

PK Analysis Set (PKAS)

The Pharmacokinetic (PK) Analysis Set (PKAS) is a subset of the FAS/SAF and will consist of all participants, who receive at least one dose of study intervention, and provide at least one measurable post-dose concentration. A measurement below lower limit of quantification (BLQ) is considered a valid measurement. Participants will be analyzed per the actual study intervention they received. All PK analyses will be based on the PK Analysis Population.

Pd Analysis Set

The pharmacodynamics (Pd) Analysis Set will consist of all participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting Pd, and provide the baseline and at least one measurable Pd endpoint postdose. Participants will be analyzed per the actual study intervention they received. All Pd analyses will be based on this analysis population.

Analyses per Analysis Set

The following table summarizes the use of the analysis sets in the different analyses.

Analyses	**DLT**	**FAS/SAF**	**PKAS**	**Pd**
DLT: Primary	✓			
Safety and Tolerability		✓		
Baseline Characteristics		✓		
Previous and Concomitant Therapies		✓		
Compliance and Exposure		✓		
Efficacy		✓		
Pharmacokinetic			✓	
Pharmacodynamic				✓

DLT = Dose Limiting Toxicity; FAS = Full Analysis Set; SAF = Safety Analysis Set; PK = Pharmacokinetic Analysis Set; Pd = Pharmacodynamic

Note: Safety, PK and Pd will be described by actual dose which might differ from planned dose.

All other analyses will be described by planned dose, according to Intention-to-Treat principle. For more details, see Section 9.

9 General Specifications for Data Analyses

The results of this study will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by study part (Part 1A and Part 1B), dose level (and regimen if different regimens tested), and by dietary status ("Fed" and "Fasted") and/or scheduled time point, as applicable.

Definition of actual dose

Unless otherwise specified, analyses of safety, efficacy and PK parameters will be conducted by actual dose. In this open label, unblinded study, actual dose is determined by considering study drug compliance during the DLT evaluation period (first 21 days from first dose of M4076) and whether the subject experienced a DLT (as per SMC determination). If a different regimen is tested, all subjects remain in the regimen to which they were assigned (i.e. subjects cannot be assigned to a different pre-specified dose level with a different dosing scheme).

In this context, compliance is defined as the cumulative actual dose taken by the subject divided by the cumulative cohort-level planned dose the subject was expected to receive. The planned dose level will be taken from the electronic case report form (eCRF) "Cohort". The following table will be used to determine actual dose level:

Table 1 Actual Dose Assignment

Compliance of planned dose	DLT Status	Compliance relative to other pre-specified dose levels	Actual dose
> 100%	Any	≥ 80% a higher pre-specified dose level	Higher pre-specified dose level
> 100%	Any	< 80% a higher pre-specified dose level (or no higher dose level)	Planned dose level
≤ 100%	DLT	Any	Planned dose level
≥ 80% and ≤ 100%	No DLT	Any	Planned dose level
< 80%	No DLT	≥ 80% of a lower pre-specified dose level	Lower pre-specified dose level
< 80%	No DLT	< 80% of the lowest pre-specified dose level (or no lower dose level)	Lowest received pre-specified dose level*

*Patient is not evaluable for DLT analysis set

Note: In case a subject received >120% cumulative dose of the planned dose but ≤ 80% of the next higher pre-specified dose the data of this subject will not be considered in Pd and efficacy summary outputs. The data will be displayed in listings and line plots but with a footnote stating the actual cumulative dose.

In the event there are subjects whose ‚actual' dose differs from the planned dose, disposition, compliance and exposure will be described by both planned and ‚actual' dose.

Period definition for Part 1B (Food effect Cohort)

For analyses related to food effect assessments, the following timepoints are defined and mapped to the visit days in the Schedule of Activities for the preliminary food effect assessments in the protocol:

Table 2 Definition of Periods including preliminary food effect assessments

Food Effect Assessment Period -Fasted		**Food Effect Assessment Period -Fed***		Part 1A Schedule	
Analysis Day	Visit Day mapped from Schedule of Activities	Analysis Day	Visit Day mapped from Schedule of Activities	Analysis Day	Visit Day mapped from Schedule of Activities
Fasted Day 1	Day -7 or Day 1	Fed Day 1	Day -7 or Day 1	Period 1 Day 5	Day 5
Fasted Day 2	Day -6 or Day 2	Fed Day 2	Day -6 or Day 2	Period 1 Day 6	Day 6
Fasted Day 3	Day -5 or Day 3	Fed Day 3	Day -5 or Day 3	Period 1 Day 7	Day 7
Fasted Day 4	Day -4 or Day 4	Fed Day 4	Day -4 or Day 4	Period 1 Day 8	Day 8

*The fed meal condition is planned to be a standard low-fat meal.

Note, that Food Effect Assessment is defined until Day 4 pre-dose. After Day 4, assessments are continued according to Part 1A Schedule of Activities (Period 1 Day 8, Period 1 Day 15, etc.). All cross-over design related analysis in Part 1B refers to the data collected within the timeframe of food effect assessment only (Day -7 until Day 4 per Schedule of Activities for Part 1B).

Listings

In the individual participant data listing all individual data for each study part (Part 1A and Part 1B) will be listed as measured. Repeated and unscheduled measurements will be included in the listings. All listings will be sorted by dose level, participant ID, and/or nominal time point, as appropriate. Data which are measured before administration of the administration of study intervention will be sorted by participant number and nominal time point (if appropriate).

Tables and Descriptive Statistics

All data will be summarized by study part (Part 1A and Part 1B), dose level (and regimen if different regimens are tested), dietary status(“Fed” and “Fasted”), day, and/or nominal time point, as appropriate Different dose levels will generally be presented in increasing order. A total column is also presented. Repeated and unscheduled measurements included in the listings will not be used

for statistical analyses or summaries, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

Presentation of continuous and qualitative variables

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, i.e. the number of participants with non-missing values (n), mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum, 95% CIs for the mean, as appropriate.

Mean, median, Q1, Q3, Min, and Max will have the same precision as collected in SDTM datasets for non-derived data. Standard deviation will be presented with one digit more than the mean. Percentage and percent change from baseline will be reported using one decimal digit, if not specified otherwise. Derived data such as duration and "time since" variables (see Section 9.3) will be displayed with one decimal digit, unless stated otherwise.

If there are no missing values, the number of participants with missing values should be indicated by a 0.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants in 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 participants still present in the trial at that visit, unless otherwise specified.

Descriptive statistics by nominal visit or time point, e.g. for laboratory measurements, will include only data from scheduled visits. Unscheduled visits will be included in the derivation of baseline or worst on-treatment values.

Significance level:

All statistical tests mentioned in this IAP are to be regarded as exploratory. No formal statistical hypothesis will be tested. If confidence intervals are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

Software

All analyses will be performed using SAS® Software version 9.4 or higher or R (www.r project.org), Version 3.5.1 or higher.

9.1 Data handling after Cut-off Date

By its nature, data after cut-off may be incomplete and subject to further change and will not be used for summary statistics, statistical analyses, listings or imputations.

Stop dates are not affected by this rule, e.g. a stop date of Adverse Events (AEs), which starts prior to the cut-off, but stops after date of cut-off, will not be changed.

These rules will be applied to all analyses performed for the primary analysis. For the final (follow-up) analysis no cut-off date will be applied: the analysis will be performed only after all the data have been collected, fully cleaned and the database has been locked.

9.2 Definition of Baseline and Change from Baseline

Definition of baseline:

Part 1A:

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

Part 1B:

In general (if not otherwise specified), the last non-missing measurement prior to the first study intervention administration will serve as the baseline measurement for efficacy as well as for safety analyses (irrespective of dietary status).

For food effect analyses on pre-defined endpoints, the 'baseline' refers to the last scheduled measurement before administration of study intervention in each food effect assessment period. However, if a participant is missing the baseline collection, the previous non-missing evaluation could become the baseline value (e.g. from screening/admission). If no baseline value exists, then the baseline value and the respective change from baseline will be treated as missing.

If an assessment that is planned to be performed before study intervention per protocol is performed on the same day as the start of study intervention, but the assessment time is not available, it will be assumed that it was performed prior and will be considered as baseline.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be analyzed similar to an unscheduled post-dose measurement.

Definition of change from baseline

absolute change from baseline = visit value – baseline value

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

9.3 Study Day / Study Intervention Day

Part 1A:

Day 1 is the day of start of study intervention, the day before is Day -1 (no Day 0 is defined). Study day / Study intervention day is defined relative to Day 1.

Part 1B:

Day 1 is the day of start of study intervention, the day before is Day -1 (no Day 0 is defined). Study day / Study intervention day is defined relative to Day 1 (irrespective of dietary status), if not otherwise specified.

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 first study intervention + 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.

9.4 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.

9.5 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:

Participants off study intervention:

Last known to be alive date collected on the 'Survival Follow-up' eCRF Participants on study intervention:

- AE start and end dates
- Date of last study intervention
- Date of last tumor assessment
- All participant assessment dates (blood draws [laboratory and PK], vital signs, performance status, ECG)
- Date of discontinuation on disposition eCRF pages (unless reason for discontinuation is lost to follow-up).

- Start and End date of Concomitant Medication and Procedures eCRF pages

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. Assessment dates after the cut-off date will not be applied to derive the last contact date.

9.6 Definition of On-treatment Period

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

9.7 Exposure time

Duration of exposure to study intervention = date of last dose of study intervention –date of first dose of study intervention +1.

9.8 Imputation of Missing Data

Unless 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.

Missing statistics, e.g. when they cannot be calculated, should be presented as “nd”. For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as “nd”.

Where tables are presented over different time points, the total of missing and non-missing observations at each time point should reflect the population still in the trial at that time. This does not apply when imputations are made beyond trial withdrawal. For example, if a participant is still in the trial at the time-point but with missing data, they should be counted in the number of missing observations.

The following table for imputation rules will be considered:

Disease history	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 intervention, the month and day will be imputed as July 1st.

	• If both day and month are missing and the year is same as the year of the first study intervention, the month and day will be imputed as January 1st. • If the date is completely missing, no imputation will be performed.
Adverse events	Incomplete AE-related dates will be imputed 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 study intervention then the onset date will be imputed by the minimum of start of study intervention and AE resolution date (if not missing). • In all other cases, the missing onset day or missing onset month will be imputed by 1. • Incomplete stop dates will be imputed by the last day of the month (if day is missing only), 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.
Previous and concomitant medication	For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Rules presented in Table 3 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

Table 3 Imputation rules for medication/procedure end dates

End date of medication/procedure			Imputation rule
Day	**Month**	**Year**	
UNK	UNK	UNK	After study intervention start (ongoing)
UNK	UNK	< Study intervention start (year)	Before study intervention start
UNK	UNK	≥ Study intervention start (year)	After study intervention start
UNK	< Study intervention start (month and year)		Before study intervention start
UNK	≥ Study intervention start (month and year)		After study intervention start
< Study intervention start (complete date)			Before study intervention start
≥ Study intervention start (complete date)			After study intervention start

UNK = Unknown

Table 4 Rules to define previous and/or concomitant medications

Start date of medication/procedure			Imputation rule (see Table 3)	Medication/ procedure
Day	Month	Year		
UNK	UNK	UNK	Before study intervention start	Previous
UNK	UNK	UNK	After study intervention start	Previous and concomitant
UNK	UNK	≤ Study intervention start (year)	Before study intervention start	Previous
UNK	UNK	≤ Study intervention start (year)	After study intervention start	Previous and concomitant
UNK	UNK	> Study intervention start (year) and ≤ Study intervention end + 30 days (year)	After study intervention start	Concomitant
UNK	≤ Study intervention start (month and year)		Before study intervention start	Previous
UNK	≤ Study intervention start (month and year)		After study intervention start	Previous and concomitant
UNK	> Study intervention start (month and year) and ≤ Study intervention end + 30 days (month and year)		After study intervention start	Concomitant
≤ Study intervention start (date)			Before study intervention start	Previous
≤ Study intervention start (date)			After study intervention start	Previous and concomitant
> Study intervention start (date) and ≤ Study intervention end + 30 days (date)			After study intervention start	Concomitant

UNK = Unknown

Dates of study intervention	Start date of study interventions: • No imputation will be done. End date of study interventions: • In case the last date of study intervention is missing or incomplete the date of last administration of study intervention will be taken from the treatment termination eCRF pages. • If the last date of study intervention is completely missing and there is no Treatment Termination eCRF page and no death date the participant should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date • If the last date of study intervention is completely or partially missing and there is EITHER and Treatment Termination 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
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 (non-imputed) day after the date of last contact and the 15th day of the month. Otherwise, it will not be imputed.
Tumor assessments	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 all 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 considered to be at 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.
Dates of subsequent anti-cancer therapy	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 efficacy analyses and in the derivation of the end of on-treatment period. 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.

9.9 Age at Time of an Event

If age at the time of an Event is derived, the following algorithm will be used for the derivation

- Year of event minus year of birth

9.10 Laboratory Toxicity grading

In NCI-CTCAE v5.0 (see Section 18.1) the following parameters are not gradable at baseline as grading implies dependencies to baseline (e.g. ALT grade 1: >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal):

- Eosinophilia (added term, grade 1 depends on baseline)
- Alanine aminotransferase increased
- Alkaline phosphatase increased
- Aspartate aminotransferase increased
- Blood total bilirubin increased
- Creatinine increased
- GGT increased
- INR increased (dependent on baseline also in v4.03)

In addition, in v5.0 the term 'Hyperglycemia' does not depend on glucose laboratory measurements anymore and is thus excluded from laboratory analyses and part of AE reporting only.

For the term 'Hemoglobin increased' the dependency to baseline is removed in v5.0. 'INR increased' is dependent on baseline values and intake of anticoagulants in both versions.

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/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 as indicated in section 9. Percentages will be presented with respect to the number of participants in FAS/SAF analysis set.

Participant disposition will be summarized as follows:

- Number of participants in each analysis population (SCR, FAS/SAF, DLT, PKAS, Pd)
- Number of participants who discontinued from the study prior to study intervention overall and grouped by the main reason for discontinuation:
    - Participant did not meet all eligibility criteria
    - Withdrew consent
    - Other (COVID-19-related and COVID-19-non-related)

The end of study intervention status will be summarized by:

- Number of participants who received at least one dose of study intervention
- Number and percentage of treated participants with ongoing study intervention
- Number and percentage of treated participants who completed study intervention (overall and by reason):
    - Death
    - Progressive disease
- Number and percentage of treated participants who discontinued the study intervention (overall and by primary reason):
    - Adverse event
    - Lost to follow-up
    - Protocol non-compliance
    - Death
    - Withdrew consent
    - Other (COVID-19-related and COVID-19-non-related)

This table will be produced twice if there are participants with differing planned dose and actual dose, one by planned dose and one by actual dose.

The end of study status will be summarized by:

- Number and percentage of participants with ongoing study intervention
- Number and percentage of participants off-treatment and in follow-up
- Number and percentage of participants who completed the study (overall and by primary reason):
    - Progressive disease
    - Death
- Number and percentage of participants who prematurely discontinued the study (overall and by primary reason)

- Adverse event
- Lost to follow-up
- Protocol non-compliance
- Death
- Progressive disease
- Withdrew consent
- Other (COVID-19-related and COVID-19-non-related)

Additionally, the number of participants screened, and enrolled in each analysis set (SCR, FAS/SAF, DLT, PK and Pd) will be provided overall by region, by country within region and by site.

Disposition of participants by allocated study intervention dose will be presented in a CONSORT Flow Diagram.

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

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 incorrect dose
- Participants that receive a prohibited 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.

Important protocol deviations 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. Any important protocol deviations are documented in SDTM datasets whether identified through site monitoring, medical review processes or programming. The management of protocol deviations is outside of this IAP document.

Clinically important protocol deviations (CIPDs) are a subset of important protocol deviations that could impact the key objectives of the study and that would lead to the exclusion of a participant from an analysis set (see Section 8.1 Definition of Analysis Sets).

CIPDs may be identified during the course of the study but will not require amendments to this IAP.

Important protocol deviations or important events that might have an effect on PK include, but may not be limited to the following:

- Adverse events, diarrhea etc. (these instances will be discussed on a case-by case basis)
- Impact of vomiting after oral administration but before 2x of median t_{max} (e.g. excluding the participant) will be assessed on a case-to-case basis for the impact on the overall result.
- Sample processing errors that may lead to inaccurate bioanalytical results
- Inaccurate dosing or dosing errors (e.g. dose administration delayed, dose change or missed doses)
- Pre-dose or trough sample collected after the actual dosing
- Non-compliance with food and drink requirements (e.g. non-fasted, incomplete meal consumption, caffeine intake)
- Concomitant medication, vitamins, dietary or herbal supplements

Should one or more of these events be available at the Data Review Meeting, its implication for PK evaluation will be discussed and agreed amongst relevant study team members (e.g. Sponsor Clinical Pharmacology/Biostatistics/Clinical Pharmacokinetics & Pharmacodynamics team representative). Appropriate action will be taken such as flagging individual values to be excluded from analysis.

The protocol deviations recorded in the Clinical Trial Management System (CTMS) may utilize different terminology. The table below displays how the terminology used in CTMS translates to the terminology used in the IAP, the SDTM and ADaM datasets, and ultimately the CSR:

CTMS	**IAP**	**SDTM**	**ADaM**
Non-important	Non-important (only for protocol deviations related to COVID-19)	Only protocol deviations related to COVID-19 are included	Only protocol deviations related to COVID-19 are included
Important	Important	Flagged with PDEVXXX code	Flagged with PDEVXXX code
Clinically Important	Clinically important	Mapped to Important	Mapped to Important

A full list of potential protocol deviations including definition and categorization is maintained by PPD in the "Study Specific Protocol Deviation List" attached to the Protocol Deviation Management Plan.

A frequency table as well as a listing of important protocol deviations, will be provided based on the FAS/SAF.

Referring to FDA, a listing of all participants affected by the COVID-19 related study disruption will be produced by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered for the Part 1A and Part 1B.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

A frequency table organized according to reason for exclusion from the DLT analysis set, as well as a listing, will be provided. More details can be found in Section 8.1.

11 Demographics and Other Baseline Characteristics

Demographic data and other baseline characteristics will be presented for the FAS/SAF analysis set using summary statistics for continuous variables and frequency statistics (i.e. counts and percentages) for categorical variables. Results will be presented as indicated in Section 9.

Listings showing demographic data and other baseline characteristics will be presented for the FAS.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening Visit eCRF pages.

The following demographic characteristics will be included:

- Sex: male, female
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, More than one race, Not collected at this site, Other
- Ethnic origin: Hispanic or Latino/Not Hispanic or Latino
- Age (years)
- Age categories: < 65 years, ≥ 65 years
- Pooled Region: North America
- Weight (kg) at Baseline
- BMI (kg/m2) at Baseline
- Eastern Cooperative Oncology Group (ECOG) Performance status (0,1,2,3,4)
- Tobacco use status (former/current/never)

Specifications for computation:

Age [years]

- Date of birth is: (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 will be used for reporting purposes.

Specifications for computation:

$$\text{BMI } [\text{kg/m}^2] = \frac{\text{weight [kg]}}{\text{height[cm]}^2} \times 10000$$

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

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the most recent MedDRA version at time of database lock, preferred term as event category and system organ class (SOC) body term as Body System category. Each participant will be counted only once within each preferred term (PT) or SOC.

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

11.3 Other Baseline Characteristics

Information on disease characteristics collected at baseline will be summarized and listed. Summary statistics will be presented for:

- ECOG Performance Status
- Site of Primary Tumor by International Classification of Diseases for Oncology (ICD-O)
- Time since initial cancer diagnosis (years) = (date of start of study treatment – date of initial cancer diagnosis + 1) / 365.25
- Time since documented locally advanced, inoperable or metastatic disease diagnosis (years) = (date of start of study treatment – date of documented locally advanced, inoperable or metastatic disease diagnosis + 1) / 365.25
- Tumor histopathologic type: Adenocarcinoma / Squamous cell carcinoma / Other
- Disease stage at initial diagnosis

- Disease stage at study entry

Incomplete dates for initial cancer diagnosis and documented inoperable or metastatic disease diagnosis will be handled as specified in Section 9.8.

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

11.4 Baseline Tumor Assessment

Information collected by the Investigator on the baseline tumor assessment collected at the screening visit on the "Tumor Assessment (according to RECIST 1.1)" eCRF pages and "Sum of Diameters (according to RECIST 1.1)" eCRF page will be presented in a listing.

11.5 Prior Anti-cancer Therapy

The prior anti-cancer therapies are collected under the "Prior Anti-Cancer Drug Therapies Details", "Prior Anti-Cancer Radiotherapy Details" and "Prior Anti-Cancer Surgeries Details", eCRF pages.

The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one type of prior anti-cancer treatment
- Participants with at least one prior anti-cancer drug therapy
- Participants with at least one prior anti-cancer radiotherapy
- Participants with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants with the following:

- At least one prior anti-cancer drug therapy
- Number of prior anti-cancer therapy regimens: 1 / 2 / 3 / ≥ 4
- Prior anti-cancer therapy regimens for metastatic or locally advanced disease
- Type of prior anti-cancer therapy
- Intent of Therapy: Neo-Adjuvant / Adjuvant / Metastatic or Locally advanced
- Best response to last prior treatment: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Not assessable / Unknown / Not applicable. Best response is derived from the last treatment regimen

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 Therapies/Procedures

The following analyses will be performed based on the FAS/SAF analysis set and presented as indicated in Section 9.

Concomitant medications are medications, other than study intervention, which are taken by participants any time during the on-treatment period, see Section 9.7.

Previous medications are medications, other than study intervention and pre-medications for study interventions, which started before first administration of study interventions.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date. To derive these flags in case of missing or partial dates, see Section 9.8.

Concomitant and previous medication each will be summarized by number and percentage of participants from the "Concomitant medications" eCRF. ATC-2nd level (Anatomical Therapeutic Chemical classification class) and PT (Preferred Term) will be summarized as given from the World Health Organization-Drug Dictionary (WHO-DD) most current version.

If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes.

The summary tables will be sorted by decreasing frequency of drug class and decreasing frequency of preferred term in a given drug class. In case of equal frequency regarding ATC classification level 2 or preferred term, alphabetical order will be used.

In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification" category. Each participant will only be counted once, even if he/she received the same medication at different times.

Any medication recorded on the "Concomitant Medications Details" eCRF page will be listed with an indication of whether the medication was previous, concomitant or both.

All **concomitant procedures**, which were undertaken during the on-treatment period will be summarized according to the CRF page "Concomitant Procedures Details". Concomitant procedures will be presented according to MedDRA SOC and PT, or in case of analyses of specific interest as classified by medical review. Number and percentage of participants with concurrent procedures (Prior, on or after the first day of study intervention or within 30 days after last dose of study intervention) overall and by type of procedure (as classified by medical review) will be presented.

A listing with the relevant information about concurrent procedures will also be produced. A flag will be added to indicate whether the procedure is:

- Prior: the procedure started before the first dose of study treatment
- Concurrent: as defined above
- Post: the procedure started after the on-treatment period or during the on-treatment period but was still ongoing at the end of it.

A procedure could therefore be prior and concurrent as well as concurrent and post-treatment.

13 Study Intervention: Compliance and Exposure

The following analyses will be performed based on the safety analysis set by dose level (and regimen if different regimens are tested) and study part.

All dosing calculations and summaries will be based on "M4076 Administration" eCRFs page.

No imputation of missing start dates of study interventions will be done. In case the last date of study intervention is incomplete the date of last study intervention administration will be taken from the M4076 Termination page.

A dose is regarded as administered if the actual dose received is > 0.

Cumulative dose (mg) is the sum of the actual doses of study intervention received overall.

Exposure duration (in weeks) is defined by:

$$\left(\frac{\text{date of last dose of study intervention} - \text{date of first dose of study intervention} + 1}{7}\right)$$

Dose intensity (mg/3 weeks period) is defined as: $\left(\frac{\text{Cumulative dose in mg}}{(\text{Duration (weeks)}/3)}\right)$

Relative Dose Intensity

The relative dose intensity (%) is calculated based on 3-weeks period by dividing the dose intensity by the planned 3-weekly cumulative dose.

The summary of study intervention exposure will include the following information:

- Exposure duration (in weeks): overall distribution and by categories of < 1 period, ≥ 1 period to < 2 periods, ≥ 2 period to < 3 periods, and ≥ 3 periods. Categories may be updated based on observed treatment duration. Counts of participants who discontinued during each period (Period 1, Period 2, Period ≥ 3) will be provided along with reason for treatment discontinuation.
- Cumulative dose (mg): overall distribution
- Dose intensity (mg/3 week): overall distribution

- Relative dose intensity (%) by categories of < 60%, ≥ 60% to < 80%, ≥ 80% to < 90%, ≥ 90% to ≤ 120%, and > 120%
- Number and percentage of participants with at least one dose reduction (overall and by primary reason):
  - Due to adverse event
  - Due to other reason
- Number and percentage of participants with at least one missed dose (overall and by primary reason):
  - Due to adverse event
  - Due to other reason
- Number of missed doses per cycles (Cycle 1, Cycle 2, Cycle ≥ 3) by categories of: 1 to 4 missed doses; 5 to 10 missed doses; ≥ 11 missed doses.

Note: Cycles are calculated as treatment periods of 3 weeks (21 days) in length.

A listing will be provided for all study intervention administrations. In Part B1, information on meal intake will be provided in addition to the study intervention administration details.

14 Efficacy Analyses

The following analyses will be performed based on the FAS/SAF by dose level (in increasing order) and summarized by study part, except when otherwise stated. In case a participant received > 120% cumulative dose of the planned dose, the data of this participant will not be included in efficacy summary outputs. The data will be displayed in listings and figures but with a footnote stating the actual cumulative dose.

14.1 Primary Estimand

No primary efficacy estimand is specified.

14.2 Further Estimands

No further estimands are specified.

14.2.1 Secondary Endpoint: Objective Response (OR)

Tumor assessments are collected on the CRF pages: “Tumor Assessment - Target Lesions”, “Sum of Diameters”, “Tumor Assessment - Non-Target Lesions”, “Tumor Assessment - New Lesions” and “Assessment of Disease based on Imaging.”

Best Overall response (BOR) will be assessed based on reported overall responses at different evaluation time points from the study intervention start date until documented disease progression

in accordance to RECIST v1.1 by investigator, taking requirements for confirmation into account as detailed below.

Only tumor assessments performed before the start of any subsequent anti-cancer therapies will be considered in the assessment of BOR. If a tumor assessment was performed on the same day as start of new anti-cancer therapy, it will be assumed that the tumor assessment was performed prior to the start of the new anti-cancer therapy, therefore the tumor assessment will be included in the assessment of BOR.

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 participant has no post-baseline tumor assessments before starting new anticancer therapy, BOR will be NE.

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

BOR Based on Confirmed Responses:

- 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) = at least one SD assessment (or better) ≥ 6 weeks after 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) ≥ 6 weeks after start date (and not qualifying for CR or PR).
- Progressive Disease (PD) = PD ≤ 12 weeks after start date of study treatment (and not qualifying for CR, PR, non-CR/non-PD or SD).
- Not Evaluable (NE): all other cases.

Confirmation of response is not necessarily required at the next scan, but could be at any subsequent scan before PD. For instance, if a participant has PR-SD-PR or PR-NE-PR at consecutive tumor assessments, the best overall response will qualify for PR.

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.

Confirmed Objective Response (OR) is defined as a confirmed best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1.

Participants who do not have an on-treatment radiographic tumor assessment due to early progression, who receive anti-tumor treatments other than the study intervention 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').

OR rate (ORR) is the proportion of participants with OR in the analysis set. No formal statistical hypotheses will be tested.

The number and percentage of participants with unconfirmed and confirmed BOR of CR, PR, SD, on-CR/non-PD, PD, and NE will be tabulated.

The unconfirmed and confirmed ORR by dose level will be presented along with the two-sided 95% CI using the Clopper-Pearson method (1934) (exact CI for a binomial proportion as computed by default by the SAS FREQ procedure using the EXACT option).

A swimmer plot displaying some key radiological milestones will be produced by dose level. For each subject, the time on treatment will be represented. In addition, the 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).

Tumor shrinkage (%) is defined as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesions and short axis for nodal lesions as reported in the "Sum of diameters (according to RECIST 1.1)" eCRF page)) per time point. The tumor response will be based on the Investigator assessment. It will be derived as:

$$\left(\frac{\text{Sum of target lesions at Week XX} - \text{ sum of target lesions at baseline}}{\text{Sum of target lesions at baseline}}\right) \text{x } 100$$

The maximum tumor shrinkage (%) will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of new anticancer therapy, as:

$$Minimum\left(\left(\frac{\text{Sum of target lesions at Week XX} - \text{ sum of target lesions at baseline}}{\text{Sum of target lesions at baseline}}\right) \text{x } 100\right)$$

The tumor shrinkage as well as the first occurrence of a new lesion and participant off study intervention will be displayed against time point (months) in a line plot (spider plot).

In addition, 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 tumor shrinkage will be created including all participants with measurable disease at baseline and at least one valid post-baseline assessment. The confirmed BOR will also be presented as an annotation on each vertical bar.

In addition, Subject data listings of tumor assessments and responses will be provided, including lesion number, description and location, type of lesion, imaging date, assessment method, diameter (mm), sum of diameter of target lesions (mm), confirmed BOR and best percent change in sum of

diameters (as recorded from the "Target Lesions", "Sum of Diameters", "Non-Target Lesions", "New Lesions" and "Assessment of disease based on imaging" eCRF pages).

14.2.2 Secondary Endpoint: Progression Free Survival (PFS)

Progression Free Survival (PFS) time is defined as the time (months) from start date to the date of the first documentation of objective PD or death due to any cause, whichever occurs first. The tumor response will be determined according to RECIST 1.1 and assessed by Investigator.

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

PFS data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death), or with an event after two or more missing tumor assessments. Participants who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the start date unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

The last adequate tumor assessment is defined as the last tumor assessment result that is not "NE" or "NA".

The censoring and event date options to be considered for the PFS analysis is presented in Table 5.

Table 5 Progression-free Survival Event / Censoring

PFS Event Status		Censoring	Date of event / censoring
Progressed or died	Before any planned tumor assessment or within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD	Event	Minimum (Date of PD, Date of death)
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first dose of study intervention, whatever is later
Neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first dose of study intervention, whatever is later

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median PFS time with two-sided 95% CIs. In particular, the PFS rate at 3, 6 and 12 months and estimates for every 6 months will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the

untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

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

14.2.3 Secondary Endpoint: Duration of Response (DoR)

DoR is defined, for participants with confirmed objective response only, as the time (months) from first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause. If a participant has not had an event (PD or death), DoR is censored at the date of last adequate tumor assessment. The censoring rules for DoR are as described for PFS (Section 14.2.2).

The last adequate tumor assessment is defined as the last tumor assessment result that is not "NE" or "NA".

DoR (months) = [date of event or censoring– first date of OR +1]/30.4375

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median DoR time with two-sided 95% CIs. In particular, DoR rate at 3, 6, 12 months and estimates for every 6 months thereafter will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and CIs for the survival function estimates at the time points defined will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980) (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

DoR will be displayed graphically and analyzed using Kaplan-Meier methodology analogous to that used for PFS as described in Section 14.2.2. If the number of participants with OR is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

15 Safety Analyses

This section includes specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

The DLT analysis will be performed on the DLT analysis set. All other safety analyses will be performed on the SAF analysis set.

15.1 Dose Limiting Toxicities (DLT) Analysis

Of note, DLT as per SMC decision will be available in the table "Review of data" in the SMC minutes. In case a new DLT appears after the DLT period, the minutes will be updated.

For primary analysis, a table will display the following (per dose level (and regimen if different regimens are tested)) and in total for Part 1A and Part 1B) for the DLT analysis set:

- Number and percentage of participants with a DLT per investigator's judgement as recorded in eCRF (using DLT flag from the AE CRF page)
- Number and percentage of participants with a DLT per SMC decision

A listing of DLTs (per investigator and/or per SMC) will be provided by dose level and participant, including whether it was judged to be a DLT by investigator and/or by SMC.

This listing will additionally contain age, sex, site of primary tumor, SOC, PT, verbatim, CTCAE grade, SAE (yes/no), DLT per investigator (yes/no), DLT per SMC, relatedness to M4076 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M4076, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

In addition, the following will be presented:

- Mean and Quantiles (2.5%, 25%, 50%, 75%, 95% and 97.5%) for the posterior probability of a participant experiencing a DLT at each of the dose levels used in the study according to the same Bayesian Logistic Regression Model (BLRM) as described in the SMC IAP (see Appendix18.2) or SMC charter (if change occurred). For this analysis either SAS or R (using the package bcrm or crmPack) will be used.

MTD suggestion from the Bayesian two-parameter logistic regression model

The MTD as suggested from the modeling will be derived as follows:

(1) The BLRM will be updated with all DLT data (SMC decision) from the dose escalation.

(2) The dose with targeted toxicity probability of 30% will be identified for each of the MCMC samples. The median of all the "30% doses" over the MCMC samples will be the fitted dose for MTD.

(3) The next lower tested dose with the upper bound of the one-sided 95% credible interval ≤ 40% and with estimated DLT probability ≥ 17% and ≤ 30% will be selected as suggested MTD.

(4) If none of the tested doses fulfill the criteria in 3), there is no MTD suggestion from the model.

This information from items (3) and (4) will be forwarded to the SMC that will decide on the determination of the MTD.

Additionally, the SMC will receive the estimated DLT probability and associated probability quantiles for all other doses tested.

The fitted dose with 30% DLT probability (from item (2)) and the two-sided 95% credibility interval will be tabulated.

For above analysis either SAS or R (using the package bcrm or crmPack) will be used.

Frequentist MTD suggestion

As second approach, the MTD as suggested by the frequentist estimation will also be derived:

(1) All DLT data from the dose escalation will be included in a two-parameter logistic regression model (intercept and slope over log of the scaled dose, no prior; if the model does not converge, it will be reported as not calculable; the program code for this analysis can be found in the TLF shells).

(2) The dose with targeted toxicity probability of 30% will be identified.

(3) The next lower tested dose will be selected as suggested MTD.

The fitted dose with 30% DLT probability (from item (2)) and the two-sided 95% confidence interval will be tabulated.

Additionally, a table will be produced, providing the estimated probability for DLT with a 95% confidence interval, based on the frequentist logistic model.

The models will be based on DLTs as identified by SMC.

15.2 Adverse Events

Adverse Events (AE) will be analyzed among the Safety analysis set and presented by dose level (and regimen if different regimens are tested) and overall, and by study part, if not otherwise specified.

Part 1A:

Treatment-emergent adverse events (TEAEs) are those events with onset or worsening dates occurring within the on-treatment periods as defined in Section 9.7.

This also includes AEs ongoing at baseline, which first improve under study intervention and then worsen irrespective of baseline. Adverse events with changes in toxicity grade/severity, seriousness or outcome of AEs are recorded as separate entries in the eCRF with associated end and start dates (start date equals end date of previous entry, supported in eCRF v8.4 by

'AECHGID' in SUPPAE). Records of the same AE will be considered as one event in the analysis. If the severity of the reported event worsens after start of treatment, the TEAE flag will be re-evaluated for the worse and the subsequent records as per the TEAE definition. If the worse record starts outside of the on-treatment period, it will not appear on the summaries/listings of TEAEs, unless otherwise specified. These events will be kept as separate records in the database in order to maintain the full detailed history of the events. The overall outcome of the adverse event is the outcome of the last event in the sequence. When such AEs are listed, start, end date and outcome should be provided together with change date, toxicity grade/severity and seriousness per episode.

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

Part 1B- Cross-over design:

Treatment-emergent AEs (TEAEs) are those events with onset dates on or after the first administration of study intervention in the first food effect assessment period. Any AE occurring before the administration of study intervention on Day 1 of the first food effect assessment period and resolved before administration of study intervention or not worsening after administration of study intervention in the first food effect assessment period will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as "pre-treatment" AEs. An AE occurring after administration of study intervention will be counted towards the last treatment received before the onset, even if the event is not resolved at the beginning of the following food effect assessment period. An AE that worsens during a later food effect assessment period will be counted towards both treatments.

In case AE-related dates are partial, the available information will be used in a conservative approach to determine whether the AE is treatment-emergent. All analyses described in Section 15.2 will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest by primary System Organ Class (SOC) and Preferred Term (PT) in alphabetic order.

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

15.2.1 All Adverse Events

Adverse Event information is collected on the "Adverse Events Details" eCRF page.

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).

If a qualifying AE is reported for a given participant more than once during study intervention, the worst toxicity and the worst relationship to study intervention will be tabulated. In case a participant had 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 9.9.

The following tables will be created, split by dose level and overall, and by study part:

- The number and percentage of participants with:
  - Any TEAEs
  - Any TEAEs by worst NCI-CTCAE severity grade (≥ 3, ≥ 4)
  - Any M4076 related TEAEs
  - Any M4076 related TEAEs by worst NCI-CTCAE severity grade (≥ 3, ≥ 4)
  - Any M4076 related TEAEs leading to permanent discontinuation of study intervention
  - Any Serious TEAEs
  - Any non-serious TEAEs
  - Any related serious TEAEs
  - Any treatment-emergent AE of special interest (AESI) Cytopenia (as reported in the eCRF)
  - Any treatment-emergent AESI Cytopenia by worst NCI-CTCAE severity grade (≥ 3, ≥ 4) (as reported in the eCRF)
  - Any TEAEs leading to death (AEs with Grade 5 or outcome "fatal" if grade 5 not applicable)
  - Any related TEAEs leading to death

In addition, all AEs will be tabulated by dose level and regimen (if different regimens tested) and overall and presented by PT and primary SOC in alphabetical order.

For Part 1B the following tables will be created in addition, split by dietary status ("Fed" and "Fasted") and overall:

- The number and percentage of participants with at least one TEAE by worst NCI-CTCAE severity grade (any grade vs. Grade ≥ 3), SOC and PT.

A horizontal mirror bar chart will be produced to display TEAEs by worst NCI-CTCAE severity grade. The figure will be split into two time periods (TEAEs occurring during Period 1 vs. TEAEs occurring on or after Period ≥ 2). AE preferred terms will be displayed along the vertical axis and the absolute number of participants with an AE in each preferred term will be displayed on the horizontal axis. The horizontal axis will be split by time (Period 1 vs. Period ≥ 2), with incidence of 0 in the center of the axis. Any TEAEs with start date during Period 1 will be displayed on the left side of the mirror plot and any TEAEs with start date on or after Period 2 will be displayed on the right side of the mirror plot. The worst grade will always be displayed, i.e. in case a change in grade occurs within a specified time period, the worst grade will be displayed. Events that occurred

in Period 1 and continued to Period ≥ 2 will be displayed on both time periods. If an event improves during Period 1 but continues to Period ≥ 2, this event will only be displayed at the left side of the mirror plot (Period 1).

Display of NCI-CTC severity grade will also differ in color. Within each bar, incidence of TEAEs of toxicity Grades 3 to 5 will be shown in a darker shade and TEAEs of toxicity Grades 1 to 2 will be displayed in a lighter shade. Only TEAEs occurring in at least two participants or with frequency higher than 10% across all dose levels, whichever is greater, will be included in the figure. Preferred terms will be sorted in order of descending frequency of incidence among participants in Period 1.

A listing of all AEs (whether treatment-emergent or not) will be provided. This listing will be sorted by study part, dose level and participant. This listing will additionally contain age, sex, site of primary tumor, SOC, PT, verbatim, CTCAE grade, SAE (yes/no), DLT per investigator (yes/no), DLT per SMC, relatedness to M4076 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M4076, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

Similarly, a listing of all adverse events Grade ≥ 3 (including non TEAEs) will be provided.

15.2.2 Adverse Events Leading to Discontinuation, Interruption or Dose Reduction of Study Intervention

The frequency (number and percentage) of participants with each of the following will be presented in a summary table:

- Any TEAEs leading to temporary discontinuation of M4076
- Any related TEAEs leading to temporary discontinuation of M4076
- Any TEAEs leading to permanent discontinuation of M4076
- Any related TEAEs leading to permanent discontinuation of M4076
- Any TEAEs leading to dose reduction of M4076*
- Any related TEAEs leading to dose reduction of M4076*

All TEAEs will be tabulated by dose level and total in a table displaying in separate columns and showing the incidence of TEAEs by SOC and PT (both sorted alphabetically).A listing of TEAEs leading to treatment discontinuation, interruption, or dose reduction of study intervention will be provided. This listing, sorted by study part, dose level and participant, will also include age, sex, site of primary tumor, SOC, PT, verbatim, CTCAE grade, SAE (yes/no), DLT per investigator (yes/no), DLT per SMC, relatedness to M4076 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M4076, outcome, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

* Note, dose reduction here is as a response to the eCRF AE page item “Action(s) taken with M4076”.

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 study intervention, death within 60 days after first dose, as well as reason for death until end of study, will be tabulated based on information from the "Death" and "Survival Follow-Up" CRFs.

- Number of Deaths
- Number of Deaths within 30 days after last dose of M4076
- Number of Deaths within 60 days after first dose of M4076
- Primary Reason of Death
  - Progressive disease and/or disease related condition
  - Event unrelated to M4076
  - Event related to M4076
  - Unknown

In addition, a listing of Deaths will be provided, defined as any AE with Grade 5, or outcome "fatal" if grade 5 not applicable. This will be sorted by study part, dose level and participant. This listing will additionally contain age, sex, site of primary tumor, SOC, PT, verbatim, CTCAE grade, SAE (yes/no), DLT per investigator (yes/no), DLT per SMC, relatedness to M4076 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M4076, if treatment was stopped before start of AE: days since stop of treatment, outcome, as well as a flag for death within 30 days of last dose of study intervention and a flag for death within 60 days of first dose of study intervention.

15.3.2 Serious Adverse Events

The frequency tables as listed in Section 15.2.1 will be prepared for serious adverse events (SAEs).

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.

15.3.3 Other Significant Adverse Events

Other safety observations - Cytopenia

The MedDRA search list for Cytopenia is based on the standardized MedDRA query (SMQ) 'Haematopoietic cytopenias SMQ broad scope.

This SMQ will be summarized overall and PT,

- by worst NCI-CTCAE severity grade (any grade vs. Grade ≥ 3)
- related according to Investigator.

A listing of AESIs as reported in the eCRF, and a listing of SMQ 'Haematopoietic cytopenias SMQ broad scope' will be provided. These listings will be sorted by study part, dose level and participant. These listings will additionally contain age, sex, site of primary tumor, SOC, PT, verbatim, CTCAE grade, SAE (yes/no), DLT per investigator (yes/no), DLT per SMC, relatedness to M4076 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M4076, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

15.4 Clinical Laboratory Evaluation

All laboratory values will be reported in SI units.

Laboratory values (including corresponding normal ranges) from local laboratories will be used for summary statistics and shift tables. In case both central and local labs are collected, summary statistics will be based on central lab collected data, while summaries of worst on-treatment abnormalities will be based on both local and central lab data.

All protocol-required clinical laboratory assessments can be found in Table 7 (see Appendix 18.1).

Laboratory results will be classified according to the NCI-CTCAE v5.0 (see Appendix 18.1). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

For the definition of baseline measurement please see Section 9.2.

Values below the detection limit will be imputed by half of the detection limit.

In case just a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g "> 7.2 mmol" will be analyzed as 7.3.

Quantitative data will be summarized using descriptive statistics presenting baseline value, maximum on treatment, and minimum on treatment as well as their changes to baseline.

Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, and High).

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 at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g.,

hyperkalemia), and vice versa. The same applies for non-gradable parameter, and description of changes from N/L to H and N/H to L will be provided, accordingly.

For **WBC differential counts** (total neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) * (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
    - derived absolute count does not meet Grade 2-4 criteria, and
    - % value < % LLN value, and
    - derived absolute count ≥ 800/mm^3
- Neutrophil count decreased:
    - derived absolute count does not meet Grade 2-4 criteria, and
    - % value < % LLN value, and
    - derived absolute count ≥ 1500/mm^3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO), if available. 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 (TBILI) 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.

Parameters with NCI-CTC grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of participants and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of participants evaluable for CTCAE grading (i.e. those participants with normal values or for whom a Grade 1, 2, 3 or 4 can be derived). Grade 0 is not defined per NCI-CTCAE but will be used in derivations for simplicity to indicate that evaluable measurements are available.

- 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.

    - In case of gradings involving baseline measurements (see Section 9.10) for the identification of grades during the on-treatment period, the shift table will present baseline normal and abnormal. Normal will include measurements below and within normal range (direction increase), or measurements within and above normal range (direction decrease).

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, i.e.:

Hematology:

- Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

Serum Chemistry:

- Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased).

Please see Appendix 1 for a list of the NCI-CTC -gradable parameters.

Parameters with NCI-CTC grades not available:

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

- Summary by worst on-treatment value (low/normal/high/missing/overall)
- 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, Reticulocytes, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Volume (MCV).

  Serum Chemistry:

- Blood Urea Nitrogen (BUN), Total Protein, Total Urea.

All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

- Coagulation: activated partial thromboplastin time (aPTT) and prothrombin time (INR).
- Urinalysis: all urinalysis parameters
- Serum and urine human chorionic gonadotropin pregnancy test

Serology (with no preclinical signs of hepatotoxicity, hepatitis B surface antigen, hepatitis C virus antibody and HIV screening).Following figures will be provided:

eDISH plot

A plot (eDISH) of peak ALT and AST versus peak total bilirubin, both relative to the upper limit of normal (ULN) will be provided. This eDISH plot (evaluation of drug-induced serious hepatotoxicity) will have reference lines at 3×ULN for ALT and AST and at 2×ULN for total bilirubin.

Line plots:

Graphical display (line plots) of platelet count, hemoglobin, Reticulocytes / Erythrocytes (% of RBC), neutrophils, lymphocytes, monocytes, creatinine, lipase, amylase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin and INR will be provided by actual time in days and by part and dose level for all analyses (with x-axis time, y-axis lab value), using different colors per dose level and different line types to identify participants.

Where feasible, reference lines for CTCAE grades should be added to graphical displays.

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each participant. Laboratory values that are outside the normal range will be flagged in the data listings, along with corresponding normal ranges and CTCAE grades.

In addition, listings of clinically significant Hematology and Biochemistry values (≥ Grade 3) will be provided.

For the cross-over design in Part 1B, laboratory parameters will be summarized indicating the dietary status at the respective time-point using descriptive statistics for absolute values and change from baseline over time. Tables will be produced for Hematology and Biochemistry laboratory parameters.

15.5 Vital Signs

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) presenting baseline value, maximum on treatment, and minimum on treatment as well as their changes to baseline.

The maximum changes of vital sign measurements screening/baseline to maximum changes after start of 1st study intervention will be grouped as follows:

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

For each participant the worst on-treatment value will be calculated. For the definition of baseline values see Section 9.2. Missing values will define a separate category.

The following summaries will be prepared for vital sign parameters as grouped above:

- Maximal shifts (changes in categories)
- Listing of highest change per participant

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

For the cross-over design in Part 1B, vital signs will be summarized for absolute values and changes from baseline by time-point and dietary status using descriptive statistics.

15.6 Other Safety or Tolerability Evaluations

15.6.1 ECOG Performance Status

ECOG Performance Status information is collected on the "ECOG Performance Status" eCRF page and as described in the following table:

Table 6 Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG Performance Status will be provided in a listing.

15.6.2 Electrocardiogram (ECG)

Standard 12-Lead ECG

12-Lead ECG information will come from the "ELECTROCARDIOGRAM - (Single) Local" eCRF page.

ECG summaries will include all 12-lead ECG assessments from the on-treatment period. All 12-lead ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

The following analyses will be performed for each applicable ECG parameters (HR, and QT, QTcF, QRS, PR intervals) by dose level, overall, and study part during the treatment period. Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

- For each of the ECG parameters (HR, QT, QTcF, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point.
- Frequency (number and percentage) of participants with notable ECG values according to the following categories:
    - QTcF* increase from baseline > 30 ms, > 60 ms
    - QTcF* > 450 ms, > 480 ms, > 500 ms

- HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
- HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
- PR ≥ 220 ms and increase from baseline ≥ 20 ms
- QRS ≥ 120 ms

The denominator to calculate percentages for each category is the number of participants evaluable for the category.

- Frequency (number and percentage) of participants with post-baseline qualitative ECG abnormalities (morphology) will be presented as a shift table showing baseline versus the worst on-treatment result (Normal, Abnormal (not clinically significant), Abnormal (clinically significant)).

For the cross-over design in Part 1B, ECG data will be summarized in addition by dietary status ("Fed" and "Fasted") and time-point using descriptive statistics for absolute values and change from baseline over time. *The QTcF (corrected by the Fridericia's formula) value will be collected in the eCRF page;

Triplicate 12-lead ECG (Digital ECG)

Triplicate 12-lead ECG will be also obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTcF intervals. Electrocardiogram (ECG) results will be read locally, and all the three results will be reported in the eCRF.

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

The average of the replicate measurements should be determined after the derivation of the individual parameter at each time point and will be used for summaries as defined in the standard 12-lead ECG section above.

Relationship of PK concentration to change from baseline QTc will be explored by concentration-QT analysis. This analysis will be described by a separate analysis plan. Results of this analysis will not be reported in CSR and may be reported as a separate analysis report.

16 Analyses of Other Endpoints/Estimands

16.1 Pharmacokinetics

All statistical analyses and descriptive summaries of PK data will be performed on the PKAS.

16.1.1 Descriptive Statistics of PK Concentration Data

Plasma PK measurements will be listed and descriptively summarized using: number of subjects (N), number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

Missing statistics, e.g. when they cannot be calculated, should be presented as “NC”. “ND” will be used if a PK sample was not taken.

Descriptive statistics will only be calculated for n>2 in which a measurement of BLQ represents a valid measurement and will be taken as zero for summary statistics of PK concentration data. Values below the LLOQ will be treated as zero for the calculation of summary statistics and graphical presentations

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. In export datasets, as well as in the SDTM PC domain, PK concentrations will be provided with full precision and will not be rounded.

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

N, n	0 decimal place
Mean, Min, Median, Max:	3 significant digits
SD:	4 significant digits
CV%:	1 decimal place

Urine concentrations and volumes will be listed but not be summarized.

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data will be descriptively summarized using: number of subjects (N), number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM). For PK parameters related to time (e.g. t_{max} t_{last}), only n, Min, Median, and Max may be reported.

Descriptive statistics will only be calculated for a PK parameter when n>2.

PK parameters read directly from the measurements (i.e. C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the SDTM PP domain, PK parameters will be provided with full precision and will not be rounded. 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:

N, n	0 decimal place
Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
SD:	4 significant digits
CV%, GeoCV%:	1 decimal place

16.1.3 Statistical Analysis of PK Parameter Data

Dose proportionality will be provided separately for $AUC_{0-\infty}$, AUC_{τ}, $AUC_{0-tlast}$ and C_{max} on study day 1 and 8 for Part 1A using a power model. The power model will have the form:

$Y = a*(dose)b$

where Y is the PK parameter, and a and b are the coefficient and exponent, respectively, of the power equation. By taking the natural logarithm (ln), the power model can be analysed using linear regression and has the form:

$ln(Y) = ln(a)+b*ln(dose) + error$

$=\alpha + \beta*ln(dose) + error,$

where α is the intercept, and β is the slope, and ln(dose) is based on the dose size for each subject. For each PK parameter, the point estimate of slope β and its 95% CI will be provided. In addition, the estimated regression line will be overlaid on the individual points in the corresponding scatter plot (log-log scale).

Dose proportionality will be declared if the 90% confidence interval (CI) for β is entirely contained within the critical region,

$$\left(1 + \frac{\ln(0.50)}{\ln(r)}, 1 + \frac{\ln(2.00)}{\ln(r)}\right)$$

where r is the ratio of the highest and the lowest dose in a given part of the study. Dose proportionality for participants who were administered the study intervention will be tested for C_{max} and $AUC_{0-\infty}$, AUC_{τ}, $AUC_{0-tlast}$ on Day 1 and at steady state.

Since the study is neither optimally designed nor powered to confirm the presence or absence of meaningful departures from dose proportionality, these results should be interpreted with caution. In addition, graphical assessment would also be considered to understand dose proportionality.

If the samples remain above LLOQ for the whole dosing interval, then $AUC_{0\text{-tlast}}$ will be the same as AUC_{τ} for Part 1A as there is another dose after 24 hours

A statistical analysis will be conducted to investigate the food effect on the treatment by comparing (fed) treatment to (fasted) treatment for Part 1B.

The natural log (ln)-transformed $AUC_{0\text{-}\infty}$, AUC_{τ} , $AUC_{0\text{-tlast}}$ and C_{max} will be analyzed using a mixed effect model. The model will include planned treatment sequence, period, and actual treatment as fixed effects, and subject within planned treatment sequence as a random effect.

For each PK parameter separately, the least squares mean (LSM) for each treatment, difference in LSMs between the fed and fasted treatments, and corresponding 90% confidence intervals (CIs) will be calculated; these values will then be back-transformed to give the geometric least square mean (GLSM), ratio of GLSMs, and corresponding 90% CIs;

Additionally, the pooled estimate (across treatments) of the within-subject coefficient of variation (CV) will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

16.1.4 General Specifications for PK Concentration and PK Parameter Data

Predose samples that occur before the first or subsequent drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study intervention administration.

Predose or trough samples which have been taken after the subsequent dosing will be reported as a protocol deviation. The resulting concentrations will be included in concentration listings but excluded from descriptive statistics of concentrations and from PK parameter estimation.

Values below the lower limit of quantification (BLQ) will be taken as zero for summary statistics of PK concentration data, PK parameter estimation (e.g. AUC) and for graphical presentations.

In case profiles have a measurable pre-dose concentration less than or equal to 5% of its C_{max} value, the participant's data will be included in the PK and statistical analyses without any adjustments. If the pre-dose value is greater than 5% of the C_{max}, the participant's data for the affected profile will be included in the PK evaluation but excluded from descriptive and further statistical evaluation after agreement with the sponsor.

Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as "N.R.". A participant who withdraws prior to the last planned observation will be included in the analyses up to the time of discontinuation.

Samples that are collected outside with a time deviation of > 10% from the protocol-scheduled time will be included in the PK parameter estimation (NCA) but will be excluded from the concentration summary and mean/median concentration plots.

PK concentrations which are erroneous due to a sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed by the Sponsor. In this case the rationale for exclusion will be provided in the CSR. Any other PK concentrations that appear implausible to the Clinical Pharmacologist/Clinical PK/PD Scientist will generally not be excluded from the analysis and data handling will be agreed with the sponsor clinical pharmacologist/PK scientist. Any implausible data will be documented in the CSR.

If important protocol deviations occurred likely to affect the PK profile of participants as specified in Section 10.2.1, the impacted concentrations and PK parameters will be excluded from summary statistics and further statistical evaluation.

Any PK concentrations or PK parameters excluded from summary statistics will be included in participant's listings and flagged; a reason for exclusion will be detailed in the CSR (e.g. a footnote or a table of exclusions). Any flags should be included in the study specific CDISC data sets.

PK concentrations and PK parameters excluded from summary statistics will not be included in mean/median figures. Mean/median plots will only contain values where n>2; if a cohort size is less than 2 individual data will be included in this plot. Footnote with details will be added.

In case of missing or incomplete urine/feces samples, affected urine/feces PK parameters will be flagged in the listings and excluded from descriptive statistics if calculated.

16.1.5 Estimation of Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA) will be used to derive PK parameters applying non-compartmental analysis (NCA).

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to generate additional PK parameters, produce tables, listings and figures.

16.1.5.1 Estimation of Pharmacokinetic Parameters in Plasma

PK parameters analysis will be calculated using the actual elapsed time since dosing, with the exception of the interim analysis for SMC. In cases where the actual sampling time is missing, calculations may be performed using the scheduled time. Details (e.g. number of samples, participants affected) will be described in the CSR. In cases actual dosing time is missing, scheduled time might be used for NCA after performance of adequate plausibility checks and agreement with the sponsor. Decision and rationale should be included in the CSR.

The following plasma PK parameters will be calculated for M4076 where appropriate

Symbol	Definition
$AUC_{0\text{-}tlast}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}tlast}$/Dose	The Dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Normalized using the actual dose, using the formula $AUC_{0\text{-}tlast}$ /Dose.
AUC_{τ}	The AUC over the dosing interval from T1=0 h to T2=τh. Calculated using the mixed log-linear trapezoidal rule (linear up, log down). For single dose, AUC_{τ} is calculated as a partial area with the defined time range. In multiple dose profiles AUC_{τ} is calculated at steady state from one pre-dose time point to the dosing interval time. In cases where the actual observation time is not equal to the scheduled observation time AUCτ will be calculated based on the estimated concentration at τhours, and not the concentration at the actual observation time where a regression has been performed.
AUC_{τ} /Dose	The dose normalized AUC over the interval from T1=0 h to T2= τ h. Normalized using actual dose, using the formula AUC_{τ} /Dose.
$AUC_{0\text{-}72}$	The AUC from time zero (= dosing time) to 72 hours post-dose. Calculated using the mixed log-linear trapezoidal rule (linear up, log down). In cases where the actual observation time is not equal to the scheduled observation time (72 hours), $AUC_{0\text{-}72}$ will be calculated based on the estimated concentration at 72 hours, and not the concentration at the actual observation time (Part 1B only).
$AUC_{0\text{-}72}$/Dose	The dose normalized AUC from time zero (= dosing time) to 72 hours post-dose. Normalized using actual dose, using the formula $AUC_{0\text{-}72}$ /Dose. (Part 1B only)
$AUC_{0\text{-}\infty}$	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 λz determination. $AUC_{0\text{-}\infty} = AUC_{0\text{-}tlast} + C_{last\ pred}/ \lambda_z$ (single dose only)
$AUC_{0\text{-}\infty}$/Dose	The dose normalized AUC from time zero extrapolated to infinity. Normalized using actual dose, using the formula $AUC_{0\text{-}\infty}$ /Dose. (single dose only)
CL/F	The apparent total body clearance of study intervention following extravascular administration. CL/F= Dose p.o. /$AUC_{0\text{-}\infty}$. (single dose)
C_{max}	Maximum observed concentration
C_{max}/Dose	The dose normalized maximum concentration. Normalized using the actual dose, and the formula C_{max} /Dose.
C_{trough}	The concentration observed immediately before next dosing (Part 1A only)
LI	The linearity index after repeated administration calculated as LI= (AUC_{τ} after multiple dose) / ($AUC_{0\text{-}\infty}$ after single dose) (Part 1A, Day 8 only)
$R_{acc(AUC\tau)}$	The accumulation ratio after repeated administration calculated as $Racc(AUC_{\tau})$ = (AUC_{τ} after multiple dose) / (AUC_{τ} after single dose) (Part 1A, Day 8 only)
$R_{acc(Cmax)}$	The accumulation factor to assess the increase in maximum concentration until steady state is reached. $R_{acc(Cmax)}$ = (C_{max} after multiple dose)/ (C_{max} after single dose) (Part 1A, Day 8 only)
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification

t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
V_z/F	The apparent volume of distribution during the terminal phase following extravascular administration. Vz/F = Dose/($AUC_{0-\infty}$*λ_z) following single dose.

The following urine PK parameters will be calculated where appropriate

Symbol	Definition
Ae_{t1-t2}	Total amount excreted between times t1 (= start) and t2 (= end) of the current collection interval. Calculated by interval Ae_{t1-t2} = Conc * $Vu(t_{1-t2})$ and cumulative.
fe_{t1-t2} %	Fraction of administered drug that is excreted unchanged in urine between times t1 (= start) and t2 (= end) of the current collection interval. Calculated by interval fet1-t2 = Aet1-t2/Dose and cumulative.
CL_R	The renal clearance of study intervention. $CL_R = Ae_{0-t}/AUC_{0-t}$.

Additional PK parameters may be calculated where appropriate.

Units for PK parameter output will be based on concentration and dose units used in the study, unless otherwise specified. In case concentration data units change within the study, PK parameters will be reported using consistent units throughout study outputs. In such cases, the Sponsor will specify relevant units for reporting before the final PK evaluation.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

In cases where the actual observation time is not equal to the scheduled observation time, AUC_τ and AUC_{0-72}, other partial areas will be calculated based on the estimated concentration at τ hours, 72h, and not the concentration at the actual observation time.

The following rules might be applied for calculation of AUC_τ, AUC_{0-72}, after agreement with the Sponsor:

- In case suitable regression cannot be performed, partial areas may be calculated using the actual sampling time provided it is within 10% of the actual sampling time.

- In cases BLQ concentrations occur at the end of the collection interval, these concentrations might be set to missing for calculations of partial AUCs. This is an exemption to the general BLQ handling rule and should be applied in case its application would result in estimation of implausible partial AUC values. Implausibility is considered in cases partial AUCs were greater than $AUC_{0-\infty}$.

- At steady state, the pre-dose concentration may be duplicated and used as the trough concentration for calculation of AUC_τ if the sample prior to the next dose is missing and vice versa.

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

Symbol	Definition
λ_z low	First (λ_z low) time point of the time interval of the log-linear regression to determine λ_z.
λ_z up	Last (λ_z up) time point of the time interval of the log-linear regression to determine λ_z.
Nλ	Number of data points (Nλ) included in the log-linear regression analysis to determine λ_z.
Rsq, adj	Adjusted goodness of fit statistic (adjusted Rsq) for calculation of λ_z
$AUC_{extra\%}$	AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. ($AUC_{extra\%}$)
Span ratio	Span ratio of interval over which $t_{1/2}$ was estimated/$t_{1/2}$

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. If warranted, further adjustment may be made by the pharmacokineticist, after agreement with the Sponsor. The last quantifiable concentration >LLOQ should always be included in the regression analysis, while the concentration at t_{max} and any concentrations BLQ which occur after the last quantifiable data point >LLOQ should not be used.

If $AUC_{extra\%}$>20% and/or the coefficient of correlation (Rsq adj) of λ_z is <0.8 and/or the observation period over which the regression line is estimated (span ratio) is less than 2-fold the resulting $t_{1/2}$, the rate constants and all derived parameters (e.g. $t_{1/2}$, $AUC_{0-\infty}$, CL/F etc.) will be listed, flagged and included in the parameter outputs and excluded from descriptive statistics and further statistical evaluation.

If $AUC_{0-\infty}$ cannot be determined reliably for all subjects and/or dose levels/treatments, an alternative AUC measure, such as AUC to a fixed timepoint or $AUC_{0-tlast}$, may be used in the statistical analysis of dose proportionality and/or food effect.

16.1.5.2 Estimation of Pharmacokinetic Parameters in Urine

For urine samples, which are collected within a time range the nominal start and end of collections times will be used for PK evaluation.

Urine concentrations which are BLQ will be set to zero.

The following urine PK parameters will be calculated for M4076 where appropriate

Symbol	Definition
Ae_{t1-t2}	Total amount excreted between times t1 (= start) and t2 (= end) of the current collection interval. Calculated by interval Ae_{t1-t2} = Conc * $Vu(t_{1-t2})$ and cumulative.

$fe_{t1\text{-}t2}$ %	Fraction of administered drug that is excreted unchanged in urine between times t1 (= start) and t2 (= end) of the current collection interval. Calculated by interval fet1-t2 = Aet1-t2/Dose and cumulative.
CL_R	The renal clearance of study intervention. $CL_R = Ae_{0\text{-}t}/AUC_{0\text{-}t}$.

Additional PK parameters may be calculated where appropriate.

16.1.6 Presentation of PK Concentration and PK Parameter Data

"Dose level" in the PK TFLs description refer to schedule and dose.

"Day" in the PK TFLs description refer to single dose or steady state.

16.1.6.1 Listings and Tables

The following PK tables will be produced (PK Analysis Set):

Part 1A + Part 1B (Day 4 predose onwards)

- Descriptive statistics of concentrations of M4076 in plasma by part, day, and dose level
- Descriptive statistics of plasma PK parameters for M4076 by part, day, and dose level (do not include diagnostic parameters).
- Descriptive statistics of dose normalized plasma PK parameters for M4076 by part, day and dose level.
- Descriptive statistics of plasma trough concentrations (C_{trough}) by part and dose level, using standard descriptive statistics for Days 2, 8, 9, 22 and predose samples for subsequent cycles

Part 1B (Food effect assessment period up to Day 4 predose)

- Descriptive statistics of concentrations of M4076 in plasma by dietary status
- Descriptive statistics of plasma PK parameters and CL_R for M4076 by dietary status (do not include diagnostic parameters).
- Descriptive statistics of dose normalized plasma PK parameters for M4076 by dietary status
- Descriptive statistics of amount and fraction excreted in urine by interval and cumulatively by dietary status.

The following PK Listings will be produced (Safety Analysis Set):

Part 1A + Part 1B (Day 4 predose onwards)

- Individual plasma concentrations of M4076 by part, day and dose level
- Individual plasma PK parameters for M4076 by part, day and dose level
- Individual dose normalized plasma PK parameters for M4076 by part, day and dose level
- Trough plasma concentrations (Ctrough) of M4076 by part and dose level, Days 2, 8, 9, 22 and predose samples for subsequent cycles.
- Plasma PK diagnostic parameters for M4076 by part, day and dose level
- Plasma M4076 PK sampling date, actual time, nominal time, deviation from time, percentage time deviation, concentration by participant, part and dose level status sorted in chronological order

Part 1B (Food effect assessment period up to Day 4 predose)

- Individual plasma concentrations of M4076 by dietary status
- Individual urine concentrations of M4076 by dietary status
- Individual plasma PK parameters and CL_R (Part 1B) for M4076 by dietary status
- Individual dose normalized plasma PK parameters for M4076 by dietary status.
- Individual amount and fraction excreted in urine, by interval and cumulatively and dietary status.
- Plasma PK diagnostic parameters for M4076 by dietary status.
- Plasma M4076 PK sampling date, actual time, nominal time, deviation from time, percentage time deviation, concentration by participant, and dietary status sorted in chronological order
- Urine M4076 PK sampling date, start and end time and date of collection interval, urine volume, concentration, excreted amount by participant and dietary status sorted in chronological order
- Phoenix WinNonlin NCA Core Output

16.1.6.2 Graphical Summaries and Individual plots (PK Analysis Set)

Part 1A + Part 1B (Day 4 predose onwards)

- Individual plasma concentration versus time plots by day, and dose level; linear and semi-log; using the actual time points. If any post-dose concentration is BLQ the line representing LLOQ may be added to the semi-log plots.

- Overlaid individual (single dose and steady-state) plasma concentration versus time plots by participant, dose level, on linear and semi-log scale. If any post-dose concentration is BLQ the line representing LLOQ will be added to the semi-log plots.

- Arithmetic mean and median M4076 plasma concentration time plots; linear (±SD for arithmetic mean) and semi-log; using scheduled (nominal) time points by day grouped by dose level. If any post-dose concentration is BLQ the line representing LLOQ will be added to the semi-log plots

- Scatter Plot of individual dose-normalized $AUC_{0-\infty}$, AUC_{τ} and C_{max} versus Dose on a linear scale by day (single dose and steady state). Include GeoMean.

- Scatter Plot of individual $AUC_{0-\infty}$, AUC_{τ} and C_{max} versus Dose on a log-log scale. A linear regression line will be overlaid, with a pointwise confidence band for the regression line for Part 1A, Day 1 and Day 8.

- Individual C_{trough} values will be plotted against study day on a linear scale, for all participants by dose level on Days 2, 8, 9, 22 and predose samples for subsequent cycles.

- Mean C_{trough} ±SD will be plotted by dose level, on a linear scale Days 2, 8, 9, 22 and predose samples for subsequent cycles.

Part 1B (Food effect assessment period up to Day 4 predose)

- Individual plasma concentration versus time plots by dietary status; linear and semi-log; using the actual time points. If any post-dose concentration is BLQ the line representing LLOQ may be added to the semi-log plots.

- Overlaid individual plasma concentration versus time plots (fasted and low-fat meal); linear and semi-log; using the actual time points. If any post-dose concentration is BLQ the line representing LLOQ may be added to the semi-log plots.

- Arithmetic mean and median M4076 plasma concentration time plots; linear (±SD for arithmetic mean) and semi-log; using scheduled (nominal) time points by dietary status. If any post-dose concentration is BLQ the line representing LLOQ will be added to the semi-log plots

- Box plot of dose-normalized $AUC_{0-\infty}$, $AUC_{0-tlast}$, AUC_{τ} and C_{max} by dietary status.

- Plot of Mean (+/- SD) Cumulative Amount of M4076 Excreted in Urine versus Mid time interval on a Linear Scale by dietary status
- Plot of Individual Cumulative Amount of M4076 Excreted in Urine versus Mid time interval on a Linear Scale by dietary status

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CCI

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[redacted]

CCI [redacted]

17 References

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18 Appendices

18.1 Appendix 1 – NCI-CTC Gradable and Non-Gradable Safety Laboratory Test Parameters and Direction(s) of Abnormality

Table 7 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean corpuscular volume (MCV)	White Blood Cell Count with absolute and percentage (%): • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Reticulocytes			
	Hemoglobin		Mean corpuscular hemoglobin (MCH)	
	Hematocrit			
Coagulation	INR, prothrombin time, partial thromboplastin time (aPTT)			
Biochemistry	Blood Urea Nitrogen and/or Urea	Potassium	Aspartate aminotransferase	Bilirubin (total and direct)
	Creatinine	Sodium	Alanine aminotransferase	Protein and albumin
	Glucose	Calcium	Alkaline phosphatase	
	Gamma glutamyltransferase (gGT)	Lipase	Amylase	
Details of liver chemistry stopping criteria and required actions are given in protocol Section 6.6.1 and Appendix 5 of the protocol.				
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Serum and urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential). Serology (with no preclinical signs of hepatotoxicity, hepatitis B surface antigen, hepatitis C virus antibody) to rule out active infection will be performed at the Investigator's discretion. HIV screening is optional at the Investigator's discretion unless required locally. All study-required laboratory assessments will be performed by a central laboratory, except for safety laboratory assessments.			

Table 8 NCI-CTC gradable parameters

Laboratory Assessment	Parameters	Name in NCI-CTC	Direction(s) of abnormality
Hematology	Hemoglobin	Anemia/Hemoglobin increased	Low/High
	Leukocytes (WBC)	White blood cell decreased / Leukocytosis	Low/High
	Neutrophils	Neutrophil count decreased	Low
	Lymphocytes	Lymphocyte count decreased / increased	Low/High
	Eosinophils	Eosinophila [a]	High
	Platelets	Platelet count decreased	Low
Biochemistry	Albumin	Hypoalbuminemia	Low
	Alanine Aminotransferase (ALT)	Alanine Aminotransferase increased [a]	High
	Aspartate Aminotransferase (AST)	Aspartate Aminotransferase increased [a]	High
	Alkaline Phosphatase	Alkaline Phosphatase increased [a]	High
	Gamma Glutamyl Transferase (GGT)	GGT increased [a]	High
	Total Bilirubin	Blood bilirubin increased [a]	High
	Amylase	Serum amylase increased	High
	Lipase	Lipase increased	High
	Creatinine	Creatinine increased [a]	High
	Sodium	Hyponatremia / Hypernatremia	Low / High
	Potassium	Hypokalemia / Hyperkalemia	Low / High
	Calcium	Hypocalcemia / Hypercalcemia	Low / High
	Glucose	Hypoglycemia / Hyperglycemia	Low / High
Coagulation	Activated Partial Thromboplastin Time	Activated Partial Thromboplastin Time prolonged	High
	Prothrombin Intl. Normalized Ration (INR)	INR increased	High

Note: parameters with both Low and High directions of abnormality are going to be split. For example, Calcium is going to be split in Calcium Low and Calcium High.

[a] on-treatment grading dependent on baseline status.

Table 9 NCI-CTC non-gradable parameters

Laboratory Assessment	Parameters
Hematology	Hematocrit
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Reticulocytes
	Reticulocytes/Erythrocytes
	Neutrophils/Leukocytes (%)
	Lymphocytes/Leukocytes (%)
	Basophils
	Basophils/Leukocytes (%)
	Eosinophils/Leukocytes (%)
	Monocytes
	Monocytes/Leukocytes (%)
Biochemistry	Total Protein Urea Nitrogen (BUN) Serum cystatin C
Coagulation	Prothrombin Time
	Prothrombin Time/Standard
Urinalysis	Blood
	Bacteria (Microscopic analysis)
	Casts (Microscopic analysis)
	Crystals (Microscopic analysis)
	Epithelial Cells (Microscopic analysis)
	Bilirubin
	Glucose in Urine
	Urobilinogen
	Ketones
	Nitrite
	pH
	Proteins in Urine
	Erythrocytes in Urine (Microscopic analysis)
	Leukocytes esterase
	Leukocytes in Urine (Microscopic analysis)
	Specific gravity

18.2 Appendix 2 – IAP for IDMC/SMC

Integrated Analysis Plan for SMCs

Study Number:	MS201512_0010
Clinical Study Protocol Title:	A First-in-human, Phase I, Open-label Study of the ATM inhibitor M4076 in Participants with Advanced Solid Tumors
Study Phase:	Phase I
Merck Compound:	M4076
Protocol Version:	07 April 2021/Version 2.0
Integrated Analysis Plan Author:	Coordinating Author PPD Merck Function PPD Merck Healthcare KGaA PPD Merck Healthcare KGaA PPD
Integrated Analysis Plan Date and Version:	02 July 2021 / Version 1.0
Integrated Analysis Plan Reviewers:	PPD Name PPD