Integrated Analysis Plan

Study Number:	MS201929_0032
Clinical Study Protocol Title:	First-in-Human Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M1069 in Participants with Metastatic or Locally Advanced Unresectable Solid Tumors
Study Phase:	Phase 1
Merck [Compound]**:**	M1069
Protocol Version:	11 November 2021 / Version 2.0
Integrated Analysis Plan Author:	

Coordinating Author

Function	Author(s) / Data Analyst(s)
PPD	

PPD	

Integrated Analysis Plan Date and Version:	22 May 2022 / Version 2.0
Integrated Analysis Plan Reviewers:	

Function	Name
PPD	

Approval Page

Integrated Analysis Plan: MS201929_0032

First-in-Human Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M1069 in Participants with Metastatic or Locally Advanced Unresectable Solid Tumors

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within EDMS 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

A2aR	Adenosine 2A receptor
AE	Adverse Event
AESI	Adverse Events of Special Interest
AUC	Area under the concentration-time curve
BID	Twice daily
BLQ	Below lower Limit of quantification
BLRM	Bayesian Logistic Regression Model
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CR	Complete Response
CRO	Contract Research Organization
eCRF	(electronic) Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV%	Coefficient of variation
CxDy	Cycle x Day y
DLT	Dose Limiting Toxicity
DLTS	Dose Limiting Toxicity analysis set
DoR	Duration of Response
ECG	Electrocardiogram
GeoCV	Geometric CV%
GeoMean	Geometric mean
IAP	Integrated Analysis Plan
ICD-O	International Classification of Diseases for Oncology
ICH	International Council for Harmonization
KM	Kaplan-Meier
LI	Linearity index after repeated administration
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose

NA	Not Applicable
NCA	Non-compartmental analysis
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
nd	Not done
N.R.	No result
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
CCI	[redacted]
PD	Progressive Disease
Pd	Pharmacodynamic
PFS	Progression Free Survival
PKAS	Pharmacokinetics Analysis Set
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RDE	Recommended Dose for Expansion
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCR	Screening analysis set
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
TRAE	Treatment-Related Adverse Event
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Rationale for the amendment

The Safety Monitoring Committee decided to make an early termination of the study (MS201929_0032) at the meeting on 17.02.2023. Because of the early termination, we omitted some Table/Listing/Figures which were originally planned in the Version 1.0 of the integrated analysis plan. The list of Table/Listing/Figures which are omitted is provided in Appendix 18.5. Note that the final database lock did not occur before the approval of the Version 2.0 of the integrated analysis plan.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	15.02.2022	PPD	Not applicable (First version)
2.0	22.05.2023	PPD	Clarification added regarding the reduction of some Table/Listing/Figures due to early termination of the study

4 Purpose of the Integrated Analysis Plan

The purpose of this integrated analysis plan (IAP) is to document technical and detailed specifications for the primary analysis of data collected for protocol MS201929_0032. Results of the analyses described in this IAP will be included either in the clinical study report (CSR) or 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 as post-hoc in the CSR.

Additional analyses not covered by this IAP like, for instance, CCI biomarker analyses not pre-defined in the protocol or additional sub-group analyses planned for health technology assessment (HTA) submission will be listed in the respective Data Analysis Responsibility form which is stored in the EDMS together with this IAP.

The IAP is based upon Section 9 (Statistical considerations) of the study protocol version 2.0 dated 11 November 2021 and is prepared in compliance with International Council for Harmonization (ICH) E9 guidance. 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 appendices.

The wording used in this IAP is chosen to best match the respective wording in the study protocol template, the CSR template, Clinical Data Interchange Standards Consortium (CDISC) requirements and special requirements for table layouts. Therefore, the following approach is used:

Generally, the term ‘participant’ will be used instead of ‘subject’ or ‘patient’. However, in tables and listings the term ‘subject’ will be used to match CDISC requirements, except for in-text tables where ‘participant’ will be used to match the CSR and protocol templates. Similarly, the term ‘study intervention’ will be used in this document instead of ‘treatment’ to match protocol and CSR templates, however, tables and listings will use ‘treatment’ for brevity reasons. Exceptions from this rule are commonly used terms like “on-treatment”, “treatment-emergent”, “treatment policy”, “subject-years”, “by-subject”, or names of electronic case report form (eCRF) pages like “Treatment Termination” page.

5 Objectives and Estimands

Objectives	Estimand Attributes
Primary	
To determine dose toxicity relationship and maximum tolerated dose (MTD, if reached) of M1069 as a monotherapy in participants with solid tumors.	**Endpoints:** • Occurrence of DLTs. • Occurrence of AEs and treatment-related adverse events. **Strategy for handling intercurrent events:** For DLTs: • Discontinuation/interruption/delay of treatment (> 20% planned treatment missed during DLT period) to prevent a DLT: composite strategy (to be considered a DLT). For other endpoints: The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy): • Treatment discontinuation • Start of subsequent anticancer therapy. **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary**: • DLT probabilities and associated credibility intervals as estimated using the BLRM model (for DLTs only) • Standard summary statistics.
To determine the RDE of M1069 for further exploratory clinical development.	**Endpoints:** In addition to safety, tolerability, PK, Pd (CCI in ex-vivo stimulated blood), post-treatment changes in TME in available paired tumor biopsies data are considered. **Strategy for handling intercurrent events:** The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy): • Discontinuation of treatment • Start of subsequent anticancer therapy. **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary:** Standard summary statistics.
Secondary	
To characterize the PK profile of M1069.	**Endpoints:** PK parameters (see Section 8.5 of the CSP) of M1069 after single dose administration and at steady state using non-compartmental analysis.

Objectives	Estimand Attributes
To evaluate indicators of clinical activity of M1069 in terms of objective response using RECIST v1.1.	**Endpoint:** Objective response using RECIST v1.1, as assessed by Investigator. **Strategy for handling intercurrent events:** • Discontinuation of treatment (treatment policy strategy; i.e. ignoring intercurrent event) • Start of subsequent anticancer therapy (treatment policy strategy; i.e. ignoring intercurrent event) • Progression according to RECIST v1.1 (while not progressed strategy). **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary**: Rate.
To evaluate indicators of clinical activity of M1069 in terms of DoR using RECIST v1.1.	**Endpoint:** Duration of response according to RECIST v1.1 as assessed by Investigator, defined as time from first documentation of objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or start of treatment. **Strategy for handling intercurrent events:** • Death within 2 scheduled tumor assessments after last evaluable assessment or first study intervention will be considered as event (composite strategy). The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy): • Discontinuation of treatment • Start of subsequent anticancer therapy. **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary**: Median DoR.
To evaluate indicators of clinical activity of M1069 in terms of PFS using RECIST v1.1.	**Endpoint:** Progression-free survival as defined from date of first study intervention to PD according to RECIST v1.1 as assessed by Investigator or death. Events are considered only if occurring within 2 scheduled tumor assessments after last evaluable assessment or start of treatment. **Strategy for handling intercurrent events:** • Death within 2 scheduled tumor assessments after last evaluable assessment or first study intervention will be considered as event (composite strategy). The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy): • Discontinuation of treatment • Start of subsequent anticancer therapy. **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary**: Median and rate

Objectives	Estimand Attributes
To assess the effect of M1069 on QT interval	**Endpoints:** Change from baseline QTc (ΔQTc) over time.

CCI

AE = Adverse event, BLRM = Bayesian 2-parameter logistic regression model, C = Cycle, CYP = Cytochrome P450, D = (Study) Day, DLT = Dose-limiting toxicity, DoR = Duration of response, MTD = Maximum tolerated dose, CCI = phosphorylated cAMP response element-binding protein, PD = Progressive disease Pd = Pharmacodynamic, PFS =Progression-free survival, PK = Pharmacokinetic, RDE = Recommended dose for expansion, RECIST = Response Evaluation Criteria in Solid Tumors, TME = Tumor Micro Environment.

6 Overview of Planned Analyses

The following analyses are planned for this trial:

- Safety Monitoring Committee (SMC) analyses (See IAP for SMC in Appendix 18.4)
- Primary analysis
- Follow-up analyses to report further efficacy and safety data will be done once the End of Study has been reached.

6.1 Analyses for SMC meetings

The Safety Monitoring Committee (SMC) will decide on dose escalation, dose de-escalation, expansion of the current dose level, or suspension of enrollment based on safety and available pharmacokinetics (PK) and available pharmacodynamics (Pd) data. Once all participants of the respective cohort have completed the dose limiting toxicity (DLT) period or discontinued from trial prematurely, a data snapshot will be taken for provision of SMC outputs.

Details of analyses for SMC meetings will be specified in a separate IAP, provided in Appendix 18.5.

6.2 Primary Analysis

The cut-off date for the primary analysis will be last subject last visit (LSLV) or 13 weeks after last subject first dose (LSFD), whichever comes first. All planned analyses identified in the Clinical Study Protocol (CSP) and in this IAP will be performed only after the cut-off date, and the database is locked for the analysis.

6.3 Follow-up Analysis

The purpose of the follow-up analysis is to report further efficacy and safety data. A subset of the primary analyses as specified in the Tables, Listings, and Figures (TLF) table of contents will be conducted when the End of Study has been reached and the database is locked.

7 Changes to the Planned Analyses in the Clinical Study Protocol

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

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

The analysis sets are specified below. The final decision to exclude participants from any analysis set will be made during a data review meeting prior to database lock except for the DLT analysis population. Decision for inclusion in DLT population depends on SMC decision.

Screening Analysis Set (SCR)

The Screening analysis set includes all participants who signed the informed consent, regardless of the participant's study intervention status in the study.

Safety Analysis Set (SAF)

The Safety analysis set will include all participants who were administered any dose of any study intervention. Analyses will consider participants as treated, meaning that participants will be classified according to the actual study intervention received.

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 the treatment.
- Did not receive 80% of the planned total dose of study intervention, but at least 80% dosing of a different (lower) 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 PK analysis set will include all participants who receive at least one dose of study intervention and provide at least one measurable post-dose concentration that is unaffected by any protocol deviations or events that affect its validity. Participants will be analyzed per the actual study intervention they received.

Pd Analysis Set

All participants, who receive at least one dose of study intervention, have no important events affecting Pd and provide at least one evaluable Pd endpoint post-dose. Participants will be analyzed per the actual study intervention they received.

All Pd analyses will be based on this analysis population.

Electrocardiogram Analysis Set (ECG)

Electrocardiogram analysis set will include all participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting ECG, and provide at least one measurable post-dose ECG endpoint.

Analyses per Analysis Set

Table 1 summarizes the use of the analysis sets in the different analyses.

Table 1 Analysis set definitions

	Analysis Set				
Analyses	**SAF**	**DLT**	**PK**	**Pd**	**ECG**
DLT		✓			
Baseline Characteristics	✓				
Previous and Concomitant Therapies	✓				
Compliance and Exposure	✓				
Efficacy	✓				
Safety and Tolerability	✓				
PK			✓		
Biomarkers	✓				
Pd				✓	
Electrocardiogram					✓

Note: Safety, efficacy, PK, and Pd will be described by actual 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

This section describes any general specifications not included in subsequent sections.

Study intervention is defined and labelled as "M1069". Unless otherwise indicated, all tables will be split by dose level; the different dose levels will generally be presented in increasing order. A total column is also presented, when applicable.

The planned dose level will be taken from the electronic case report form (eCRF) "Cohort". General rules if actual dose differs from planned dose (determined during the DLT period) are listed in Table 2.

Table 2 General rules for data analysis if actual dose differs from the planned dose

<table>
<tr><th>Cumulative actual dose received ≥ 80% of cumulative planned dose or has DLT during DLT period</th><th>Cumulative actual dose received < 80% of cumulative planned dose and has no DLT during the DLT period</th></tr>
<tr><td>Planned dose level ≥ actual dose received:
Use planned dose as actual dose
Planned dose level < actual dose received:

Use planned dose level, unless actual dose received ≥ 80% of a higher planned or tested dose, then use this higher dose level as actual</td><td>Cumulative actual dose received ≥ 80% of a lower dose level
DLT/safety analysis: Use this lower dose as actual

Efficacy analysis: Use planned dose

Cumulative actual dose received < 80% of any tested dose
DLT analysis: Not evaluable

Safety analysis: Use lowest single dose received as actual dose

Efficacy analysis: Use planned dose</td></tr>
<tr><td colspan="2">Missed more than 20% of dose administrations during DLT period:
DLT analysis: Not evaluable
Safety analysis: Use lowest single dose received as actual dose
Efficacy analysis: Use planned dose</td></tr>
<tr><td colspan="2">Had a DLT:
Use planned dose as actual dose</td></tr>
</table>

The "start date" for this study is the date of first study intervention administration of M1069.

There is no formal family-wise Type I error control for this study, as all analyses are considered descriptive.

Significance level

There is no formal significance level for this study and all analyses are considered descriptive. No formal statistical hypothesis will be tested. If confidence or credibility intervals are mentioned, the level will be 95% unless otherwise specified in this IAP.

Presentation of continuous and qualitative variables:

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

- number of participants with non-missing values (n)
- mean, standard deviation (SD)
- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum (Min), maximum (Max)

Mean, median, Q1, Q3, Min, and Max will have the same precision as collected in Study Data Tabulation Model (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 fewer than 5 observations summarized, only the number of subjects (N), number of subjects with non-missing values, the mean, minimum, maximum will be given.

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 of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

For variables where a participant may have more than one category due to multiple responses per participant, the number of participants included in each category will be summarized as a percentage from all participants. Therefore, the total frequency across categories may not equal the total number of all participants in that analysis set.

Deviations from this definition might apply to the PK analysis (see section 16.1 for definitions).

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.

Software

All analyses will be performed using R (version 3.6.3 or higher (R Core Team, 2021)) or SAS® Software (version 9.4 or higher). For the Bayesian computations, the bcrm (version 0.5.4 or higher (Sweeting et al, 2013)) or the crmPack (version 1.0.0 or higher (Bove et al, 2019)) packages or SAS PROC MCMC are used.

For PK analyses, see Section 16.1 for software to be used.

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 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

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

If an assessment that is planned to be performed before treatment per protocol is performed on the same day as the start of study intervention, respectively, 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 treated in the same manner as an unscheduled post-dose measurement (i.e. permissible for worst on-treatment values, but not for by nominal visit or time point summaries).

Absolute and percent changes from baseline are defined as

absolute change from baseline = visit value – baseline value

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

9.3 Study Day / Study Treatment Day

Treatment Day 1 is treatment start date of first administration of the study intervention; the day before is defined as Treatment Day - 1 (no Treatment Day 0 is defined).

9.4 Definition of Duration and ‘time since’ Variables

If not otherwise specified, duration 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 administration + 1).

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

9.5 Conversion Factors

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

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

9.6 Date of Last Contact

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

- All participant assessment dates (blood draws [laboratory and PK], vital signs, performance status, electrocardiogram (ECG), tumor assessments, ophthalmological assessments)
- Start and end dates of anti-cancer therapies administered after study intervention discontinuation.
- AE start and end dates
- Last known to be alive date collected on the 'Subject Status/Survival Follow-up' eCRF
- Study drug start and end dates
- Date of discontinuation on disposition eCRF pages (unless reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the participant reported in the eCRF will be used in this 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.

9.7 Definition of On-treatment Period

The on-treatment period is defined as the time from the first dose of study treatment day (i.e. first dose of M1069 on Cycle 1 Day 1) to the last administration day of study treatment + 30 days, or the cut-off date or death, whichever occurs first.

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.

Incalculable statistics should be presented as "not done" (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 subject is still in the trial at a particular time point but with missing data, they should be counted in the number of missing observations associated with that time point.

The following 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) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2022, and study treatment start date is 15/JAN/2022, then the imputed AE onset date will be 15/JAN/2022. If the end date or resolution date indicates that the AE has stopped before start of treatment, this date will be used for imputation instead of start of treatment date.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2022, and study treatment start date is 19/NOV/2022, then the imputed AE onset date will be 19/NOV/2022.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if 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. If stop date of AE is after date of cut-off this date will be kept.

Previous and concomitant medication/procedure

For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Rules presented in Table 3 and Table 4 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

Table 3 Stopping rules for medication/procedure end dates

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

UNK = Unknown

Table 4 Rules to define previous and/or concomitant medication

Start date of medication/procedure			Stopping rule (see Table 3)	Medication/procedure
Day	Month	Year		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	<= Treatment start (year)	Before treatment start	Previous
UNK	UNK	<= Treatment start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Treatment start (year) and <= Treatment end [+ 30] days (year)	After treatment start	Concomitant
UNK	<= Treatment start (month and year)		Before treatment start	Previous
UNK	<= Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and <= Treatment end [+ 30] days (month and year)		After treatment start	Concomitant
<= Treatment start (date)			Before treatment start	Previous
<= Treatment start (date)			After treatment start	Previous and concomitant

Start date of medication/procedure			Stopping rule (see Table 3)	Medication/procedure
Day	Month	Year		
> Treatment start (date) and <= Treatment end [+ 30] days (date)			After treatment start	Concomitant

UNK = Unknown

Dates of study treatment

Start date of study treatments:

- No imputation will be done.

End date of study treatments:

- In case the last date of study drug is missing or incomplete the date of last administration of study drug will be taken from the treatment termination eCRF page.
- If the last date of study drug is completely missing and there is no End of Treatment (EOT) 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 drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date) then imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

  = min (EOT date, death date), for all other case

Death date

In general, missing, or partial death dates will not be imputed. However, 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 (see Section 9.6) and the 15th day of the month.

Tumor assessments

All investigation dates (e.g. X-ray, computed tomography (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.

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

A table should display the following (per dose level, regimen, and overall):

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

- Number of participants in each analysis population (SCR, SAF, DLT, PK, ECG, and Pd)
- Number of participants who discontinued from the study prior to study treatment overall and grouped by the main reason (e.g., the failed specific inclusion or exclusion criteria, withdrawal of consent and other)
- Number of participants ongoing treatment.
- Number of participants with completed treatment
- Number and percentage of treated participants.

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.

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

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.

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

All protocol deviations are documented in SDTM datasets whether identified through site monitoring, medical review, or programming.

A full list of potential protocol deviations including definition and categorization is maintained by clinical research organization (CRO) in the "Study Specific Protocol Deviation List" attached to the Protocol Deviation Management Plan.

Important protocol deviations will be listed by participant. A frequency table for IPDs, separated for such pre-/post inclusion deviations, as well as a listing of IPDs, will be provided based on the Safety analysis set.

A listing of all participants affected by the coronavirus disease of 2019 (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 and when it was altered.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

All criteria/reasons leading to the exclusion of a participant from an Analyses Population (e.g., DLT analysis set and PK analysis set will be summarized and listed by dose level.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening/Cycle 1 Day 1 Demographics, Vital Signs, and Eastern Cooperative Oncology Group (ECOG) 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, Not collected at this site, Other. More than one race (Combination 1, Combination 2, etc.). Participants with more than one race ticked in the eCRF will only be reported in the "More than one race" category.

- Ethnic origin: Hispanic or Latino/Not Hispanic or Latino
- Age (years)
- Weight (kg)
- Height (cm)
- Age categories: < 65 years, ≥ 65 years
- Pooled Region: North America, Europe, Asia
- Geographic Region: North America, Western Europe, Eastern Europe, Asia
- ECOG Performance status

Specifications for computation:

- Body mass index (BMI) [kg/m²] = $\frac{weight\,[kg]}{height[cm]^2} \times 10000$
- Site codes will be used for the determination of the participant's pooled region and geographic region.

11.2 Medical History

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

- 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
- Disease stage at initial diagnosis
- Disease stage at study entry
- Hepatitis B and C and human immunodeficiency virus (HIV) (Positive, Negative, Indeterminate, Not Done)

Baseline characteristics with respect to vital signs, physical examinations, and clinical laboratory assessments will be part of Section 15 (Safety Analyses). Also, the baseline values for safety electrocardiogram (ECG) and ophthalmological assessments will be part of Section 15.

11.4 Prior Anti-cancer Therapy

Analysis of Prior anti-cancer therapy will be performed.

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
- Any prior anti-cancer therapy regimens: missing / 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 / Unknown
- Best response to last prior treatment: Complete Response (CR) / Partial Response (PR) Stable Disease (SD) / Non-Complete Response, Non-Progressive Disease (Non-CR / Non-PD) / Progressive Disease (PD) / Unknown / Not Evaluable (NE).

The prior anti-cancer drugs will also be summarized based on the number and percentage of participants by the drug class and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

12 Previous or Concomitant Therapies/Procedures

Concomitant treatments are medications, other than study treatment, which are assigned according to the rules within Section 9.8

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

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date.

Concomitant and previous treatment each will be summarized by number and percentage of participants from the "Concomitant Medications Details" eCRF. ATC-2nd level and preferred term will be tabulated as given from the World Health Organisation Drug Dictionary (WHO-DD) dictionary most current version. If any previous or concomitant medication is classified into multiple Anatomical Therapeutic Chemical (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 drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), 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.

All concomitant medications and concomitant procedures, which were undertaken during the on-treatment period will be listed together according to the eCRF pages "Concomitant Medications Details" and "Concomitant Procedures Details".

13 Study Intervention: Compliance and Exposure

The following analyses will be performed based on the SAF by dose level (in increasing order) and regimen.

All dosing calculations and summaries will be based on "M1069 Administration Details" eCRF pages.

In case the last date of study drug is incomplete, the date of last study drug administration will be taken from the "M1069 Termination" eCRF page (Last M1069 administration date).

The duration of therapy (in weeks) is defined as:

Duration = [(date of last dose – date of first dose) + 1] / 7

The cumulative dose (in mg) is defined as:

Cumulative dose (mg) = [(capsules dispensed) – (capsules returned)] * dose level (mg)

(Summed over all dose levels taken by the subject if dosing changes occurred.)

The dose intensity (mg/week) is calculated as follows

$$\text{dose intensity} = \left(\frac{\text{Total cumulative dose}}{\text{Duration of therapy (weeks)}}\right)$$

The relative dose intensity (%) is defined as the dose intensity divided by the planned cumulative dose per cycle, calculated as follows

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{Total Cumulative dose (mg)}}{\text{Total Planned dose (mg)}}\right) * 100$$

The following summary tables by dose group and overall will be provided:

- Duration of therapy (weeks)
- Total number of doses taken overall
- Cumulative dose (mg)
- Dose intensity (mg/week)
- Relative dose intensity (%)
- Dose adjustments and missed doses

A listing of treatment exposure and compliance will also be created to summarize the relevant information for each subject:

- Start and change day (Cycle and day in cycle)
- Start and change date (Date and time of administration)
- Actual dose and regimen

The first item in the list (Start and change day (Cycle and day in cycle)) will be derived. A line plot will show the dose received versus the study day (color code by planned dose).

14 Efficacy Analyses

The following analyses will be performed based on the SAF by dose level (in increasing order). In case the received cumulative dose of a participant is higher than planned cumulative dose the participant will not be considered in efficacy analyses.

Duration of response (DoR), objective response (OR), progression-free survival (PFS) according to RECIST v1.1 (Eisenhauer et al, 2009) are assessed per Investigator. Any complete response (CR) or partial response (PR) should be confirmed, preferably at the next subsequent scheduled imaging interval, but no sooner than 6 weeks after the initial documentation of CR or PR.

14.1 Objective Response (OR)

Overall response will be assessed based on reported overall responses at different evaluation time points from the study treatment start date until documented disease progression or death/end of study in accordance to RECIST v1.1 by investigator, taking requirements for confirmation into account as detailed below.

Tumor assessments will be considered irrespective of any subsequent anti-cancer therapies, since treatment policy strategy is used for handling intercurrent events.

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 overall response is the following: CR, PR, SD, PD, NE. If a subject has no post-baseline tumor assessments before starting new anticancer therapy, best overall response will be NE.

Overall response Based on Confirmed Responses:

- Complete Response (CR) = at least two determinations of CR at least 6 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, or CR followed by PR) at least 6 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.

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.

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

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

A waterfall plot of maximum tumor shrinkage will be created by dose level including all participants with measurable disease at baseline and at least one valid post-baseline assessment.

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 treatments prior to reaching confirmed CR or PR, or who die, progress, or drop out for any reason prior to reaching confirmed CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response (OR) 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 best overall response of CR, PR, SD, PD, and NE will be tabulated.

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

14.2 Progression Free Survival (PFS)

All analyses in this section will be performed for primary analysis.

Progression Free Survival (PFS) time is defined from date of first study intervention to the first documentation of PD according to RECIST v1.1 as assessed by Investigator or death. The tumor response will be determined according to RECIST v1.1 and assessed by the 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".

Table 5 Date of event/censoring definition for PFS analysis

Status		Censoring	Date of event / censoring
Progressed or died	Within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD or first dose of study drug administration	Event	Minimum (Date of PD, Date of death)

Status		Censoring	Date of event / censoring
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first dose of study drug administration, 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 drug administration, whatever is later

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

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, 9, and 12 months will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) 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 (2002) (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. Kaplan-Meier plots will also be presented.

14.3 Duration of Response (DoR)

Duration of Response (DoR) is defined, for participants with confirmed objective response only (as defined in section 14.1.1.1), as the time from first documentation of OR (CR or PR) to the date of first documentation of objective 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.

DoR analysis will be performed

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, the DoR rate at 3, 6 and 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 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 (2002) (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.

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 primary safety endpoints during Dose Escalation are the occurrence of DLTs, AEs and treatment-related adverse events (TRAEs).

Except for the analysis of DLTs (will be performed on the DLTS), all safety analyses will be performed on the SAF.

15.1 Dose Limiting Toxicities (DLTs) Analysis

Of note, DLT as per SMC decision will be available in the table "Review of cohort" in the SMC minutes or recommendation form. In case any additional information leads to change in judgement of the SMC regarding DLTs, it will be added to the minutes.

A table will display the following (per dose level, regimen and in total) 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, grade, SAE (yes/no), relatedness to M1069 (yes/no), start date (+treatment day), stop date (+treatment day), action taken with M1069, if treatment was stopped before start of AE: days since stop of treatment, outcome, and investigator term.

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) (Neuenschwander et al, 2008) as described in the IAP for SMC (see Appendix 18.4) or SMC charter (if change occurred). This analysis will be done using the bcrm (version 0.5.4 or higher) or the crmPack (version 1.0.0 or higher) packages in R (version 3.5.1 or higher).

15.1.1 MTD suggestion from the Bayesian two-parameter logistic regression model

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

The posterior median and one-sided 95% credibility interval of the suggested MTD will be provided.

This information 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.

15.1.2 A frequentist approach

As a second approach, the dose with DLT probability of 30% will be estimated using a frequentist approach. This is done using the following steps:

1) All DLT data from the dose escalation will be included in a two-parameter logistic regression model. The model consists of an intercept and a slope over log of the scaled dose without any prior.
2) If the model does not converge, it will be reported as not calculable.
3) The dose with maximum likelihood estimate of DLT probability of 30% will be identified, if converges.

The estimated DLT probability and the two-sided 95% confidence interval for the dose in 3) will be provided.

For all the above analyses, the bcrm R package or the crmPack R package or SAS software will be used.

15.2 Adverse Events

AEs will be analyzed among the SAF and presented by dose level (in increasing order). Only participant counts will be presented with frequency.

Treatment-emergent adverse events (TEAE) are those events with onset dates occurring within the on-treatment periods as defined in Section 9.8.

- **TRAEs**: AEs with relationship missing or yes.
- **SAEs**: Serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = 'Yes').
- **AEs Leading to Treatment Discontinuation**: AEs leading to permanent discontinuation of study treatment (as recorded on the Adverse Events Details eCRF page, Action taken with M1069 = 'Drug withdrawn').
- **AEs Leading to Death**: AEs leading to death (as recorded on the Adverse Events Details eCRF page, if outcome = 'Fatal').
- **Adverse events of special interest (AESI)** (see Appendix 18.3 for the list of AESI)

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.

TEAEs will be summarized by number and percentage of participants with at least one TEAE in the category of interest, by primary MedDRA and PT (both sorted alphabetically), unless otherwise stated. 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.

The severity of adverse events will be graded using the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, except where CTCAE grades are missing. No imputation of missing grades will be performed.

Adverse events will be coded according to the latest MedDRA version at the time of the data cut-off.

Incomplete AE-related dates will be handled as defined in Section 9.8.

15.2.1 All Adverse Events

The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following, tabulated by dose level and total:

- TEAEs
- TEAEs with NCI-CTCAE Grade ≥ 3
- TEAEs with NCI-CTCAE Grade ≥ 4
- TRAEs
- TRAEs with NCI-CTCAE Grade ≥ 3

- TRAEs with NCI-CTCAE Grade ≥ 4
- TEAEs leading to permanent discontinuation of M1069
- TEAEs leading to dose reduction of M1069
- TEAEs leading to interruption of M1069
- Serious TEAEs
- Serious TRAEs
- TEAEs leading to death (AEs with Grade 5 or outcome "fatal" if grade 5 not applicable)
- TRAEs leading to death
- TEAESI

- All TEAEs / TRAEs / Grade ≥3 TEAEs / Grade ≥3 TRAEs / Serious TEAEs / Serious TRAEs / TRAEs leading to death by SOC and PT: All AEs 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)
- TEAEs excluding SAEs (Clinical trial.gov and EudraCT -requirement) by SOC and PT

Also, TEAEs will be summarized by worst severity (according to NCI-CTCAE version 5.0) per participant, using preferred term as event category and primary SOC. Analysis by worst severity will be provided by dose level and total.

If a qualifying AE is reported for a given participant more than once during study intervention, the worst severity 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.

A listing of all AEs will be provided. This listing will be sorted by regimen, dose level and participant. This listing will additionally contain age, sex, site of primary tumor, SOC, PT, CTCAE grade, SAE (yes/no), DLT per investigator (yes/no), DLT per SMC, relatedness to M1069 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M1069, 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 Treatment

A listing of TEAEs leading to treatment discontinuation, interruption, or dose reduction of study drug will be provided. This listing, sorted by dose level and subject ID, will also include age, sex, site of primary tumor, end of treatment date, SOC, PT, AE investigator term, start date (+treatment day), stop date (+treatment day), relatedness to M1069 (yes/no), grade, action taken with M1069,

outcome, SAE (yes/no), duration (in days), if treatment was stopped before start of AE: days since stop of treatment.

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

15.3.1 Deaths

All deaths as well as primary reason for death will be tabulated based on information from the "Death" eCRF page.

A listing of Deaths will be provided, defined as any AE with Grade 5, or outcome "fatal" if grade 5 is not applicable. This will be sorted by regimen, dose level, and participant. This listing will additionally contain age, sex, SOC, PT, grade, SAE (yes/no), DLT per investigator (yes/no), relatedness to M1069 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M1069, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

15.3.2 Serious Adverse Events

The listing 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

A listing of AEs of special interest (AESI) will be provided. This will be sorted by dose level, regimen, and participant. This listing will additionally contain age, sex, SOC, PT, Investigator Term, grade, SAE (yes/no), DLT per investigator/SMC (yes/no), relatedness to M1069 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M1069, if treatment was stopped before start of AE: days since stop of treatment, and outcome. See Appendix 18.3 for the definition of AESIs.

AESI will be summarized by worst severity (according to NCI-CTCAE version 5.0) per participant, using preferred term as event category and primary SOC. Analysis by worst severity will be provided by dose level and total.

15.4 Clinical Laboratory Evaluation

Laboratory values (including corresponding normal ranges) from the local laboratory will be used for summary statistics and shift tables.

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0. Some of the severity grades are based on laboratory measurements in conjunction with clinical findings. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (e.g., hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived).

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 (n, mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and absolute changes from baseline to each nominal visit over time. The End of treatment visit will be summarized separately. 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 severity 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 severity (e.g., hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction severity (e.g., hyperkalemia), and vice versa.

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 a complete list of protocol required laboratory assessments, please refer to Appendix 18.1 Direction(s) of abnormality for parameters with and without NCI-CTCAE grades are presented in Appendix 18.2

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 for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- 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.

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:

- 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

For white blood cells (**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])

- The last measurement before study treatment (including unscheduled measurements) will serve as the baseline measurement.

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

Listings of clinically significant Hematology and Biochemistry values (≥ grade 3) will be provided.

The time windows given in Table 6 will be applied to allocate measurements to treatment day. In case of multiple blood samples are collected in the same window, the value closest to the target day will be used for analysis. If there are two values with the same time before and after the target day, the earlier value will be used for analysis.

Table 6 Time windows for safety laboratory analysis

Treatment day	Window Definition
C1D1 *C1D8* *C1D15* *C2D1* *C2D8* *C2D15* *C3D1* *C3D15* *C4D1* *C4D15* *C5D1* *C5D15*	*As per schedule of assessments in the CSP*
CXD1 (after Cycle 5, even cycles) CXD8 (after Cycle 5, odd cycles) CXD15 (after Cycle 5, even cycles)	
End of Study Intervention (within 7 days of decision to discontinue)	*As per schedule of assessments in the CSP*
Safety Follow-up/Discontinuation (30 days after last dose)	*As per schedule of assessments in the CSP*

Since the number of participants will decrease over time, time windows will not be applied for the complete treatment period. For summaries by timepoint, the last available laboratory measurement will be presented in addition to the timepoints defined above.

The coagulation parameters, urinalysis parameters, microscopic urinalysis parameters and pregnancy test will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

Line plots

Graphical display (line plots) of neutrophils, platelets, and lymphocytes will be provided by actual time in days and dose level for all analyses (with x-axis time, y-axis lab value), using different colors per regimen, dose level and different line types to identify participants.

Hepatotoxicity assessment

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

15.5 Vital Signs

Vital signs will be performed and assessed at the scheduled treatment days according to the Schedule of Activities (SoA) Tables 1 and 2 of the CSP. Vital signs include height (Screening only), weight, temperature (°C), pulse rate (beats/min), respiratory rate (breaths/min), systolic and diastolic blood pressure (mmHg).

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

All vital signs parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each treatment day over time for the primary analysis. End of treatment will be summarized separately for the primary analysis. The changes computed will be the differences from baseline.

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

Table 7 The groups of changes of vital signs

Body temperature increase		< 1°C, 1-<2°C, 2-<3°C, ≥ 3 °C
Pulse 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 9.1 Missing values will define a separate category.

The following summaries will be prepared for vital signs 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.

15.5.1 ECOG

Analysis of ECOG will be performed. A frequency table will be provided with the number and percentage of participants in each ECOG status category and change of category from baseline by visit, by dose level and total.

A shift table will also be provided, where shift from baseline to the maximal on-treatment value will be summarized using normal, abnormal and missing categories.

15.5.2 Triplicate ECG Endpoints

Triplicate 12-lead ECGs in digital format will be obtained using a Holter ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Subsequent ECGs will be obtained as single recordings (normal nontriplicate safety ECGs). For immediate safety assessments, ECG will be locally analyzed at each time point.

This analysis will be done on the ECG analysis set.

For each of the ECG parameters (HR, and QT, QTcF, QRS, PR intervals), descriptive statistics for the average at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be presented. This table will be split by actual dose, regimen and overall.

Qualitative ECG abnormalities according to the categories specified in Table 6 will be listed for each participant and time point and the corresponding notable values and abnormality findings will be included in the listings for all analyses.

Additionally, data will be displayed by cohort and dose level, in a listing for the main analysis. Abnormal values of ECG will be flagged according to the criteria presented in Table 8.

Table 8 Potentially clinically significant abnormalities criteria for ECG

Parameter	Potentially Clinically Significant Abnormalities (PCSA) Criteria
Pulse rate	≤ 50 bpm and decrease from baseline ≥ 20 bpm. ≥ 120 bpm and increase from baseline ≥ 20 bpm.
PR interval	≥ 220 ms and increase from baseline ≥ 20 ms.
QRS	≥ 120 ms.
QTc absolute	Borderline: 430-450 ms (Male), 451-470 ms (Female) Prolonged: > 450 ms (Male), >470 ms (Female) ≥ 500 ms
QTc change from baseline	Borderline: Increase from baseline ≥ 30 ms and ≤ 60 ms Prolonged: Increase from baseline > 60 ms

Concentration-QTc analysis.

Time-matched, replicate ECGs and PK samples collected will be used to perform concentration-QTc analysis to evaluate QTc prolongation risk. This will be part of a separate cross-study analysis and will be described in a separate statistical analysis plan (SAP).

ECG Endpoints by Local Read (including single safety ECGs)

Information on ECGs by local read will be presented in the same way as the triplicate 12 lead ECG stated above.

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16 Analyses of Other Endpoints/Estimands

16.1 Pharmacokinetics

PK evaluation will be performed by the Clinical PK/Pd Group, Merck Healthcare KGaA, Darmstadt, Germany, or by a CRO selected by the Sponsor.

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

16.1.1 Descriptive Statistics of PK Concentration Data

PK measurements will be descriptively summarized using: n, Mean, SD, coefficient of variation (CV%), Min, median and Max.

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. In case ≤2, individual data will be reported in summary tables.

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

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data will be descriptively summarized using: n, Mean, SD, CV%, Min, Median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval (CI) for the GeoMean (LCI 95% GM, UCI 95% GM). For PK parameters related to time (e.g. t_{max}), only n, Min, Median, and Max may be reported.

Descriptive statistics will only be calculated for a PK parameter when n>2. In case ≤2, individual data will be reported in summary tables.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	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

An analysis of dose proportionality of M1069 PK parameters [$AUC_{0-\infty}$, $AUC_{0-tlast}$, AUC_{τ}, and/or C_{max}] over the range of administered dose levels will be quantified as part of an exploratory analysis using the power model on the original parameters ($\ln[\text{PK parameter}] = \alpha + \beta \times \ln[\text{dose}]$). The intercept α and the slope β together with 90% CIs will be estimated and presented. This analysis will be conducted separately by parameter, study day (Day 1 and Day 8 of Cycle 1), and dosing frequency (i.e., BID or QD), depending on whether sufficient data are available for analysis at each of these levels. For a given parameter, study day, and dosing frequency, a minimum of 3 values must be available at a dose level, for that dose level to be included in the dose proportionality analysis.

16.1.4 General Specifications for PK Concentration and PK Parameter Data

Pre-dose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study intervention administration. The same applies to the pre-dose sample of a multiple dose day.

Pre-dose 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 prior to the first dose, the participant's data will be included in the PK and statistical analyses without any adjustments.

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.

If samples are collected outside of the windows specified in Table 2 of the protocol, these will be included in the PK parameter estimation (NCA) but will be excluded from the concentration summary and mean/median concentration plots (unless the samples were systematically collected at a specific non-scheduled time across ≥2 subjects, due to error or for some other reason).

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 not be excluded from the analysis. 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 participants 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. In case ≤2 patient profiles will be available for a certain cohort, individual profiles will be included in mean/median plots and individual data reported in summary tables (in such cases, the outputs will be flagged accordingly).

16.1.5 Estimation of Pharmacokinetic Parameters in Plasma

The computer program Phoenix® WinNonlin® version 8.3, or higher (Certara, L.P., Princeton, New Jersey, USA) will be used to derive PK parameters applying non-compartmental analysis (NCA).

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary North Carolina, USA, windows version 9.4 or higher) may be used to generate additional PK parameters, or to produce tables, listings and figures.

PK parameters will be calculated using the actual elapsed time since dosing. 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 rational should be included in the CSR. Otherwise, there will be no further imputation of missing data.

The following M1069 plasma PK parameters will be calculated where appropriate on Days 1 and 8 of Cycle 1:

Symbol	Definition	Calculation
$AUC_{0\text{-}tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}).	Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}tlast}$ / Dose	The dose normalized $AUC_{0\text{-}tlast}$.	Calculated as $AUC_{0\text{-}tlast}$ / Dose, where Dose is the actual dose (in mg).
AUC_{τ}	The AUC over the dosing interval τ.	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, AUC_{τ} will be calculated based on the estimated concentration at τ hours, and not the concentration at the actual observation time (see further details on calculation of AUC_{τ} below). For single dose, AUC_{τ} is calculated as a partial area with the defined time range. For multiple dose, AUC_{τ} is calculated from the pre-dose time point to the end of the dosing interval.
AUC_{τ} / Dose	The dose normalized AUC_{τ}.	Calculated as AUC_{τ} / Dose, where Dose is the actual dose (in mg).
$AUC_{0\text{-}\infty}$	The AUC from time zero (= dosing time) up to infinity with extrapolation of the terminal phase.	$AUC_{0\text{-}\infty} = AUC_{0\text{-}tlast} + C_{last\ pred} / \lambda_z$, where $C_{last\ pred}$ is the predicted concentration at the t_{last}, calculated from the log-linear regression line for λ_z determination. Calculated on C1D1 only.
$AUC_{0\text{-}\infty}$ / Dose	The dose normalized $AUC_{0\text{-}\infty}$.	$AUC_{0\text{-}\infty}$ / Dose, where Dose is the actual dose (in mg). Calculated on C1D1 only.
C_{max}	Maximum observed concentration.	
C_{max} / Dose	The dose normalized C_{max}.	Calculated as C_{max} / Dose, where Dose is the actual dose (in mg).
t_{max}	The time to reach the C_{max} in a dosing interval.	In case multiple/identical C_{max} values occur, the first occurrence will be used.
$t_{1/2}$	The terminal half-life.	$t_{1/2} = \ln(2) / \lambda_z$, where λ_z is the terminal first order (elimination) rate constant determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve.

Symbol	Definition	Calculation
CL/F	The apparent total body clearance following extravascular administration.	$CL/F = Dose_{[p.o.]} / AUC_{0-\infty}$ after single dose. $CL/F = Dose_{[p.o.]} / AUC_{\tau}$ after multiple dose.
V_Z/F	The apparent volume of distribution during the terminal phase following extravascular administration.	$V_z/F = Dose / (AUC_{0-\infty} \times \lambda_z)$ following single dose. $V_z/F = Dose / (AUC_{\tau} \times \lambda_z)$ following multiple dose.
LI	The linearity index after repeated administration.	LI = (AUC_{τ} after multiple dose) / ($AUC_{0-\infty}$ after single dose)
$R_{acc(Cmax)}$	The accumulation ratio of C_{max} after repeated administration.	Calculated as $R_{acc(Cmax)}$ = (C_{max} after multiple dose) / (C_{max} after single dose)
$R_{acc(AUC\tau)}$	The accumulation ratio of AUC_{τ} after repeated administration.	Calculated as $R_{acc(AUC\tau)}$ = (AUC_{τ} after multiple dose) / (AUC_{τ} after single dose)

Pre-dose concentrations on C1D8, C1D15, and Day 1 of subsequent cycles (i.e., C_{trough}), and the concentration at 2 hours postdose on C2D1 (i.e., C_{2h}) will also be reported. 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}, C_{trough}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

The following rules may be applied for calculation of AUC_{τ}:

- In cases where the actual observation time is not equal to the scheduled observation time, AUC_{τ} will be calculated by extrapolation to τ, if λ_z is estimable. 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 case 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 where partial AUCs are greater than $AUC_{0-\infty}$.
- At steady state, if AUC_{τ} is not estimable via extrapolation, 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. In such cases, $AUC_{0-tlast}$ might be estimated based on observed Clast.

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

- First (λ_z lower) and last (λ_z upper) time point of the time interval of the log-linear regression to determine λ_z.
- Number of data points (N_{λ}) included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (Rsq adj) for calculation of λ_z.
- AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$ ($AUC_{extra\%}$).
- Span, the ratio of the interval over which $t_{1/2}$ is estimated to the $t_{1/2}$ estimate, calculated as (λ_z upper - λ_z lower)/$t_{1/2}$.

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 BLQ concentrations which occur after the last quantifiable data point >LLOQ should not be used.

If $AUC_{extra\%}$ >20.0% and/or Rsq adj of λ_z is <0.800 and/or the observation period over which the regression line is estimated (Span) 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, V_z/F etc.) will be listed, flagged and included in the parameter outputs and excluded from descriptive statistics and further statistical evaluation.

For calculation of dose-related and dose-normalized parameters, no dose adjustment is required since M1069 dose administered is expressed as the free base dose.

16.1.6 Presentation of PK Concentration and PK Parameter Data

16.1.6.1 Listings and Tables

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

- Descriptive statistics of concentrations by analyte, matrix, day and treatment group
- Descriptive statistics of PK parameters by analyte, matrix, day and treatment group
- Descriptive statistics of dose-normalized PK parameters by analyte, matrix, day and treatment group
- Descriptive statistics of trough concentrations (C_{trough}) and C_{2h} (Days with sparse sampling) by analyte, matrix, day and treatment group
- Summary of assessment of dose proportionality

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

- Individual concentrations by analyte, matrix, day and treatment group
- Individual PK parameters by analyte, matrix, day and treatment group
- Individual dose-normalized PK parameters by analyte, matrix, day and treatment group
- Trough concentrations (C_{trough}) and C_{2h} (Days with sparse sampling) by analyte, matrix, day and treatment group
- PK Sampling date, actual time, nominal time, deviation from time, percentage time deviation and concentration by participant, analyte, matrix and treatment group sorted in chronological order
- Concentrations and PK parameters excluded from descriptive statistics
- Phoenix WinNonlin NCA Core Output

16.1.6.2 Graphical Summaries and Individual plots (PK Analysis Set)

- Individual concentration versus time plots on C1D1 and C1D8; linear and semi-log; using the actual time points by participants, day, analyte, matrix and treatment group; if any post-dose concentration is BLQ the line representing LLOQ may be added to the semi-log plots. C1D1 and C1D8 data will be overlaid on these plots.

- Overlaid individual concentration versus time plots for C1D1 and C1D8; linear and semi-log; by analyte, matrix and treatment group. Separate plots for C1D1 and C1D8, and for each treatment group.
- Arithmetic mean concentration time plots; linear (±SD) and semi-log; using scheduled (nominal) time points by day, analyte, matrix and treatment group; if any post-dose concentration is BLQ the line representing LLOQ will be added to the semi-log plots
- Median concentration time plots; linear and semi-log; using scheduled (nominal) time points by day, analyte, matrix and treatment group; 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 AUCs and C_{max} versus Dose on a linear scale. If different dosing frequencies (e.g., BID or QD) are evaluated in this study, these different dosing frequencies will be overlaid on the same plot using different symbols
- Individual C_{trough} values will be plotted against cycle/day (ordinal axis) on a linear scale, for all participants by treatment group.
- Mean C_{trough} ±SD will be plotted against cycle/day (ordinal axis) by treatment group, on a linear scale.
- If a fed versus fasted treatment group is evaluated, Scatter Plot of individual AUCs and C_{max} versus category (i.e., food condition on ordinal axis) on a linear scale. Geometric mean values for each group will be overlaid.

16.2 Biomarkers

16.2.1 Pharmacodynamics

Pharmacodynamics (Pd) biomarker analyses from whole blood and tumor tissue samples will be performed. Collection timepoints of biomarker samples are indicated in the Schedule of Assessments (SoA) Tables 1 and 2 of the CSP.

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16.3 Exposure-response analysis for safety, efficacy, population PK, PK/Pd analysis

These analyses will be part of a separate cross-study analysis and will be described in a separate SAP.

17 References

1. R Core Team (2021). “R: A language and environment for statistical computing. R Foundation for Statistical Computing”. Vienna, Austria. URL: https://www.R-project.org/
2. Sweeting M, Mander A, Sabin T (2013). “bcrm: Bayesian Continual Reassessment Method Designs for Phase I Dose-Finding Trials”. R package version 0.5.4.
3. Bove DS, Yeung WY, Palermo G, Jaki T (2019). “Model-Based Dose Escalation Designs in R with crmPack.” Journal of Statistical Software, 89(10), 1-22. URL: https://doi.org/10.18637/jss.v089.i10.
4. Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). “New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1)”. European Journal of Cancer; 45:228-47.
5. Brookmeyer, R., and Crowley, J. (1982). “A Confidence Interval for the Median Survival Time”. Biometrics, 38(1), 29-41. https://doi.org/10.2307/2530286
6. Kalbfleisch J, Prentice RL. “The Statistical Analysis of Failure Time Data”. New York, NY: John Wiley & Sons; 2002: 31- 52.
7. Neuenschwander, B., Branson, M. and Gsponer, T. (2008). “Critical aspects of the Bayesian approach to phase I cancer trials”. Statistics in Medicine, 27: 2420-2439. https://doi.org/10.1002/sim.3230

18 Appendices

18.1 Protocol-Required Clinical Laboratory Assessments

The protocol-required clinical laboratory tests are in the following table. All safety-required clinical laboratory tests will be performed by a local laboratory.

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean corpuscular volume (MCV)	White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Hemoglobin		Mean corpuscular hemoglobin (MCH)	
	Hematocrit			
	Erythrocytes		Reticulocytes	
Biochemistry	Blood Urea Nitrogen/total urea	Potassium	Aspartate aminotransferase	Total bilirubin/indirect bilirubin
	Creatinine	Sodium	Alanine aminotransferase	Total protein
	Glucose	Calcium	Alkaline phosphatase	CRP
	Albumin	Amylase	Lactate dehydrogenase	Ferritin
	Lipase	Magnesium	Uric acid	Creatinine Clearance
Coagulation	aPTT (sec)	PT (sec)	INR	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick • Microscopic examination (if blood or protein is abnormal).			
Other Screening Tests	• FSH • Serum (at Screening) and highly sensitive urine (during M1069 treatment) hCG pregnancy test (as needed for a WOCBP). • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody).			

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

NCI-CTCAE v5.0 gradable parameters

Category	Parameter	Name in NCI-CTCAE	Direction(s) of abnormality	Comments on derivation
Serum chemistry				
Electrolytes	Calcium	Hypocalcemia	Low	Grading performed using corrected calcium

Category	Parameter	Name in NCI-CTCAE	Direction(s) of abnormality	Comments on derivation
		Hypercalcemia	High	Grading performed using corrected calcium
Electrolytes	Potassium	Hypokalemia	Low	Grade 2 cannot be numerically distinguished from Grade 1. Grade 2 will not be derived.
		Hyperkalemia	High	
Electrolytes	Sodium	Hyponatremia	Low	
		Hypernatremia	High	
Enzymes/liver	Alanine Aminotransferase	Alanine Aminotransferase increased	High	
Enzymes/liver	Alkaline Phosphatase	Alkaline Phosphatase increased	High	
Enzymes/liver	Aspartate Aminotransferase	Aspartate Aminotransferase increased	High	
Enzymes/liver	Total bilirubin	Blood bilirubin increased	High	
Metabolism	Glucose	Hypoglycemia	Low	
Renal/kidney	Creatinine	Creatinine increased	High	
Metabolism and nutrition disorders	Albumin	Hypoalbuminemia	Low	
		Hypocalcemia	Low	Grading performed using corrected calcium
Investigations	Amylase	Serum Amylase increased	High	
Investigations	Gamma-glutamyl transpeptidase	GGT increased	High	
Investigations	Lipase	Lipase Increased	High	
Hematology				
Platelets	Platelets Count	Platelet count decreased	Low	
Red blood cells	Hemoglobin	Anemia	Low	Grade 4 relies solely on clinical assessment and cannot be numerically derived
		Hemoglobin increased	High	
White blood cells/differential	White Blood Cell Count	White blood cell decreased	Low	
		Leukocytosis	High	Only Grade 3 numerically defined
White blood cells/differential	Absolute Lymphocytes Count	Lymphocyte count decreased	Low	
		Lymphocyte count increased	High	
White blood cells/differential	Absolute Neutrophils Count	Neutrophil count decreased	Low	
White blood cells/differential	Eosinophils	Eosinophilia	High	Only Grade 1 numerically defined

NCI-CTCAE v5.0 non-gradable parameters

Category	Parameter (LBTEST)	Abnormality Description	Direction(s) of abnormality
Serum chemistry			
Enzymes/liver	Alanine Aminotransferase *	Alanine Aminotransferase increased	High
Enzymes/liver	Alkaline Phosphatase *	Alkaline Phosphatase increased	High
Enzymes/liver	Aspartate Aminotransferase *	Aspartate Aminotransferase increased	High
Enzymes/liver	Total bilirubin *	Blood bilirubin increased	High
Metabolism	Glucose	Hyperglycemia	High
Plasma proteins	Total protein	Total protein low	Low
Renal/kidney	Blood Urea Nitrogen	Blood urea nitrogen high	High
Investigations	Gamma-glutamyl transpeptidase	GGT increased	High
Hematology			
Red blood cells	Hematocrit	Hematocrit low/high	Low/High
Red blood cells	Mean Corpuscular Hemoglobin	Mean corpuscular hemoglobin low/high	Low/High
Red blood cells	Mean Corpuscular Volume	Mean corpuscular volume low/high	Low/High
Red blood cells	Reticulocytes	Reticulocytes low/high	Low/High
White blood cells/differential	Basophils	Basophils high	High
White blood cells/differential	Monocytes	Monocytes low/high	Low/High

* indicates parameter is NCI-CTCAE gradable with comparison to baseline and will therefore be included in the analysis of non-gradable parameters for this study.

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[redacted]	[redacted]
[redacted]	2000158 Retinal disorders (SMQ)

18.4 Integrated Analysis Plan for SMC

Integrated Analysis Plan

Study Number:	MS201929_0032
Clinical Study Protocol Title:	First-in-Human Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M1069 in Participants with Metastatic or Locally Advanced Unresectable Solid Tumors
Study Phase:	Phase 1
Merck Compound:	M1069
Protocol Version:	11 November 2021 / Version 2.0
Integrated Analysis Plan Authors:	Coordinating Author PPD
Integrated Analysis Plan Date and Version:	09 December 2021 / Version 1.0
Integrated Analysis Plan Reviewers:	PPD

Approval Page

Integrated Analysis Plan: MS201929_0032

First-in-Human Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M1069 in Participants with Metastatic or Locally Advanced Unresectable Solid Tumors

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within EDMS 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

ADaM	Analysis Data Model
AE	Adverse Event
AEIR	Adverse Event Incidence Rate
ANCOVA	Analysis of COVARIANCE
ANOVA	Analysis of VARIANCE
ATC	Anatomical Therapeutic Chemical classification
AUC	Area under the concentration-time curve
AUC_{last}	AUC from time zero (dosing time) to the last sampling time, t_{last}
AUC_{last}/Dose	Dose normalized AUC_{last}
$AUC_{0-\infty}$	AUC from time zero (dosing time) extrapolated to infinity
$AUC_{0-\infty}$/Dose	Dose normalized $AUC_{0-\infty}$
AUC_{τ}	AUC over the dosing interval
AUC_{τ} /Dose	Dose normalized AUC_{τ}
$AUC_{extra\%}$	Percent of $AUC_{0-\infty}$ that is extrapolated
BLQ	Below the LLOQ
BLRM	Bayesian Logistic Regression Model
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Apparent total body clearance
C_{max}	Maximum observed concentration
C_{max}/Dose	Dose normalized C_{max}
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
CV%	Coefficient of variation
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
EDMS	Electronic Document Management System

EEA	European Economic Area
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FU	Follow-up
GBS	Global Biostatistics
GeoCV	Geometric CV%
GeoMean	Geometric mean
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
irAE	Immune-related adverse event
IRC	Independent Review Committee
IRR	Infusion related reaction
ITT	Intention To Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LI	Linearity index
LLOQ	Lower limit of quantification
LOCF	Last Observation Carried Forward
MAR	Missing At Random
MCAR	Missing Completely At Random
mFAS	Modified Full Analysis Set
MN	Miettinen & Nurminen
MNAR	Missing Not At Random
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
ORR	Objective Response Rate
PD	Progressive Disease
Pd	Pharmacodynamics
PFS	Progression Free Survival
PT	Preferred Term
PGx	Pharmacogenetics/Pharmacogenomics
PK	Pharmacokinetics
PR	Partial Response
$R_{acc(AUC\tau)}$	Accumulation ratio for AUC_τ after repeated administration
$R_{acc(Cmax)}$	Accumulation ratio for C_{max} after repeated administration
SAE	Serious Adverse Event
SCR	Screening analysis set
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
$t_{1/2}$	Apparent terminal half-life
t_{max}	Time to reach the maximum observed concentration
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
WHO-DD	World Health Organization Drug Dictionary
V_Z/F	Apparent volume of distribution during the terminal phase

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	09.12.2021	PPD	Initial Version

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the analyses performed for the Safety Monitoring Committee (SMC) reviews of data collected for the protocol MS201929_0032. Results of the analyses described in this IAP will be used (amongst other data) by the SMC to decide upon doses of future cohorts. This IAP describes the Bayesian two-parameter logistic regression model analysis methods used to make a recommendation to the SMC for dose escalation as in the protocol. Additionally, this IAP will describe preliminary PK for M1069, as well as patient profiles and statistical outputs summarizing safety data. Statistical outputs will be produced if a SMC is taking place or whenever statistical outputs are needed. The patient profiles and statistical outputs on safety and lab data will be produced on the raw data export available at cut-off. PK analyses will be provided by the Clinical Pharmacology representative and will usually include all available data up to the current cohort. Pd biomarker analysis as represented by pCREB inhibition in blood will be provided by the Clinical Biomarker Lead. Availability of respective data will be lagging one cohort behind the actual dose escalation, which means that Pd biomarker data from the first cohort should be available starting from the SMC for the 2nd cohort.

The IAP is based upon Section 9 (Statistical considerations) of the study protocol and protocol amendments and is prepared in compliance with ICH E9.

5 Objectives and Estimands

Objectives	Estimand Attributes
Primary	
To determine dose toxicity relationship and maximum tolerated dose (MTD, if reached) of M1069 as a monotherapy in participants with solid tumors.	**Endpoints:** • Occurrence of DLTs. • Occurrence of AEs and treatment-related adverse events. **Strategy for handling intercurrent events:** For DLTs: • Discontinuation/interruption/delay of treatment (> 20% planned treatment missed during DLT period) to prevent a DLT: composite strategy (to be considered a DLT). For other endpoints: The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy): • Treatment discontinuation • Start of subsequent anticancer therapy. **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary**: • DLT probabilities and associated credibility intervals as estimated using the BLRM model (for DLTs only) • Standard summary statistics.
To determine the RDE of M1069 for further exploratory clinical development.	**Endpoints:** In addition to safety, tolerability, PK, Pd (pCREB in ex-vivo stimulated blood), post-treatment changes in TME in available paired tumor biopsies data are considered. **Strategy for handling intercurrent events:** The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy): • Discontinuation of treatment • Start of subsequent anticancer therapy. **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary:** Standard summary statistics.
Secondary	
To characterize the PK profile of M1069.	**Endpoints:** PK parameters (see Section **Error! Reference source not found.** of the study protocol) of M1069 after single dose administration and at steady state using non-compartmental analysis.

Objectives	Estimand Attributes
To evaluate indicators of clinical activity of M1069 in terms of objective response using RECIST v1.1.	**Endpoint:** Objective response using RECIST v1.1, as assessed by Investigator. **Strategy for handling intercurrent events:** • Discontinuation of treatment (treatment policy strategy; i.e. ignoring intercurrent event) • Start of subsequent anticancer therapy (treatment policy strategy; i.e. ignoring intercurrent event) • Progression according to RECIST v1.1 (while not progressed strategy). **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary**: Rate.
To evaluate indicators of clinical activity of M1069 in terms of DoR using RECIST v1.1.	**Endpoint:** Duration of response according to RECIST v1.1 as assessed by Investigator, defined as time from first documentation of objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or start of treatment. **Strategy for handling intercurrent events:** • Death within 2 scheduled tumor assessments after last evaluable assessment or first study intervention will be considered as event (composite strategy). The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy): • Discontinuation of treatment • Start of subsequent anticancer therapy. **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary**: Median DoR.
To evaluate indicators of clinical activity of M1069 in terms of PFS using RECIST v1.1.	**Endpoint:** Progression-free survival as defined from date of first study intervention to PD according to RECIST v1.1 as assessed by Investigator or death. Events are considered only if occurring within 2 scheduled tumor assessments after last evaluable assessment or start of treatment. **Strategy for handling intercurrent events:** • Death within 2 scheduled tumor assessments after last evaluable assessment or first study intervention will be considered as event (composite strategy). The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy): • Discontinuation of treatment • Start of subsequent anticancer therapy. **Population:** Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary**: Hazard ratio.

Objectives	Estimand Attributes
[redacted]	

AE = Adverse event, BLRM = Bayesian 2-parameter logistic regression model, C = Cycle, CYP = Cytochrome P450, D = (Study) Day, DLT = Dose-limiting toxicity, DoR = Duration of response, MTD = Maximum tolerated dose, pCREB = phosphorylated cAMP response element-binding protein, PD = Progressive disease, Pd = Pharmacodynamic, PFS =Progression-free survival, PK = Pharmacokinetic, QT interval, corrected, RDE = Recommended dose for expansion, RECIST = Response Evaluation Criteria in Solid Tumors.

6 Overview of Planned Analyses

The following analyses are planned for this trial:

- SMC analyses (this IAP, it will be added as an appendix of the main IAP, once available)
- Primary analysis of trial (main IAP)

Once all patients of the respective cohort have completed the DLT period or discontinued from trial prematurely, a data snapshot will be taken for provision of SMC outputs. The usual data snapshot is taken at the end of this day. In cases where enrollment of the last subject in a dosing cohort is delayed, the SMC may decide (based on available data) upon enrollment and dose for the next dosing cohort before all subjects in a cohort have completed the dosing cycle and thus the snapshot is set to an earlier date. The SMC can also determine any other date, e.g., for an ad-hoc SMC.

There will be no data cut-off applied (all data in the data transfer are considered).

The patient profiles and statistical outputs on safety and lab data for SMCs will be produced on a raw data export. Patient profiles and statistical outputs are produced using R (version 3.5.1 or higher [1]). The R packages and their versions used for this purpose are listed in Software subsection of Section 9. Patient profiles and statistical outputs are displayed as tables and figures in an HTML document, which we refer to as the statistical outputs HTML document hereafter. No SDTM transfers are foreseen for analyses for SMCs.

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

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's study intervention status in the study.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
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. • 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 of. The final decision on evaluability for dose escalation analysis will be made by the SMC (e.g., considering relevant deviations from dosing schedule).
PK	The PK set will include all participants who receive at least one dose of study intervention and provide at least one measurable post-dose concentration. Participants will be analyzed per the actual study intervention they received.
Pd	All participants, who receive at least one dose of study intervention, have no important events affecting Pd and provide at least one measurable Pd sample post-dose. Participants will be analyzed per the actual study intervention they received. All Pd analyses will be based on this analysis population.

The Bayesian model will be based on the DLT set, all other safety analyses for SMCs on the SAF set.

The patient profiles will be provided for all participants in the SAF set.

Note: As is the nature of dose escalation studies, analyses will be performed by dose (and regimen if regimen is changed).

9 General Specifications for Data Analyses

Analyses will be displayed separately by dose and overall.

Significance level:

There will be no statistical tests performed in the SMC analyses. If confidence or credibility intervals are mentioned, the level will be 95% unless otherwise specified.

Presentation of continuous and qualitative variables:

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

- number of participants, number of participants with non-missing values
- mean, standard deviation
- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum, maximum

If there are fewer than 5 observations summarized, only the number of subjects (N), number of subjects with non-missing values, the mean, and the values themselves will be given.

Qualitative variables will be summarized by counts and percentages.

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

Deviations from this definition might apply to the PK analysis (see section 16.1 for definitions).

Definition of baseline:

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

If an assessment that is planned to be performed before treatment per protocol is performed on the same day as the start of treatment, respectively, 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

Change from baseline = visit value – baseline value

Percent Change from Baseline = 100 * (visit value – baseline value) / baseline value

Definition of duration:

If not otherwise specified, duration will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of first study drug administration + 1).

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

Conversion factors:

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

Handling of missing data:

Unless otherwise specified (Sections 15 and 16) 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".

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 subject is still in the trial at the time-point but with missing data, they should be counted in the number of missing observations.

Further information after data transfer (such as fatal outcome) might be taken from the Safety database or reported by the investigator at the SMC meeting.

Treatment day definition

Treatment day is defined relative to the date of first study drug administration (M1069). Treatment Day 1 is treatment start date of first administration of the study drug; the day before is defined as Treatment Day -1 (no Treatment Day 0 is defined).

Software

All analyses will be performed using R (version 3.6.3 or higher [1]). For the Bayesian computations, the bcrm (version 0.5.4 or higher [2]) or the crmPack (version 1.0.0 or higher [3]) packages are used. For the statistical output HTML document, the rmarkdown (version 2.7.7 or higher [4]), the flextable (version 0.6.5 or higher [5]), the knitr (version 1.32 or higher [6]), and the ggplot2 (version 3.3.3 or higher [7]) packages will be used.

The computer program Phoenix® WinNonlin® version 8.3, or higher (Certara, L.P., Princeton, New Jersey USA) will be used to derive PK parameters applying Non-compartmental analysis (NCA).

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

A table of disposition from the statistical outputs HTML document should display the following (per study part, per dose level and in total):

- Number of subjects screened (total only)
- Number of subjects discontinued prior to treatment start with tabulation of primary reason (total only)
- Number of subjects who received at least one dose of study intervention (safety analysis set)
- Number of subjects in preliminary DLT set: All subjects who fulfill the dosing criterion (≥ 80% of the planned dose) or had DLT per investigator. Due to final DLT decision by SMC this may be different from final DLT Analysis set.
- Number of subjects with a DLT per investigator's judgement as recorded in eCRF
- Number of subjects with ongoing treatment
- Number of subjects with documented end of treatment (of subjects in safety analysis set) with tabulation of primary reason

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Except for the dosing criterion for the DLT analysis set, this is not applicable for this IAP for SMCs.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

Subjects who did not receive at least 80% of the planned cumulative dose are excluded from the DLT analysis set unless they can be considered in another dose level as described above.

11 Demographics and Other Baseline Characteristics

Not applicable for this IAP, some individual data to appear as part of the patient profiles.

12 Previous or Concomitant Therapies/Procedures

Not applicable for this IAP, some individual data to appear as part of the patient profiles.

13 Study Intervention: Compliance and Exposure

Not applicable for this IAP, some individual data to appear as part of the patient profiles.

14 Efficacy Analyses

Not applicable for this IAP, some individual data to appear as part of the patient profiles.

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 primary objective of this study is defining the safety profile, determining the MTD (if available) and RDE. This is the IAP for SMCs, therefore safety analyses are the primary analyses.

Safety analyses will be done on the safety analysis population and according to the as-treated principle, except for the Bayesian modelling that will be performed on the DLT analysis set.

15.1 DLT analysis

The primary objective of the SMC meetings is to regularly monitor the overall safety of the subjects enrolled in the trial. An important part of that is reviewing DLTs. Besides individual medical judgement on DLTs, a summary analysis of DLTs is performed using a Bayesian two-parameter logistic modeling approach [8] to model the relation of dose to the occurrence of DLTs. The results from updating this model will assist the SMC in their dosing decisions.

A listing of DLTs as flagged by investigator in eCRF can be obtained from the statistical outputs html document by filtering the AE listing. It is possible that there is a discrepancy between final SMC decision and investigator flag for DLTs in eCRF. The listing will contain dose level, subject ID, SOC, PT, start date (+treatment day), stop date (+treatment day), duration, relatedness to M1069 (yes/no), grade, action taken with M1069, outcome, SAE (yes/no), DLT per investigator (yes/no).

A DLT profile plot of all subjects in the SAF Analysis Set with DLT decisions from previous SMCs will be produced. This will show an open square for all subjects who did not have a DLT, a closed square for those who experienced a DLT, and an open circle for those who were excluded from the DLT Analysis Set. This plot will have Cohort Number or subject index on the x-axis and dose level (mg) on the y-axis. See mock figure F_SMCDE.DLTplot in the Appendix 2 in Section 18.

Bayesian two-parameter logistic model

Summary statistics of the posterior probability distribution of the DLT rate for each predefined dose level will be updated by estimation according to the logistic model. Using data from all subjects evaluable for DLT or who experienced a DLT at the completion of a new cohort (and data from all previous cohorts: DLT analysis set), the Bayesian logistic regression model provides a recommended dose level for the next cohort based on minimal loss. This recommendation will be shared with the SMC after the DLT discussion. In preparation of the SMC, the model will be updated with potential scenarios' data (e.g., 3 subjects evaluable on current dose level, 0 DLTs, the same with 1 DLT, 2 subjects evaluable 0 DLT etc.), to have the results ready at SMC.

The model-based recommendation for the next dose level is the dose level that minimizes the loss function. The loss function is defined as the sum of products of the probability to lie within each of the toxicity regions, and the associated loss term:

- 1 × P (Under-Dosing) + 0 × P (targeted toxicity) + 1 × P (excessive toxicity) + 2 × P (unacceptable toxicity).

The following toxicity regions will be defined:

	Probability of DLT	Loss term (weight in loss function)
Under-Dosing	(0.0, 0.20]	[1]
Target toxicity	(0.20, 0.35]	[0]
Excessive toxicity	(0.35, 0.60]	[1]
Unacceptable toxicity	(0.60, 1.00]	[2]

The dose suggested by the model for the next cohort will be based on minimizing the Bayesian Risk.

This Bayesian escalation approach will be used to assist the SMC to select the next dose from a predicted set of acceptable doses. It is possible to choose a dose(s) not within the pre-specified dose-escalation plan. In this case the estimated posterior probabilities of the selected dose will also be provided to the SMC. The SMC may choose a different dose than suggested by the Bayesian escalation approach.

The model will continue to be updated at each SMC until the SMC has decided to stop dose escalation.

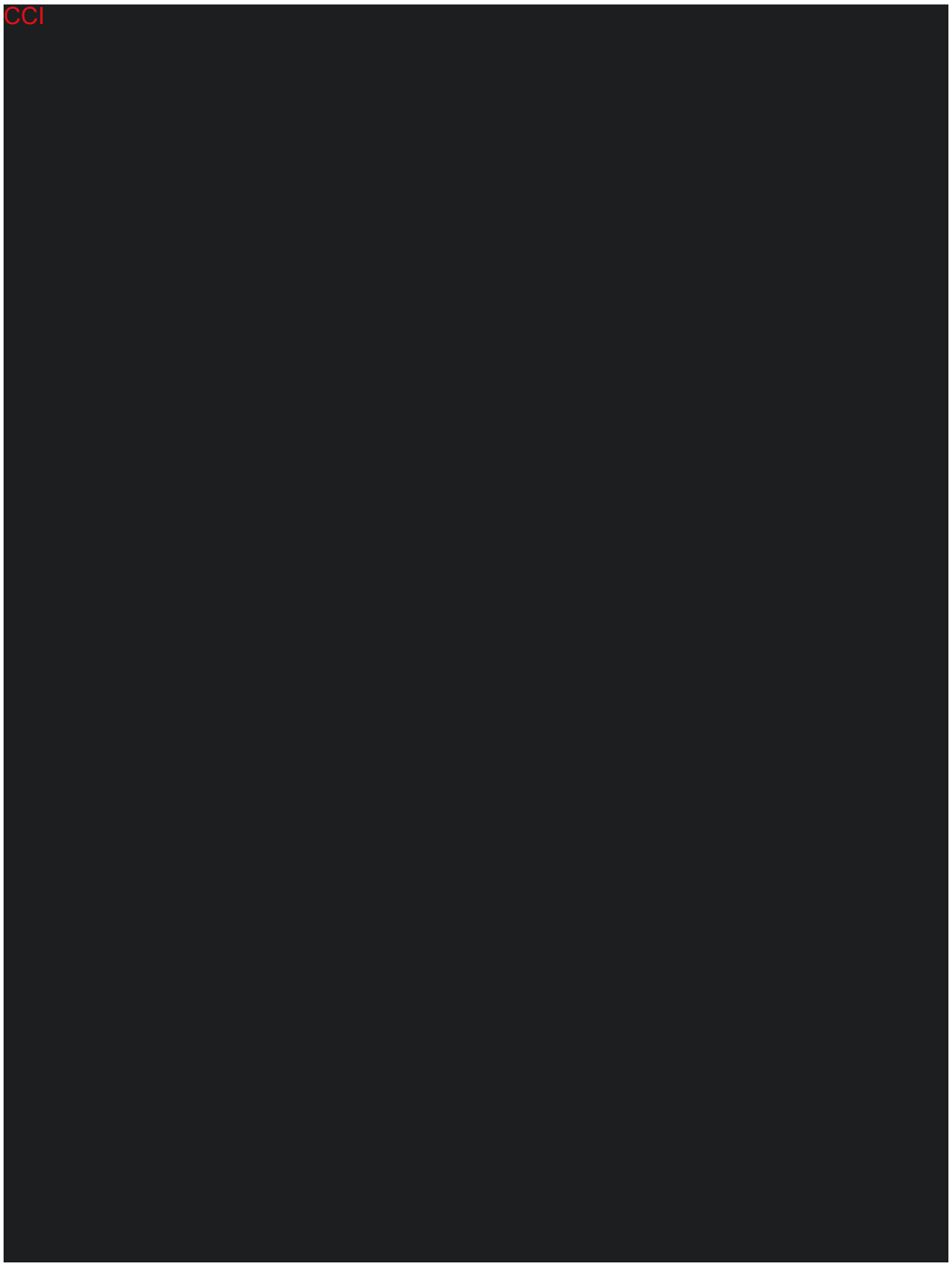
Prior distribution and likelihood are used to calculate the posterior probabilities based on the Bayes theorem.

The likelihood is defined based on a binomial distribution, modelling the rate of subjects with at least 1 DLT.

The relationship between dose and toxicity rate is defined by

$$P(DLT|d_j, \alpha, \beta) = \frac{\exp\left(\alpha + \exp(\beta) * \log\left(\frac{d_j}{d_{ref}}\right)\right)}{1 + \exp\left(\alpha + \exp(\beta) * \log\left(\frac{d_j}{d_{ref}}\right)\right)}$$

with bivariate normally distributed parameters (α, β), using the following parameterization for the dose escalation part of the study: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in regimen or change from fasted to fed condition, these will also be documented in the SMC charter prior to the first SMC with patients with the new regimen / fasting status.

Handling of changes in regimen

The SMC may decide to change the dosing schedule to a once daily (QD) regimen. In such a case the dose toxicity model will be extended, or a separate model will be set up.

15.2 Patient profiles

The SMC will receive patient profiles containing the following data in graphical and/or listing format in the statistical outputs html document:

- Subject disposition (still in trial, or withdrawn with reason for withdrawal)
- Demographics and baseline characteristics (e.g., cancer diagnosis, date of diagnosis)
- Medical history
- History of disease under study
- Previous and concomitant medications
- Prior anti-cancer drug therapies
- Prior anti-cancer radiotherapy
- Prior anti-cancer surgeries
- Concomitant procedures
- Study drug administration, and dose adjustments
- All serious and non-serious AEs (with details like e.g., grade, start and stop date), including but not limited to:
  - DLTs according to investigator
  - AESIs
  - AEs leading to dose reduction or temporary discontinuation
  - AEs leading to permanent treatment discontinuation
  - AEs leading to death
- Laboratory data (hematology, coagulation, biochemistry, urinalysis)
- ECG results (QTc)
- Vital signs (Blood pressure, pulse, temperature, weight)

Patient profiles will be provided for the current cohorts under review and updated patient profiles will be provided for subjects from previous cohorts that had changes from last SMC meeting.

15.3 Adverse Events

The severity of adverse events will be graded using the NCI-CTCAE version 5.0, except where CTCAE grades are missing. No imputation of missing grades will be performed. Adverse events will be coded according to the latest MedDRA version at the time of the data cut-off.

- **TEAEs**: Any AEs that are reported (serious and non-serious) will be considered treatment emergent adverse events (TEAEs), with the exception of those that started prior to the first dose of study treatment (unless a worsening of the event is recorded after the first dosing, in which case the event will be counted as a TEAE), or AEs starting more than 30 days after the last dose of study treatment. TEAEs are those events with onset dates occurring within the on-treatment periods from start of treatment up to (including) 30 days after end of treatment.
- **Related Adverse Events**: AEs with relationship missing, unknown or yes.
- **SAEs**: Serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = 'Yes').
- **AEs Leading to Treatment Discontinuation**: AEs leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = 'Drug withdrawn').
- **AEs Leading to Death**: AEs leading to death (as recorded on the AE eCRF page, Outcome = 'Fatal').
- **Adverse Events of Special Interest**: AEs for which the investigator ticked "yes" for the question: Is this an adverse event of special interest?

AEs will be summarized by MedDRA PT as event category and MedDRA primary SOC as summary category. In general, each subject will be counted only once within each PT or SOC.

AEs with missing classifications regarding relationship to study treatment, and those with start date on or after the start of study treatment, will be considered as related to the study treatment.

15.3.1 All Adverse Events

Adverse events will be summarized visually 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) as body system category in the statistical outputs html document.

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 not be imputed for SMC outputs.

AE summaries will be restricted to TEAEs only, unless otherwise specified. The AE summaries will include the number and percentage of subjects with at least one TEAE, by MedDRA SOC and PT (both sorted alphabetically), unless otherwise stated.

All AEs will be summarized by regimen (if different regimens are tested), dose level and overall, showing the incidence of TEAEs, by SOC and PT (both sorted alphabetically).

A listing of AEs will be provided in the statistical outputs html document. The listing will contain dose level, subject ID, SOC and PT. This listing will additionally contain age, sex, site of primary tumor, end of treatment date, SOC, PT, investigator term, start date (+treatment day), stop date (+treatment day), duration, relatedness to M1069 (yes/no), grade, action taken with M1069, outcome, SAE (yes/no), DLT per investigator (yes/no).

Additionally, a listing of all adverse events grade ≥ 3 (incl non TEAEs), SAEs (also including non-treatment emergent SAEs) and AESI can be obtained by filtering the AE listing of the statistical outputs html document.

15.3.2 Adverse Events Leading to Discontinuation of Study Intervention

A listing of TEAEs leading to treatment discontinuation, interruption, or dose reduction of study drug can be obtained by filtering the AE listing of the statistical outputs html document.

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

15.4.1 Deaths

Not applicable for this IAP, they are included in other listings.

15.4.2 Serious Adverse Events

SAEs are shown in the patient profiles and part of the listing of all adverse events in the statistical outputs html document.

15.5 Clinical Laboratory Evaluation

Laboratory values (including corresponding normal ranges) from the Lab will be used for patient profiles, an eDISH plot, and line plots.

Laboratory results will be classified according to the latest NCI-CTC Version [at the moment 5.0]. Some of the toxicity gradings are based on laboratory measurements in conjunction with clinical findings. The classification will be derived from the laboratory results at a given assessment, thus ignoring additional clinical findings, except for the evaluation of blood glucose toxicity grade 1 and 2, where the fasting state is required. Ignoring the fasting state might lead to overreporting of grade 1 and 2 events. Therefore, blood glucose grading will focus on grade 3 and 4 reporting only.

3 different line plots (with x-axis time, y-axis lab value in absolute units, in multiple normal limit and percent change from baseline) will be provided by dose level and overall, using different colors per regimen, dose level and different color grading to identify participants. For the following lab parameters, line plots with the lab value in terms of multiple normal limits will be provided for individual participants:

- Neutrophils
- Platelets
- Lymphocytes

Lab values that are > 2xULN or < LLN/2 will be indicated in the plot.

Additionally, a plot for the most extreme lab values showing the peak percent change form baseline per participant will be provided using different colors per regimen and dose level.

Hepatotoxicity assessment

A plot of peak ALT and peak 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. Subjects outside the lower left box will be identified by subject-ID.

15.6 Vital Signs

Not applicable for this IAP, except for display of individual values in patient profiles

15.7 Other Safety or Tolerability Evaluations

A listing of AEs of special interest can be obtained by filtering the AE listing of the statistical outputs html document.

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16 Analyses of Other Endpoints/Estimands

16.1 Pharmacokinetics

PK evaluation will be performed by the Clinical PK/PD Group, Merck Healthcare KGaA, Darmstadt, Germany, or by a CRO selected by the Sponsor.

16.1.1 Descriptive Statistics of PK Concentration Data

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

A concentration below the lower limit of quantification (BLQ) represents a valid measurement and will be taken as zero for summary statistics of PK concentration data.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only.

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

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

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data will be descriptively summarized using: 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}), only n, Min, Median, and Max may be reported.

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. 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	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 General Specifications for PK Concentration and PK Parameter Data

Pharmacokinetic data (concentrations and PK parameters) will be presented in listings, tables, and graphs as shown in Appendix 3.

Predose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study intervention administration. The same applies to the pre-dose sample of a multiple dose study.

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 prior to the first dose, the participant's data will be included in the PK and statistical analyses without any adjustments.

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.

PK concentrations which are erroneous due to a sampling processing or analytical error may be excluded from the PK analysis if agreed by the Sponsor.

Any PK concentrations or PK parameters excluded from summary statistics will be included in participants listings and flagged; a reason for exclusion will be detailed.

PK concentrations and PK parameters excluded from summary statistics will not be included in mean figures.

16.1.4 Estimation of Pharmacokinetic Parameters in Plasma

PK parameters will be calculated using the nominal time since dosing.

The following plasma PK parameters will be calculated where appropriate:

Symbol	Definition	Calculation
$AUC_{0\text{-}tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}).	Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}tlast}$ / Dose	The dose normalized $AUC_{0\text{-}tlast}$.	Calculated as $AUC_{0\text{-}tlast}$ / Dose, where Dose is the nominal dose (in mg).
AUC_{τ}	The AUC over the dosing interval τ.	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. For multiple dose, AUC_{τ} is calculated from the pre-dose time point to the end of the dosing interval.
AUC_{τ} / Dose	The dose normalized AUC_{τ}.	Calculated as AUC_{τ} / Dose, where Dose is the nominal dose (in mg).
$AUC_{0\text{-}\infty}$	The AUC from time zero (= dosing time) up to infinity with extrapolation of the terminal phase.	$AUC_{0\text{-}\infty} = AUC_{0\text{-}tlast} + C_{last\ pred} / \lambda_z$, where $C_{last\ pred}$ is the predicted concentration at the t_{last}, calculated from the log-linear regression line for λ_z determination. Calculated on C1D1 only.
$AUC_{0\text{-}\infty}$ / Dose	The dose normalized $AUC_{0\text{-}\infty}$.	$AUC_{0\text{-}\infty}$ / Dose, where Dose is the nominal dose (in mg). Calculated on C1D1 only.
C_{max}	Maximum observed concentration.	
C_{max} / Dose	The dose normalized Cmax.	Calculated as C_{max} / Dose, where Dose is the nominal dose (in mg).
t_{max}	The time to reach the C_{max} in a dosing interval.	In case multiple/identical C_{max} values occur, the first occurrence will be *used.*
$t_{1/2}$	The terminal half-life.	$t_{1/2} = \ln(2) / \lambda_z$, where λ_z is the terminal first order (elimination) rate constant determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve.
CL/F	The apparent total body clearance following extravascular administration.	CL/F = Dose / $AUC_{0\text{-}\infty}$ after single dose.
CL_{SS}/F	The apparent total body clearance at steady state following extravascular administration.	CL_{SS}/F = Dose/ AUC_{τ}.

Symbol	Definition	Calculation
V_Z/F	The apparent volume of distribution during the terminal phase following extravascular administration.	V_Z/F = Dose / ($AUC_{0-\infty} \times \lambda_Z$) following single dose. V_Z/F = Dose / ($AUC_{\tau} \times \lambda_Z$) following multiple doses.
LI	The linearity index after repeated administration.	LI = (AUC_{τ} after multiple dose) / ($AUC_{0-\infty}$ after single dose)
$R_{acc(Cmax)}$	The accumulation ratio of C_{max} after repeated administration.	Calculated as $R_{acc(Cmax)}$ = (C_{max} after multiple dose) / (C_{max} after single dose)
$R_{acc(AUC\tau)}$	The accumulation ratio of AUC_{τ} after repeated administration.	Calculated as $R_{acc(AUC\tau)}$ = (AUC_{τ} after multiple dose) / (AUC_{τ} after single dose)

C_{trough} (predose concentration) on C1D8, C1D15, and Day 1 of subsequent cycles will also be reported. 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

The parameters C_{max} 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}.

For calculation of $AUC_{0\text{-}tlast}$, if the concentration at the last sampling time point is missing and concentrations did not fall to BLQ prior to that time point, $AUC_{0\text{-}tlast}$ will not be estimated.

AUC_τ will be calculated by extrapolation to τ (12 hours in case of BID or 24 hours in case of QD), if λ_z is estimable.

The following rules may be applied for calculation of AUC_τ:

- 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 $AUC_{0\text{-}\infty}$.
- At steady state, if suitable regression cannot be performed, the pre-dose concentration may be duplicated and used as the trough concentration for the NCA and for calculation of AUC_τ and other PK parameters.

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

- First (λz lower) and last (λz upper) time point of the time interval of the log-linear regression to determine λz.
- Number of data points (Nλ) included in the log-linear regression analysis to determine λz.
- Goodness of fit statistic (adjusted Rsq) for calculation of λz.
- AUC from time tlast extrapolated to infinity given as percentage of $AUC_{0\text{-}\infty}$. ($AUC_{extra\%}$)
- Span ([λz upper - λz lower]/$t_{1/2}$)

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 greater than the lower limit of quantification (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 $AUC_{extra\%}$ is >20.0% and/or the coefficient of correlation (Rsq adj) of λz is <0.800 and/or the observation period over which the regression line is estimated (span) 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.

For calculation of dose-related parameters, no dose adjustment is required since dose administered is expressed as the free base dose.

17 References

1. R Core Team (2021). "R: A language and environment for statistical computing. R Foundation for Statistical Computing". Vienna, Austria. URL: https://www.R-project.org/

2. Sweeting M, Mander A, Sabin T (2013). "bcrm: Bayesian Continual Reassessment Method Designs for Phase I Dose-Finding Trials". R package version 0.5.4. URL: https://cran.r-project.org/package=bcrm

3. Sabanes Bove D, Yeung WY, Palermo G, Jaki T (2019). "Model-Based Dose Escalation Designs in R with crmPack." Journal of Statistical Software, 89(10), 1-22. URL: https://doi.org/10.18637/jss.v089.i10.

4. Allaire JJ, Xie Y, McPherson J, Luraschi J, Ushey K, Atkins A, Wickham H, Cheng J, Chang W, Iannone, R (2021). "rmarkdown: Dynamic Documents for R". R package version 2.7. URL: https://rmarkdown.rstudio.com.

5. Gohel D (2021). "flextable: Functions for Tabular Reporting". R package version 0.6.5. URL: https://CRAN.R-project.org/package=flextable.

6. Xie Y (2021). "knitr: A General-Purpose Package for Dynamic Report Generation in R". R package version 1.32.

7. Wickham H (2016). "ggplot2: Elegant Graphics for Data Analysis". Springer-Verlag New York.

8. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine. 2008; 27:2420-39. URL: https://doi.org/10.1002/sim.3230

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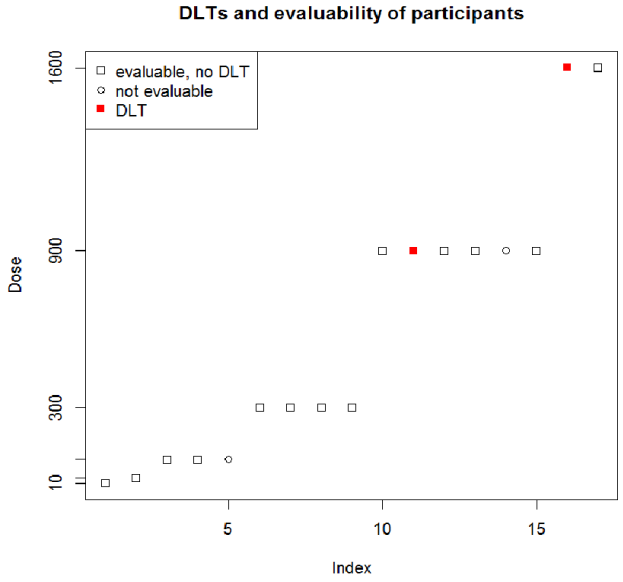
Appendix 2 – Mock Figures

F_SMCDE.DLTplot



Appendix 3 – Pharmacokinetic Outputs for SMC

Table 1: Summary of Key Plasma M1069 PK Parameters on C1D1 by Dose

COHORT_N	DOSE (mg)	N	Cmax (ng/mL)	Tmax (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	AUCtau (h*ng/mL)	t1/2(h)
1	xx							
2	xx							
3	xx							

Note: Table will present Geometric mean (GeoCV%) for all parameters, except for Tmax where Median (Min, Max) will be presented.

Table 2: Summary of Key Plasma M1069 PK Parameters on C1D8 by Dose

Note: Layout will be similar to Table 1. Parameters presented on this table: Cmax, Tmax, AUCtau, Half life, Rac(Cmax), Rac(AUCtau)

Table 3: Individual Values and Summary Statistics of M1069 Plasma Concentrations by Dose and Nominal time on C1D1 and C1D8

				Nominal Time (h)														
				0.00	0.50	1.00	1.50	2.00	4.00	6.00	8.00							
Cohort	Day	DOSE (mg)	Subject	Concentration (ng/mL)														
1	1	xx	CCI [redacted]															
			N															
			Mean															
			SD															
			CV%															
			Min															
			Median															
			Max															

Table 4: Individual Values and Summary Statistics of M1069 Plasma Concentrations by Dose for Troughs and Non-Serial PK Days

			CYCDAY					
			C1D08	C1D15	C2D01		C4D01	C6D01
			Time (h)	Time (h)	Time (h)		Time (h)	Time (h)
			0.00	0.00	0.00	2.00	0.00	0.00
COHORT	DOSE (mg)	CCI	Concentration (ng/mL)					
Cohort 1	xx							
		N						
		Mean						
		SD						
		CV%						
		Min						
		Median						
		Max						

Table 5: Individual Values and Summary Statistics of M1069 Plasma PK Parameters by Dose on C1D1

COHORT_N	DOSE (mg)	CCI	Cmax (ng/mL)	Tmax (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	AUCtau (h*ng/mL)	Halflife (h)	CL_F (L/h)	Vz_F (L)
1	xx									
		N								
		Mean								
		SD								
		CV%								
		Min								
		Median								
		Max								
		Geometric Mean								
		Geometric CV%								
		CI 95% Lower GEO Mean								
		CI 95% Upper GEO Mean								

Table 6: Individual Values and Summary Statistics of M1069 Plasma PK Parameters by Dose on C1D8

Note: Layout will be similar to Table 5. Parameters presented on this table: Cmax, Tmax, AUCtau, Half life, CL/F, Vz/F, Linearity Index (LI), Racc(Cmax), Racc(AUCtau)

Table 7: Individual Values and Summary Statistics of M1069 Plasma Dose-normalized PK Parameters by Dose on C1D1 and C1D8

Note: Layout will be similar to Table 5. Parameters presented on this table: Cmax/D, AUClast/D, AUCinf/D, and AUCtau/D on C1D1, and Cmax/D, AUClast/D, and AUCtau/D on C1D8.

Table 8: Individual Diagnostic PK Parameters on C1D1 and C1D8 by Dose

				Parameter				
				AUC_Extrap_pred	Lambda_z_lower	Lambda_z_upper	No_points_lambda_z	Rsq_adjusted
				Units	Units	Units	Units	Units
				%	h	h		
COHORT_N	DOSE (mg)	PKDAY	CCI	Estimate				
1	xx	1						
			9357					

Figure 1: Individual M1069 Plasma Concentration-time Profiles by Dose on C1D1 and C1D8 – Linear Scale

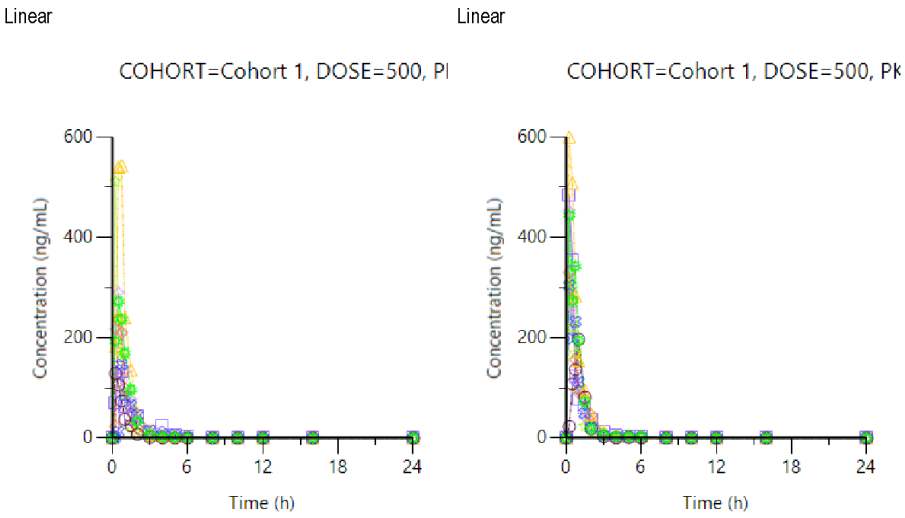


Figure 2: Individual M1069 Plasma Concentration-time Profiles by Dose on C1D1 and C1D8 – Semilogarithmic Scale

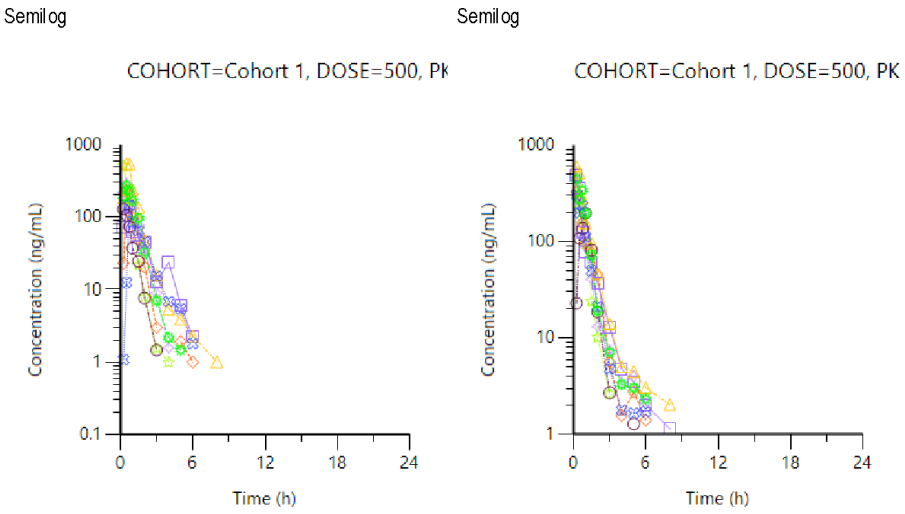


Figure 3: Mean (±SD) M1069 Plasma Concentration-time Profiles by Dose on C1D1 – Linear Scale

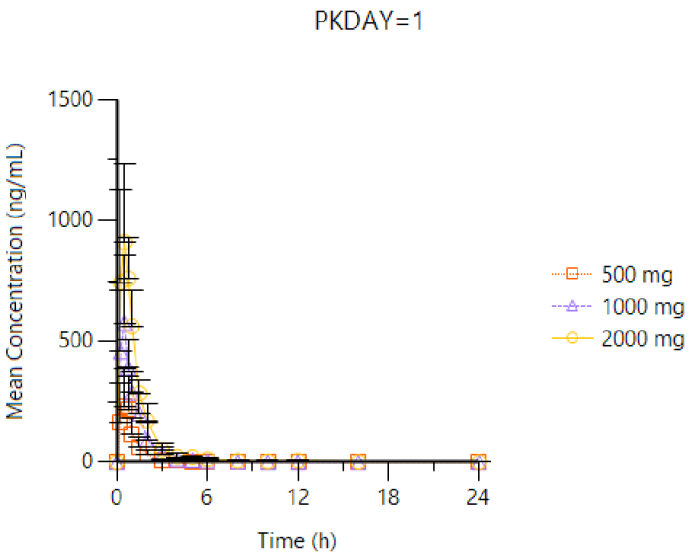


Figure 4: Mean (±SD) M1069 Plasma Concentration-time Profiles by Dose on C1D8 – Linear Scale

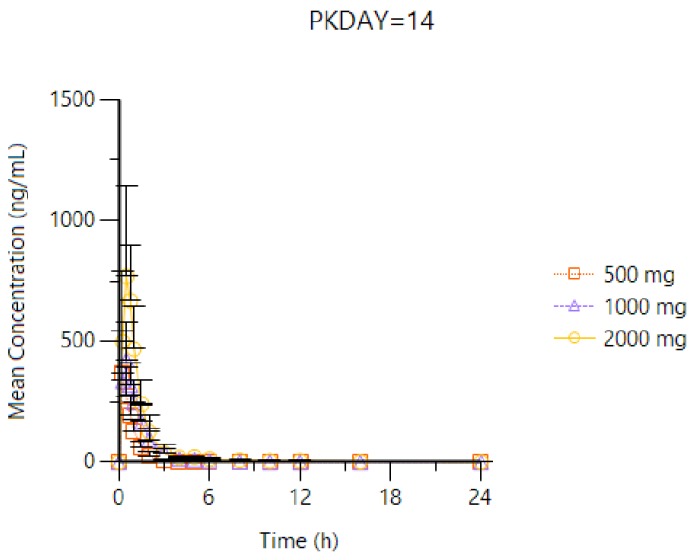


Figure 5: Mean M1069 Plasma Concentration-time Profiles by Dose on C1D1 – Semilogarithmic Scale

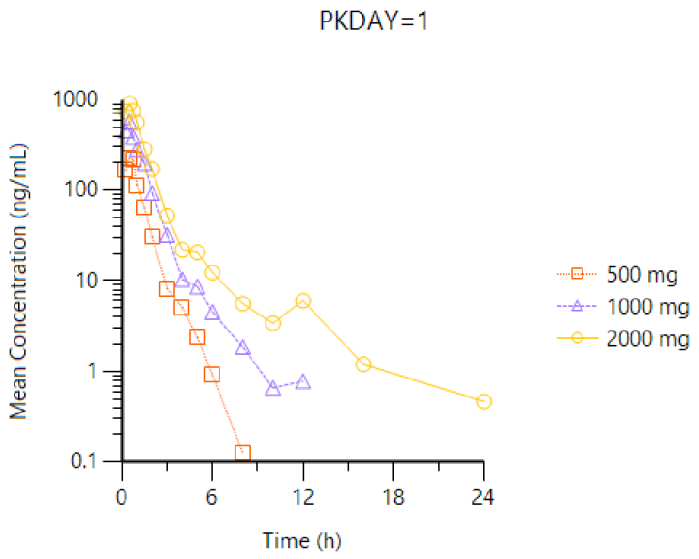


Figure 6: Mean M1069 Plasma Concentration-time Profiles by Dose on C1D8 – Semilogarithmic Scale

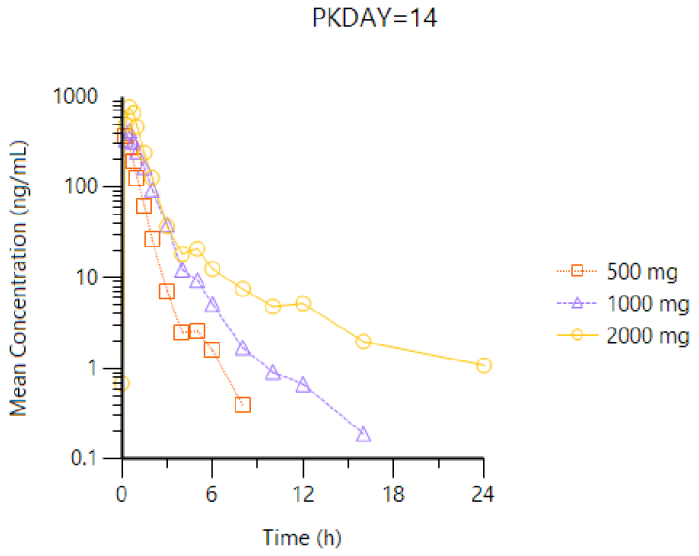
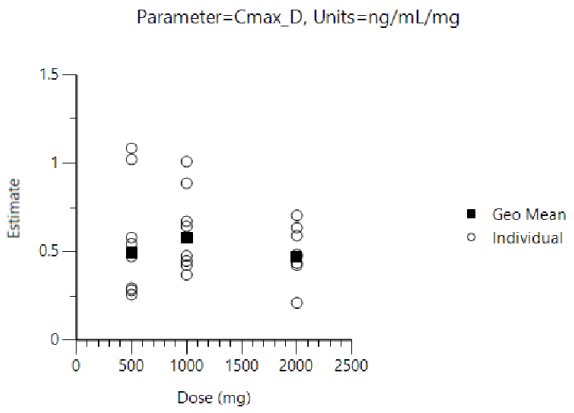


Figure 7: Individual and Geometric Mean Values of Key Dose-normalized PK Parameters versus M1069 Dose on C1D1



Note: Parameters presented: Cmax/D, AUClast/D, AUCinf/D, AUCtau/D

Figure 8: Individual and Geometric Mean Values of Key Dose-normalized PK Parameters versus M1069 Dose on C1D8

Note: Layout will be similar to Figure 7. Parameters presented: Cmax/D, AUCtau/D

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