Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS201408-0005
Title	Phase I, First-in-Human, Open-Label, Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M4112 an IDO1/TDO2 Inhibitor as Single Agent CCI [redacted] CCI [redacted] in Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors
Study Phase	I
Investigational Medicinal Product(s)	M4112 as single agent CCI [redacted] CCI [redacted]
Clinical Study Protocol Version	08 September 2017 / Version 2.0
Integrated Analysis Plan Author	

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Signature Page

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Merck Responsible	Date	Signature
PPD	Via ELDORADO approval process	

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
AUC_{0-8}	AUC from time zero (= dosing time) to 8 hours postdose
AUC_{0-8}/Dose	Dose-normalized AUC_{0-8}
CCI	[redacted]
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CIPD	Clinically Important Protocol Deviation
C_{max}	Maximum Observed Concentration
C_{max}/Dose	Dose-normalized C_{max}
C_{pre}	Predose (trough) observed concentration
C_{pre}/Dose	Dose-normalized C_{pre}
CnDn	Cycle and Study Day, e.g., Cycle 1 Day 1 (C1D1), Cycle 2 Day 1 (C2D1)
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV%	Coefficient of Variation
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
GBS	Global Biostatistics
IAP	Integrated Analysis Plan

ICH	International Conference on Harmonization
irAE	Immune-Related Adverse Event
CCI	[redacted]
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantification of the assay
LPS	Lipopolysaccharide
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number of subjects
n	Number of non-missing values
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NR	No Result
PCSA	Potentially Clinically Significant Abnormalities
PD	Progressive Disease
Pd	Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
QTcF	QT interval with Frederica's correction
$R_{acc(AUC0-8)}$	Accumulation factor to assess the increase in exposure via AUC_{0-8} following multiple dosing
$R_{acc(Cmax)}$	Accumulation factor to assess the increase in maximum concentration following multiple dosing
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class

StDev	Standard Deviation
TEAE	Treatment Emergent Adverse Event
t_{max}	Time to reach the maximum observed concentration
CCI	[redacted]
ULN	Upper Limit of Normal
ULOQ	Upper limit of quantification of the assay
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	07 Feb 2019	PPD	N/A – First version

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP), authored together by Biostatistics and Quantitative Pharmacology, is to document technical and detailed specifications for the final analysis of data collected for the M4112 monotherapy dose escalation phase of protocol MS201408-0005. Due to termination of the study prior to commencement of Part IB and Part IC, only analyses for Part IA are covered in this IAP. Results of the analyses described in this IAP may be included in the Clinical Study Report (CSR) or a separate report. Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

A separate Statistical Analysis Plan (SAP) has been created to document analyses prepared for Safety Monitoring Committee (SMC) meetings (Appendix 18.2). The IAP is based upon Section 8 (Statistics) of the study protocol and protocol amendments and is prepared in compliance with ICH E9.

5 Objectives and Endpoints

5.1 Part IA (Dose Escalation – M4112 as Single Agent)

	Objective	Endpoint	IAP Section
Primary Objective	• To determine safety and tolerability or, if observed, the MTD, and to define the RP2D of M4112 as single agent in subjects with solid tumors	• DLTs in subjects receiving M4112 as single agent during the first 4 weeks (Day 1 to Day 28 of Cycle 1) of treatment	15.1
		• TEAEs and TRAEs according to NCI-CTCAE 4.03 (including deaths) in subjects receiving M4112 as single agent from start of treatment up to the last Safety Follow-up Visit	15.2, 15.3
		• Treatment-emergent changes from baseline in clinical laboratory measures, vital signs, ECOG PS, and physical examination findings in subjects receiving M4112 as single agent up to the last Safety Follow-up Visit	15.4, 15.5, 15.7
Secondary Objectives	• To characterize the PK parameters of M4112 as single agent	• Plasma PK parameters for M4112: AUC_{0-8}, C_{max}, t_{max}, $AUC_{0-8/Dose}$, $C_{max/Dose}$ (Days 1 and 15 of Cycle 1); $R_{acc(AUC0-8)}$ and $R_{acc(Cmax)}$ (Day 15/Day 1 of Cycle 1); C_{pre}, and $C_{pre/Dose}$ (Days 8 and 15 of Cycle 1 and Day 1 of Cycle 2)	16.1.2
	• To assess QT prolongation potential by central tendency, outlier analysis and the slope of exposure-QTc analysis to evaluate preliminary clinical activity parameters using RECIST 1.1	• Slope of concentration-QTc (cQTc) regression based on time-matched ECG readings (3 or more replicates) and PK samples during Cycle 1 at Day 1 and Day 15, central tendency and outlier analyses for absolute QTcF, and delta QTc	15.6.1
	• To evaluate preliminary clinical activity parameters using RECIST 1.1	• BOR, DCR, and PFS using RECIST 1.1, up to confirmed tumor progression	14.1, 14.2
Exploratory Objectives	CCI		16.2
			16.2

AUC = area under the concentration-time curve; AUC_{0-8} = AUC from time zero (= dosing time) to 8 hours postdose; AUC_{0-8}/Dose = dose-normalized AUC_{0-8}; BOR = best overall response; C_{max} = maximum observed concentration; C_{max}/Dose = dose-normalized C_{max}; C_{pre} = predose (trough) observed concentration; C_{pre}/Dose = dose-normalized C_{pre}; DCR = disease control rate; DLT = dose limiting toxicity; PFS = progression free survival; PK = pharmacokinetic; $R_{acc(AUC0-8)}$ = accumulation factor to assess the increase in exposure via AUC_{0-8} following multiple dosing; $R_{acc(Cmax)}$ = accumulation factor to assess the increase in maximum concentration following multiple dosing; TEAE = treatment emergent adverse event; t_{max} = time to reach the maximum observed concentration.

6 Overview of Planned Analyses

The planned analyses have been impacted by the decision to terminate this study early, prior to commencement of Parts IB and IC. In addition to the SMC analyses (detailed in a separate SAP, finalized on 30 Jan 2018), only a single, abbreviated final analysis will be performed. This final analysis will occur only after the last subject has completed the treatment phase of the study, with all study data in-house, all data queries resolved, and the database locked.

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

7 Changes to the Planned Analyses in the Clinical Study Protocol

As a result of the decision to terminate this study early, only the M4112 monotherapy treatment arm (Part IA) was completed; the combination arms of CCI and CCI, as described in the protocol CCI were never opened for enrollment.

The following protocol-specified analyses will not be completed:

- Duration of response (DOR) and time to tumor response
- Concentration-QTc slope analysis of time-matched, replicate ECGs and PK samples
    - Summary statistics and scatterplots will be produced instead of linear modeling (Section 15.6.1)

CCI

The PK parameters specified for calculation in the protocol included C_{min} (defined as minimum observed postdose [trough] concentration) and C_{min}/Dose. These parameters have been revised/clarified to C_{pre} and C_{pre}/Dose, where C_{pre} is defined as the predose (trough) observed concentration and may not reflect the true value at the end of the dosing interval.

The Dose Escalation Analysis Set was renamed to "DLT Analysis Set". The definition was updated for clarifications.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. They are coded as "Critical" or "Major" in the Clinical Trial Management System (CTMS) if identified via monitoring; they may also be identified from the database by medical review or programmatically.

The subject-level important protocol deviations to be identified by programming for this study are defined in Section 18.1.

The following types of deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest:

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion
- Clinically important protocol deviations (CIPDs) are defined as deviations leading to the exclusion of a subject from an analysis set (refer to Section 8.2)

Other events/factors related to PK, which include, but may not be limited to, events that could affect PK, will be evaluated on a case-by-case basis by the PK Scientist:

- Vomiting immediately following oral dosing
- Sample processing errors that may lead to inaccurate bioanalytical results
- Incomplete data (e.g. due to lost samples, insufficient sample volumes for assay)
- Inaccurate dosing, dose reductions, missed dose(s) just prior to a PK dose, or dosing errors

In case of a deviation or event that may affect PK data, collected PK data which is likely to be affected may be excluded from the study results after consultation and agreement with Sponsor or Sponsor representative.

In general, data will not be excluded from the PK Analysis Set because of large PK sampling time deviations (since actual elapsed times will be used for PK analysis) or inadequate fasting prior to or following a PK dose. Additionally, given the patient population involved, data will not be excluded for an inaccurate dosing interval prior to a PK dose (though the affected doses will be identified in a data listing), or for concomitant medication violations.

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

Protocol deviations will be classified as CIPDs or not, and confirmed prior to or at the Data Review Meeting before database lock.

8.2 Definition of Analysis Sets and Subgroups

The analysis sets of subjects whose data will be included in the analyses described in this IAP are defined in Table 1.

Table 1 Analysis Sets

Population	Description
Screening (SCR)	All subjects who sign informed consent.
DLT	All subjects who received at least one dose of study intervention and meet at least one of the following criteria: - Received at least 5 planned cumulative total daily doses of M4112 in the first cycle (first 28 days) or - Experienced at least one DLT during the DLT period, regardless of the administered number of doses of study intervention/completion of the DLT period
Safety	The Safety Analysis Set will include all subjects who receive at least 1 dose of study treatment.
Concentration-QTc Analysis Set	The cQTc Analysis Set will include all subjects with at least baseline and one on treatment measurement of time-matched ECG and M4112 plasma concentration collected during the dose-escalation phase.
M4112 Pharmacokinetic	All subjects from the Safety Analysis Set without clinically important protocol deviations/violations or events that would affect PK (see Section 8.1). Subjects in the PK Analysis Set must have received at least 1 dose of M4112 and must have sufficient M4112 plasma concentration data to enable the calculation of at least 1 PK parameter. Sufficient concentration data is defined as at least 3 valid, postdose concentration points in the PK profile to obtain any PK parameter.
Pharmacodynamics	All subjects who received at least 1 dose of M4112 and provide the predose and at least 1 postdose sample for Pd assessment.

cQTc = concentration-QTc response; DLT = dose-limiting toxicities; ECG = electrocardiogram;
Pd = pharmacodynamics; PK = pharmacokinetic; QTc = corrected QT interval.

There are no subgroup analyses planned for this study.

9 General Specifications for Data Analyses

All analyses will be prepared by planned dose level, unless indicated otherwise.

Details on PK data presentation can be found in Section 16.1.

CCI [redacted].

Data handling after cut-off date:

In general, this is not applicable, as the analyses described will be conducted after all subjects have completed their involvement in the study.

Pooling of centers:

Because of the small number of subjects in each center, data will be pooled across centers.

Significance level:

There is no formal significance level for this study and all analyses are considered descriptive.

Presentation of continuous and qualitative variables for Demographics and Other Baseline Characteristics, Efficacy, and Safety:

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

- number of subjects (N), number of nonmissing values (n)
- mean, standard deviation
- median, 25th Percentile - 75th Percentile (Q1-Q3), minimum, and maximum

If there are no missing values this should be indicated by a 0.

Qualitative variables will be summarized by counts and percentages.

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

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

Definition of baseline:

In general, the last nonmissing measurement prior to the first study treatment will serve as the baseline measurement. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine predose on Study Day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on Study Day 1 will be considered to have been obtained after study treatment administration.

Definition of duration:

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

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

Definition of study day/treatment day:

Treatment day is defined relative to the date of first dose of any study treatment. Day 1 represents the first day of treatment; the day before is defined as Day –1 (no Day 0 is defined).

Definition of treatment period:

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anticancer drug therapy – 1 day).

Conversion factors and reporting standards:

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

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

For reporting conventions, mean, median, Q1, Q3, min, and max will have the same precision (number of digits) as SDTM data for non-derived values; standard deviation will have one additional decimal place. Percentages will be reported to one decimal place. The rounding will be performed to closest integer/first decimal using the common midpoint between the two consecutive values (e.g., 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6).

Unscheduled visits:

Data collected at unscheduled visits will be included and analyzed in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, StDev, median, minimum, maximum, and quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs, and vital signs will include only data from scheduled visits.

Summary statistics over time:

For descriptive statistics over time by nominal visit or time point (for non-PK data only), only those planned visits/time points that have at least 5 subjects overall (regardless of the number in each planned dosing cohort) will be included in the summary tables and figures. The exception is the End-of-Treatment and Safety Follow-up visits, which will be included in the summary statistics regardless of the number of subjects who completed the visit.

Visit windowing:

The assignment of visit window is described in Table 2 for the purpose of by-visit analyses of laboratory assessment, vital sign, and ECG data:

- Baseline will be derived as described above.
- Both scheduled and unscheduled assessments are included for visit windowing.
- No visit windowing will be performed at End-of-Treatment or Safety Follow-up visits. Instead, the earliest nonmissing observation among the unscheduled or scheduled assessments for each visit will be used for the analysis.
- If there are multiple assessments for any specified visit and some of them are from scheduled visits with nonmissing assessment results, the assessment from scheduled visit that is closest to the planned study day will be used for analysis. If two scheduled visits are equally spaced around the assigned study day, the earlier of the two will be used.

- If there are multiple assessments for any specified visit and none of them are from scheduled visits, the assessment with nonmissing results and closest to the planned study day will be used for analysis.
- If there are two or more unscheduled assessments with nonmissing results and the same distance to the planned study day, the assessment prior to the planned study day will be used in deriving visit window. For example, if the lab assessment was done on both Study Day -1 and 1, then the assessment on Study Day -1 will be used for visit windowing.

Table 2 Visit Window Definition for Safety Assessment

Assigned Study Day (Inclusive)		Planned Study Day (AWTARGET)	Analysis Visit (N) (AVISITN)	Analysis Visit (AVISIT)	Assessments
From (AWLO)	To (AWHI)				
-28	1		0	Screening	Lab, VS, ECG
-1	2	1	1.1	Cycle 1 Day 1	Lab, VS, ECG
7	9	8	1.8	Cycle 1 Day 8	Lab, VS, ECG
14	16	15	1.15	Cycle 1 Day 15	Lab, VS, ECG
21	23	22	1.22	Cycle 1 Day 22	Lab, VS
28	30	29	2.1	Cycle 2 Day 1	Lab, VS, ECG
42	44	43	2.15	Cycle 2 Day 15	Lab, VS
54	60	57	3.1	Cycle 3 Day 1	Lab, VS
68	74	71	3.15	Cycle 3 Day 15	Lab, VS
82	88	85	4.1	Cycle 4 Day 1	Lab, VS, ECG
96	102	99	4.15	Cycle 4 Day 15	Lab, VS
110	116	113	5.1	Cycle 5 Day 1	Lab, VS
124	130	127	5.15	Cycle 5 Day 15	Lab, VS

Further windows can be calculated based on the following general algorithm starting from the planned study day in Cycle X:

Planned study days in Cycle X = (X – 1) * 28 + 1 and (X – 1) * 28 + 15

Assigned study days (inclusive) = [(X – 1) * 28 – 3] days to [(X – 1) * 28 + 3] days

Handling of missing data:

Unless otherwise specified, missing data will not be replaced.

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

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

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

Handling of missing data for PK parameter calculations are discussed under Section 16.1.

Pharmacokinetic parameters will be derived using the validated computer program Phoenix® WinNonlin® 6.4 or higher, and/or SAS® (Statistical Analysis System, PPD) Windows Version 9.4 or higher. All other analyses will be performed using SAS® Windows Version 9.4 or higher. For the outputs of the Bayesian two parameter logistic model updates, East 6.0 or R (version 3.1.0 or higher [3]) and the R package bcrm [4] or CRMpack or SAS proc MCMC will be used.

10 Study Subjects

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

10.1 Disposition of Subjects and Discontinuations

The following will be summarized overall and by planned dose level, with the percentages calculated based on the number of subjects in the Screening Analysis Set.

- Total number of subjects screened (i.e., subjects who gave informed consent)
- Number of subjects who discontinued from the study prior to treatment overall and grouped by the main reason (e.g., the failed specific inclusion or exclusion criteria, withdrawal of consent)
- Number of treated subjects
- Number of subjects who completed the dose escalation period
- Number of subjects who discontinued the treatment, grouped by main reason
- Number of treated subjects who discontinued the study, grouped by main reason

The percentages for subjects treated will be based on the number of subjects in the safety population for each treatment sequence and on the number of screened subjects in the overall group.

In the corresponding individual listing, date of informed consent, protocol version, first and last

date of dosing and study termination date will be presented, as well as primary reason for study and treatment discontinuation.

The listing of screening failures will include the following information:

- Date of informed consent
- Protocol version
- Date of screening failure
- Reason for noninclusion

The disposition listings will be sorted by dose group and subject ID.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

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

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

Important protocol deviations will be determined for all subjects by either medical or PK review processes or programming based on the inclusion/exclusion criteria or other criteria presented in the protocol or described in Section 18.1.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

The exclusion of subjects from analysis populations, e.g. due to clinically important protocol deviations, will be summarized by counts and frequencies for all occurring reasons of exclusion for each analysis population.

Exclusions will also be listed, including:

- Population that the subject is excluded from
- Reason of exclusion

11 Demographics and Other Baseline Characteristics

If not stated otherwise, summaries will be presented for the Safety Analysis Set.

11.1 Demographics

Demographic characteristics will be listed (sorted by dose group and subject ID) and summarized by dose group and overall as follows:

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Collected, Other
  - Ethnic origin: Hispanic/Latino (Yes/No), Japanese (Yes/No)
  - Age (years): summary statistics
  - Age categories:
    - < 65 years, ≥ 65 years
    - < 65, $65 - 74$, $75 - 84$, ≥ 85
  - Eastern Cooperative Oncology Group (ECOG) Performance Status
- Physical measurements
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2)

Specifications for computation:

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

11.2 Medical History

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized as the numbers and percentages of subjects by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each subject 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.

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

11.3 Disease History and Prior Anti-Cancer Therapies

Information regarding disease characteristics collected on the "Disease History" CRF page will be summarized and/or listed as follows:

- Primary tumor histology
- Site and subsite(s) of primary tumor
- Time since initial cancer diagnosis (months), defined as (date of first study treatment – date of initial diagnosis)/30.4375
- Time since documented locally advanced, inoperable, or metastatic disease diagnosis (months), defined as (date of first study treatment – date of documented locally advanced, inoperable, or metastatic disease diagnosis)/30.4375
- Time since of last progression of disease prior to study entry (months), defined as (date of first study treatment – date of last disease progression)/30.4375
- TNM classification at initial diagnosis and at study entry

The prior anticancer treatments and procedures are collected under "Prior anti-cancer therapy", "Prior anti-cancer radiotherapy", and "Prior anti-cancer surgeries" pages from the CRF.

Prior anti-cancer drug therapy will be listed including the following information:

- Regimen number
- Intent and type of therapy
- Reason for discontinuation
- Best response
- Date of documented progression disease (if applicable)
- For each drug given as part of the regimen:
  - Name of drug (coding as described in Section 12)
  - Start and end date

Prior anti-cancer radiotherapy will be listed including the information:

- Regimen number
- Location
- Start and end dates
- Total dose

- Number of fractions

Prior anti-cancer surgeries will be listed including the following information:

- Name of surgery
- Date of surgery
- Intent of surgery
- Outcome of surgery

A summary of prior anti-cancer therapies will be added to the disease history, displaying number of surgeries, radiotherapy regimes and anti-cancer drug regimes.

Baseline characteristics with respect to vital signs, physical examinations, ECGs, and laboratory tests will be part of Section 15 (Safety Evaluation).

12 Previous or Concomitant Medications/Procedures

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

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

Previous medications are medications, other than study medications and premedications for study drug, which started before first administration of study drug.

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

All reported previous medications will be listed.

All **concomitant procedures**, which were undertaken at any time during the study, will be summarized according to the CRF page "Concomitant Procedures". Concomitant procedures will be classified by medical review.

The number of subjects with concomitant procedures overall and by type of procedure (as classified by medical review) will be tabulated.

All relevant concomitant medication and procedure data will be listed.

13 Treatment Compliance and Exposure

All dosing calculations and summaries will be based on the "M4112 Administration Details" CRF page. The Safety Analysis Set will be used for these analyses.

Handling of missing data:

- If the total actual dose is missing, the planned dose level as entered in the CRF will be used.
- In case the last medication end date is incomplete, the date of M4112 administration will be taken from the "M4112 Termination" page.

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

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

The cumulative dose of M4112 (in mg) is defined as:

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

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

Dose intensity (mg/week) will be calculated as follows:

$$\text{Dose intensity (mg/week)} = \left(\frac{\text{Total cumulative dose of M4112 (mg)}}{\text{Duration of therapy (weeks)}}\right)$$

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

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{Total cumulative dose of M4112 (mg)}}{\text{Total planned dose of M4112 (mg)}}\right) * 100\%$$

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:

- Cycle and day in cycle
- Date and time of administration
- Actual dose

- Whether dose has been adjusted, and if yes, reason why
- Reason for no dose (if applicable)

14 Efficacy Analyses

The Safety Analysis Set will be used for all efficacy analyses, unless otherwise noted. All efficacy endpoints will be listed and summarized descriptively.

14.1 Progression Free Survival

Progression free survival (PFS) time, according to RECIST 1.1 as assessed by the Investigator, is defined as the time from first study treatment to the date of the first documentation of objective PD or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death) or for patients with an event after two or more subsequent missing response assessments (i.e., twice the scheduled time interval between two subsequent response assessments – this interval is 8 weeks through Cycle 7, and 12 weeks thereafter). Patients who do not have a baseline tumor assessment or who do not have any postbaseline tumor assessments will be censored at treatment 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.

Data will be taken from the "Assessment of Disease Based on Imaging" CRF page. The date of the overall response assessment is the earliest date for imaging of target, nontarget, and new lesions taken at that response assessment.

The censoring and event date options to be considered for the PFS analysis are presented in Table 3. The last adequate tumor assessment is defined as a tumor assessment with a result other than "NE" or "NA".

Table 3 Outcome and Event Dates for PFS Analysis

Scenario	Date of Event / Censoring	Outcome
No baseline assessment	Date of first study treatment	Censored [a]
Progression or death ≤ xx weeks after last tumor assessment or ≤ xx weeks after treatment start date, where xx is 16 weeks if the last assessment is at Screening or Cycle 3 (Evaluation Visit 1), 20 weeks if the last assessment is at Cycle 5 (Evaluation Visit 2), and 24 weeks if the last assessment is at Cycle 7 (Evaluation Visit 3) or later.	Date of progression or death	Event
Progression or death > xx weeks after the last tumor assessment, where xx is 16 weeks if the last assessment is at Screening or Cycle 3 (Evaluation Visit 1), 20 weeks if the last assessment is at Cycle 5 (Evaluation Visit 2), and 24 weeks if the last assessment is at Cycle 7 (Evaluation Visit 3) or later.	Date of last adequate tumor assessment	Censored
No progression	Date of last adequate tumor assessment	Censored
Treatment discontinuation due to "Disease progression" without documented progression	Not applicable	Information collected on treatment discontinuation page is ignored since outcome should be derived based on documented progression only. General censoring rule is applied.
New anti-cancer therapy given	Date of last adequate tumor assessment before anti-cancer therapy is given	Censored

[a]If the subject dies ≤ 16 weeks after treatment start date, the death is an event with date on death date.

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics (median survival time; 6- and 12-month survival rate estimates) including the corresponding two-sided 95% confidence intervals (CIs). The CI for the median will be calculated according to Brookmeyer and Crowley (1982), and CIs for the survival function estimates at the aforementioned time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980) (conftype=loglog default option in SAS PROC LIFETEST). The estimate of the standard error will be computed using Greenwood's formula.

14.2 Best Overall Response & Disease Control Rate

Best Overall Response (BOR) will be determined according to RECIST 1.1. It is defined as the best response obtained among all tumor assessment visits after the date of first study drug administration until documented disease progression. The BOR rate is defined as the number of subjects with BOR either confirmed CR or PR, relative to the number of subjects belonging to the study of interest.

Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression. BOR will be based on the investigator assessment of overall response and is defined as the best result obtained among all tumor assessment visits from baseline until end of treatment or determination of progressive disease. Local evaluations of target, non-target and new lesions are used to assess BOR. The date of the overall response assessment is the earliest date for imaging of target, non-target and new lesions of images taken at that response assessment.

BOR will be defined as the best response across all time points (for example, a subject who has SD at the first assessment, PR at the second assessment, and PD at the last assessment has a BOR of PR). The order to obtain the BOR is the following: CR, PR, SD, PD and NE.

BOR will be summarized by tabulating the number and percentage of subjects with CR, PR, SD, PD or NE as BOR. The table will also include the objective response rate (ORR) and the corresponding 95% Clopper-Pearson confidence intervals (Clopper & Pearson, 1934). The ORR will be defined as the rate of subjects who achieve either a CR or PR.

Disease control rate (DCR) is based on each subject's confirmed BOR according to RECIST 1.1 as assessed by the Investigator. Tumor assessments after the treatment start date, and prior to documented disease progression or start of further anticancer treatment are taken into consideration in deriving the BOR. Clinical deterioration is not considered as documented disease progression. If a tumor assessment was performed on the same day as the start of a new anti-cancer therapy, it is assumed that the tumor assessment was performed prior to the start of the new anti-cancer therapy; therefore, this tumor assessment is included in the assessment of BOR.

Table 4 summarizes the derivation rules described by Eisenhauer, et al. for the BOR when confirmation from subsequent assessment is needed.

Table 4 Best Overall Response When Confirmation of Response is Required

Overall Response 1st Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = nonevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Disease control is defined as BOR of CR, PR, or SD. Both CR and PR must be confirmed by repeat assessment performed at least 4 weeks after the criteria for response are first met. Confirmation of response must not necessarily be at the next scan, but could be at any subsequent scan before PD. When SD is believed to be the best response, the assessment must be at least 6 weeks after the start of a trial drug, and measurements must have met the SD criteria at least once. If the minimum time of 6 weeks is not met, the subject's BOR depends on the subsequent assessments. For example, a subject who has SD at the first assessment, PD at the second assessment and does not meet the minimum duration for SD, will have a BOR of PD. The same subject lost to follow-up after the first SD assessment would be considered NE for BOR.

DCR will be calculated by dose level and overall, along with the overall two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

The listing of tumor assessments (including e.g. lesion number, description and location, type of lesion, imaging date, assessment method, diameter (mm), sum of diameter of target lesions (mm), BOR (confirmed and unconfirmed) will be provided by subject as recorded from the "Target Lesions", "Sum of Diameters", "Non-Target Lesions", "New Lesions" and "Assessment of disease based on imaging" CRF pages.

14.3 Swimlane Plots

A swimlane plot displaying some key radiological milestones will be produced, color-coded by planned dose level. Time in weeks will be displayed along the horizontal axis, and subject ID along the vertical axis. Subjects will be arranged from top to bottom in descending order of follow-up time. For each subject, the time from treatment start until end of follow-up will be represented by a horizontal bar. In addition, there will be different symbols to mark the following events: confirmed CR, confirmed PR, ongoing SD, PD, end of treatment, and death.

15 Safety Analyses

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

Safety analyses will be done on the Safety Analysis Set, unless otherwise specified.

15.1 Dose Limiting Toxicities

The occurrence of dose limiting toxicities (DLTs) during the DLT evaluation period (i.e., during the first treatment cycle of 28 days) is a primary endpoint of this study. The DLT set will be used for the analysis of the primary endpoint. Please refer to Section 6.2.4 of the Clinical Study Protocol MS201408-0005 for the detailed definition of a DLT.

The number and proportion of subjects experiencing DLTs will be reported by dose level. Posterior probabilities (2.5%, 25%, 50%, 75%, and 97.5% quantiles) for a DLT by tested dose level will be estimated using the BLRM specified in the protocol.

Details of the DLTs will be presented in a listing sorted by SOC and PT, including: DLT, SOC, PT, relationship to M4112, seriousness, dose group, time since last and first administration of M4112, and subject's age/sex/site of primary tumor.

In addition, a DLT profile plot of all subjects in the Safety Analysis Set will be produced. This will show a closed square for all subjects who were considered evaluable (in DLT set) and did not have a DLT during Cycle 1, an open square for those who experienced a DLT during Cycle 1, and an open circle for those who were excluded from the DLT Set. This plot will have Cohort Number on the x-axis and dose level (mg) on the y-axis.

15.2 Adverse Events

The severity of AEs will be graded using the NCI-CTCAE v4.03. If a particular AE's severity is not specifically graded by this guidance, the Investigator uses the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment. The latest MedDRA version at the time of data cut-off will be used to code AEs according to System Organ Class (SOC) and Preferred Term (PT).

- **Treatment Emergent Adverse Events** (TEAEs) are events with onset dates occurring during the on-treatment period, or those that worsen in severity during the on-treatment period. All analyses will be based on TEAEs unless otherwise specified.
- **Related Adverse Events** have a relationship to study treatment of "Related" as reported by the Investigator on the Adverse Events CRF page, or unknown (i.e., no answer to the question "Relationship M4112").
- **Serious Adverse Events** (SAEs) are those recorded on the Adverse Events CRF page as Serious Adverse Event = "Yes".
- **Adverse Events Leading to Treatment Discontinuation** are those recorded on the Adverse Events CRF page as Action(s) taken with M4112 = "Drug withdrawn".
- **Adverse Events Leading to Dose Modifications** are those recorded on the Adverse Events CRF page as Action(s) taken with M4112 = "Dose reduced".
- **Adverse Events Leading to Treatment Interruption** are those recorded on the Adverse Events CRF page as Action(s) taken with M4112 = "Drug interrupted".
- **Adverse Events Leading to Death** are those recorded on the Adverse Events CRF page as Outcome = "Fatal" as well as AEs of Grade 5.
- **Adverse Events of Special Interest** (AESIs) for M4112 include liver toxicities and immune-related AEs (irAEs) / autoimmune disorders. Any AESI is indicated as such by the Investigator on the Adverse Events CRF page and is also reported as an SAE.

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study treatment then the onset date will be replaced by the minimum of start of study treatment and AE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the 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, outcome of AE is ongoing at cut-off.
- Further information after cut-off (like fatal outcome) might be taken from safety database and included separately into CSR.

15.2.1 All Adverse Events

Adverse events will be summarized by worst severity per subject, using MedDRA PT as event category and SOC as summary category, in alphabetical order. If an AE is reported for a given subject more than once during treatment, the worst severity and the worst relationship to study treatment will be tabulated.

There will be a listing of all AEs, sorted by SOC and PT.

The following frequency tables will be prepared, by dose level and overall; in addition, the tables will be provided by PT and primary SOC in alphabetical order:

- Any TEAE
- TEAEs related to M4112
- Any serious TEAEs
- Any nonserious TEAEs
- Any serious TEAEs related to M4112
- TEAEs with NCI-CTCAE severity Grade ≥ 3
- TEAEs related to M4112 with NCI-CTCAE severity Grade ≥ 3
- TEAEs leading to treatment discontinuation, dose modification, treatment interruption, and death
- TEAEs related to M4112 leading to treatment discontinuation, dose modification, treatment interruption, and death
- AESIs
- TEAEs by SOC and PT

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Summary tables for nonserious AEs, applying frequency threshold of 5% when excluding SAEs, by SOC and PT, will be provided.

15.3 Deaths, Other Serious Adverse Events, and Adverse Events of Special Interest

15.3.1 Deaths

The following will be tabulated based on information from the "Death" CRF page.

- Number of deaths
- Number of deaths within 30 days after last dose of M4112
- Number of deaths within 60 days after first dose of M4112
- Reason for death

In addition, date and cause of death will be provided in an individual subject data listing together with selected study treatment information (dose level and date of first / last administration). This listing will also include flags for death within 30 days of last study treatment and death within 60 days of first study treatment, as well as MedDRA coding for AEs with fatal outcome (including those with a toxicity grade of 5 and those with an outcome of "fatal").

15.3.2 Serious Adverse Events

A listing will display all SAEs, sorted by SOC and PT, including: AE, SOC, PT, relationship to M4112, planned dose level, time since last and since first administration of M4112, and subject's age, sex, and race (also see Section 15.2.1).

15.3.3 Adverse Events of Special Interest

A listing of all AESIs will be provided, sorted by SOC and PT, including: AE, SOC, PT, relationship to M4112, planned dose level, time since last and since first administration of M4112, and subject's age, sex, and race (also see Section 15.2.1).

15.4 Clinical Laboratory Evaluation

On-study laboratory assessments are any sample collected after the first administration of any study drug, and within 30 days from last study drug administration.

Laboratory results will be classified according to the NCI-CTC Version 4.03 as provided by the central laboratory. Additional laboratory results that are not part of NCI-CTC will be presented according to the categories: below normal limits, within normal limits and above normal limits (according to the laboratory normal ranges).

The worst on-study grade (from any visit, scheduled or unscheduled) will be summarized considering only subjects with postbaseline laboratory samples: Laboratory tests by NCI-CTC grade (0, 1, 2, 3, 4, any).

Quantitative data will be examined for trends using descriptive statistics (mean, StDev, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline to each visit over time. Qualitative data based on reference ranges will be described according to the categories (i.e., Low, Normal, and High). The number of subjects with clinical laboratory values below, within, or above normal ranges at baseline compared to endpoint will be tabulated for each test by dose level. Shift tables of baseline versus endpoint (as well as the worst value at any post-baseline visit) will be presented. Abnormalities classified according to NCI-CTCAE toxicity grading version 4.03 will be described using the worst grade. In case of missing data at the end of the treatment period, the last known postbaseline value will be carried forward.

NCI-CTC grades available:

Shifts from baseline in NCI-CTC grade to the worst postbaseline grade will be summarized separately for hematology and chemistry laboratory parameters. Each summary will be presented by parameter for each dose level and overall.

The categories for worst post-baseline grade are as follows:

- Any higher grade
- Grade 3 or 4
- Grade 4

NCI-CTC grades not available:

For parameters where there is no toxicity grade defined, shifts from baseline will be considered from within normal limits to above the upper limit of normal (ULN) or to below the lower limit of normal (LLN).

All CTC gradable and non-CTC gradable parameters will be listed for each measurement. Parameters will be grouped by category. Abnormal laboratory values will be listed.

Listings will include at least the following items:

- Planned dose level
- Subject identification number
- First/last dosing date
- Parameters
- Visit
- Date (treatment day)
- Analysis value
- SI unit
- Change from baseline
- Reference range status (Low, Normal, High)
- CTC grade (with associated CTC name)
- Baseline flag (Yes/No)
- Worst value on-treatment flag (Yes/No)

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the Investigator as being clinically significant will be shown in a data listing. These are grade $\geq$3 non hematologic toxicities and grade $\geq$ 4 hematologic toxicities.

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

Hepatotoxicity assessment:

A plot of peak ALT versus peak total bilirubin, both relative to the ULN, will be provided. This eDISH (evaluation of drug-induced serious hepatotoxicity) plot will have reference lines at 3xULN for ALT and 2xULN for total bilirubin. Each subject will get a special character/color combination; the color will represent dose level, and the characters within each color will be used to distinguish the subjects from one another, with ID numbers presented in a legend (sorted by dose level and subject ID number).

15.5 Vital Signs

The maximum on-treatment changes from baseline in vital sign measurements will be grouped as indicated in Table 5:

Table 5 Analysis Categories for Vital Sign Parameters

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

For each patient the worst on-treatment value will be calculated. Missing values will define a separate category.

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

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

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

15.6 Electrocardiograms

Triplicate 12-lead electrocardiogram (ECG) results will be presented in a listing, which will include planned dose level, subject identifier, age, sex, race, study visit and day, date/time of assessment, planned ECG time point, ECG parameter (unit), result, and clinical significance. Parameters to be included are as follows:

- Heart rate (beats/min)
- RR duration (msec)
- PQ/PR duration (msec)

- QRS duration (msec)
- QT duration (msec)
- QTc – Fridericia's correction (msec)
- ECG interpretation (normal vs. abnormal) as assessed by Investigator

Quantitative data for the aforementioned parameters will also be summarized using descriptive statistics, based on the average values of the triplicate measurements.

The incidence and percentage of subjects with potentially clinically significant abnormalities (PCSA) for 12-lead ECG parameters will be summarized during the on-treatment period. The PCSA criteria are provided in Table 6 below.

Table 6 Potentially Clinically Significant Abnormalities Criteria for ECG

Test	Potentially Clinically Significant Abnormalities (PCSA) Criteria
Heart Rate (HR)	≤ 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
QTcF absolute	Interval ≥ 450 - < 480 msec Interval ≥ 480 - < 500 msec Interval ≥ 500 msec
QTcF change from baseline	Increase from baseline ≥ 30 - < 60 msec Increase from baseline ≥ 60 msec

QTc will be corrected based on Fridericia's formula (QTcF= QT/ $\sqrt[3]{RR}$) where RR=60/HR. Baseline QTcF will be derived from the visit that other ECG parameters are flagged as baseline. If there are multiple assessments at the same visit and time point, the average will be calculated for each parameter and used for the analysis.

15.6.1 Relationship of QTc Changes to Treatment Exposure

A secondary objective of the protocol was to assess QT prolongation potential by central tendency, outlier analysis and the slope of exposure-QTc analysis. Time-matched ECG readings (3 or more replicates) were to be collected at -45, -30, and -15 minutes predose and at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose, just prior to PK sample collections during Cycle 1 at Day 1 and Day 15 during Part IA (M4112 monotherapy) and uploaded for central ECG reading. ECG readings collected on Cycle 1 Day 8 (predose) and Cycle 2 Day 1 (predose and 2 hours postdose) were also to be uploaded. As the study was terminated early, the following analyses are planned to address the potential relationship of QTc changes to the plasma M4112 exposure, based on the Concentration-QTc Analysis Set:

- The average QTc value at each time point will be plotted for each planned dose level for C1D1, C1D8, C1D15 and C2D1.

- The change from baseline will be calculated as the mean change in QTc at each time point (including C1D1, C1D8, C1D15 and C2D1) **minus** the mean of 3 predose time points (-45, -30 and -15 minutes) on C1D1 and plotted for each time point (if possible, these will be plotted in a joint plot – change in QTc on the left axis and M4112 plasma concentration on the right axis with time on the x-axis).

- The change from baseline for each time-matched sample will be plotted against the corresponding M4112 plasma concentration for all days and all planned dose levels (combined and separately) in a scatter plot.

Because the data is limited, no linear modeling will be applied.

15.7 ECOG Performance Status

The ECOG shift from baseline to highest score during the on-treatment period will be summarized. ECOG performance status with shift from ECOG = 0 or 1 to ECOG = 2 or higher will also be presented in a data listing with subject identifier and other relevant information.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

16.1.1 Plasma Concentrations

M4112 Concentrations

All descriptive summaries of M4112 plasma concentrations will be performed on the PK Analysis Set. Any concentrations excluded from the PK Analysis Set will be listed and flagged.

Pharmacokinetic concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory or clinical laboratory. Actual elapsed sample collection times will be analyzed unrounded (maximum of 14 significant digits), but will be rounded to two decimal places with units of hours for reporting purposes in by-subject listings.

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

Concentration values below the lower limit of quantification of the assay (LLOQ) will be taken as zero for summary statistics of PK concentration data.

In case of concentrations above the upper limit of quantification of the assay (ULOQ), the concentration will be set to missing.

Missing concentrations (e.g., no sample, insufficient sample volume for analysis, no result, or result not valid) will be reported and used generally as no result ("NR").

M4112 plasma concentration data will be descriptively summarized by study day and nominal time using: number of subjects (N); number of nonmissing values (n), arithmetic mean (Mean), standard deviation, coefficient of variation (CV%), minimum (Min), Median, and maximum (Max). If N is less than 3, only n, Min, and Max will be presented.

Descriptive statistics of plasma 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 for concentrations:

Mean, Min, Median, Max:	3 significant digits
Standard Deviation:	4 significant digits
CV%:	1 decimal place

Individual concentration-time profiles showing all subjects separately by dose group and study day (C1D1 and C1D15), and showing study days (C1D1 and C1D15) separately by subject will be created using the actual time points and the numeric concentration data. Arithmetic mean concentration-time profiles by dose group separately for each study day (C1D1 and C1D15), and by study day (C1D1 and C1D15) separately for each dose group will be provided using scheduled (nominal) time points and the numeric concentration data. All concentration-time plots for PK data will be presented both on a linear and on a semi-logarithmic scale. Mean plots will include standard deviation bars when plotted on a linear scale.

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[redacted]

16.1.2 Plasma Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated using standard noncompartmental methods and the actual administered dose. Pharmacokinetic parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits. In cases where the actual sampling time is missing, calculations will be performed using the nominal time. Otherwise, there will be no further imputation of missing data.

The following parameters will be calculated from M4112 plasma concentrations on the study days specified.

Symbol	Definition
AUC_{0-8}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to 8 hours postdose, calculated on C1D1 and C1D15. Calculated using the mixed log linear trapezoidal rule (linear up, log down).
AUC_{0-8} /Dose	The dose-normalized AUC_{0-8}, calculated on C1D1 and C1D15. Normalized using the actual dose, using the formula AUC_{0-8} /Dose.
C_{max}	Maximum observed concentration, calculated on C1D1 and C1D15.
C_{max}/Dose	The dose-normalized C_{max}, calculated on C1D1 and C1D15. Normalized using the actual dose, and the formula C_{max} /Dose.
t_{max}	The time to reach the maximum observed concentration (in case of multiple/identical C_{max} values, the first occurrence will be used), calculated on C1D1 and C1D15.
C_{pre}	Predose (trough) observed concentration, calculated on C1D8, C1D15, and C2D1.
C_{pre}/Dose	The dose-normalized C_{pre}, calculated on C1D8, C1D15, and C2D1. Normalized using the actual dose, and the formula C_{pre} /Dose.
$R_{acc(AUC0-8)}$	The accumulation factor to assess the increase in exposure via AUC_{0-8} following multiple dosing. $R_{acc(AUC0-8)}$ = (AUC_{0-8} after multiple dose [C1D15])/ (AUC_{0-8} after single dose [C1D1]).
$R_{acc(Cmax)}$	The accumulation factor to assess the increase in maximum concentration following multiple dosing. $R_{acc(Cmax)}$ = (C_{max} after multiple dose [C1D15])/ (C_{max} after single dose [C1D1]).

For all dose-normalized parameters, no adjustment of dose (e.g., for molecular weight differences between salt and free form) is required as M4112 is not a salt.

Partial area (AUC_{0-8}) will be calculated using the nominal dosing interval if the PK sample at 8 hours postdose is taken at ≥8 hours. If the 8-hour sample is taken earlier than 8 hours, then the actual time and concentration at the nominal 8-hour time point will be used to calculate this parameter as long as the time deviation at 8 hours is not >10 min (ie, the protocol-allowed window at this time point); otherwise this parameter will be set to missing.

Concentrations below the LLOQ at any point in the profile will be taken as zero for calculating AUC. 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 drug administration.

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

All statistical analyses and descriptive summaries of PK parameters will be performed on the PK Analysis Set. Any PK parameters excluded from the PK Analysis Set will be listed and flagged.

Pharmacokinetic parameters will be analyzed unrounded, but will be rounded to 3 significant digits for reporting, except for parameters directly obtained from the source data (such as C_{max}) which will be reported with the same precision as the source data, and t_{max} which will be reported to 2 decimal places. In export datasets, as well as in the SDTM PP/XD domain, PK parameters will be provided with full precision, and will not be rounded.

Calculated PK parameters will be descriptively summarized by study day using: N, n, Mean, standard deviation, CV%, Min, Median, Max, geometric mean (GeoMean), and geometric coefficient of variation (GeoCV%). GeoMean and GeoCV% will not be presented for t_{max}. If N is less than 3, only n, Min, and Max will be presented.

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, except for t_{max} which will use the same level of decimal precision (instead of significant digits) as specified below:

Mean, Min, Median, Max, GeoMean:	3 significant digits
Standard Deviation:	4 significant digits
CV%, GeoCV%:	1 decimal place

Individual C_{pre} values on C1D8, C1D15, and C2D1 will be plotted against actual time points (in days) on a linear scale, for all subjects by dose group. Arithmetic mean C_{pre} (with standard deviation bars) will also be plotted versus nominal time (in days) by dose group, on a linear scale.

The analysis of dose proportionality of PK parameters of M4112 over the range of administered dose levels will be quantified as part of an exploratory analysis using the power model on the original parameters ($\ln[\text{PK parameter}] = \alpha + \beta \times \ln[\text{dose}]$). This analysis will be based on $AUC_{0\text{-}8}$ (C1D1 and C1D15), C_{max} (C1D1 and C1D15), and C_{pre} (C1D8, C1D15, C2D1) and will be conducted separately by parameter and study day. The intercept α and the slope β together with 90% CIs will be estimated and presented. A p-value testing whether $\beta = 1$ will also be presented. For a given parameter, a minimum of 3 values must be available for a dose level, for that dose level to be included in the dose proportionality analysis.

Dose proportionality will also be assessed graphically by presenting scatter plots of individual and geometric mean values of $AUC_{0\text{-}8}$ (C1D1 and C1D15), C_{max} (C1D1 and C1D15), and C_{pre} (C1D8, C1D15, C2D1) and dose-normalized $AUC_{0\text{-}8}$ (C1D1 and C1D15), C_{max} (C1D1 and C1D15), and C_{pre} (C1D8, C1D15, C2D1) versus Dose on a linear scale. Plots will be prepared separately by PK parameter and study day.

[redacted]

17 References

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Adobe Acrobat Document

18 Appendices

18.1 Protocol Deviations Identified by Programming and Clinically Important Events

Inclusion and exclusion criteria are referenced according to Protocol MS201408-0005 version 2.0 dated 08-Sep-2017.

	Description	Code	Clinically Important?	Protocol Section	Proposed Check / Comment
Inclusion / Exclusion Criteria					
Violated eligibility criteria	Any "no" response to inclusion criteria and/or any "yes" response to exclusion criteria, and subject was subsequently entered into the study	INCEXC01			Violations should be documented on the Study Entry CRF page, which is mapped to the IE domain in SDTM
Informed Consent / Subject Information					
Late ICF signature	ICF was signed after study procedure was done	INFCON03			Check that no dates are prior to ICF date
Investigational Product					
Overdose	Subject received >=110% of the calculated dose for that particular administration	INVPR06			Flag if relative dose intensity >=1.10
Pharmacokinetics-Related					
Vomiting	Vomiting immediately following oral dosing that can affect a PK result	PK001			Manual check by PK scientist
Sample processing errors	Errors that lead to inaccurate bioanalytical results	PK002			Manual check by PK scientist
Inaccurate dosing, dose reductions, dose errors, missed doses	Inaccurate dosing, dose reductions, dose errors, or missed doses that can affect the PK results on one or more PK days	PK003			Manual check by PK scientist

18.2 Integrated Analysis Plan for SMCs

Clinical Trial Protocol Identification No.	MS201408-0005
Title:	Phase I, First-in-Human, Open-Label, Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M4112 an IDO1/TDO2 Inhibitor as Single Agent CCI CCI CCI in Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors
Trial Phase	I
Investigational Medicinal Product(s)	M4112 as single agent CCI CCI CCI)
Clinical Trial Protocol Version	08 September 2017 / Version 2.0
Statistical Analysis Plan Author	PPD and PPD
Statistical Analysis Plan Date and Version	30 Jan 2018 / Version 1.0
Statistical Analysis Plan Reviewers	PPD, Medical Responsible, Merck KGaA PPD, EMD Serono, Inc. PPD, Merck KGaA PPD Merck KGaA PPD Merck KGaA PPD EMD Serono, Inc. PPD EMD Serono, Inc.

1 Signature Page

Integrated Analysis Plan for SMCs: MS201408-0005

Phase I, First-in-Human, Open-Label, Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M4112 an IDO1/TDO2 Inhibitor as Single Agent CCI CCI CCI in Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors

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

Merck responsible Signature	Date
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2 Table of Contents

3 List of Abbreviations and Definition of Terms

ADA	Anti-drug antibody
AE(s)	Adverse event(s)
AESI(s)	Adverse event(s) of special interest
AUC	Area under the drug concentration-time curve
AUC_{0-8}	Area under the drug concentration-time curve from 0 to 8 h postdosing
BID	Twice daily
BOR	Best overall response
C_{max}	Maximum plasma concentration observed postdose
C_{min}	Minimum observed postdose (trough) plasma concentration
CTCAE 4.03	Common Terminology Criteria for Adverse Events Version 4.03
cQTc	Concentration-QTc
DCR	Disease control rate
DLT	Dose-limiting toxicities
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
eDISH	Evaluation of drug-induced serious hepatotoxicity
iAP	Integrated analysis plan
IC_{50}	Half maximal effective concentration
IDO	Indoleamine-2, 3-dioxygenase
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
OBD	Optimal biological dose
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PT	Preferred Term
QD	Once daily

QTc	Corrected QT interval
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SMC	Safety Monitoring Committee
SOC	System Organ Class
TDO	Tryptophan-2, 3-dioxygenase
TEAE	Treatment emergent adverse event
CCI	[redacted]
TLFs	Tables, Listings, and Figures
t_{max}	Time to reach maximum concentration
TRAE	Treatment related adverse event
CCI	[redacted]
ULN	Upper limit of normal

4 Modification History

Unique Identifier for iAP Version	Date of iAP Version	Author	Changes from the Previous Version
1.0	30 January 2018	PPD	N/A – first version

5 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 protocol MS201408-0005. Results of the analyses described in this iAP will be used (amongst other data) by the SMC to decide upon dose and size of future cohorts. This iAP will specify the Bayesian two-parameter logistic regression model used to make a recommendation to the SMC for dose escalation. Additionally, this iAP will describe preliminary PK analyses for M4112, as well as Tables, Listings, and Figures (TLFs) summarizing safety data. The latter will only be applicable if an SMC meeting is adjourned and at data of at least 6 treated subjects in the respective treatment arm. The TLFs (except for the overall listing of AEs, the PK analyses and CCI analyses) will be produced on the SDTM data available at cut-off (usually from previous cut-off) except a listing of all AE and a listing of all AE>=grade 3, that will be produced in JReview along with the patient profiles. CCI

The iAP is based upon Section 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

6 Summary of Clinical Trial Features

Objectives:

Primary Objectives

Part IA (Dose Escalation – M4112 as Single Agent)

- To determine safety and tolerability or, if observed, the maximum tolerated dose (MTD), and to define the recommended Phase II dose (RP2D) of M4112 as single agent in subjects with solid tumors.

CCI

CCI

- CCI [redacted]

Secondary Objectives

Part IA (Dose Escalation – M4112 as Single Agent)

- To characterize the PK parameters of M4112 as single agent
- To assess QT prolongation potential by central tendency, outlier analysis and the slope of exposure-QTc analysis
- To evaluate preliminary clinical activity parameters using RECIST 1.1.

CCI [redacted]

CCI [redacted]

- CCI [redacted]

Methodology:

This study is a Phase I, open-label study designed to determine the safety, tolerability, PK, PD, and preliminary antitumor activity of M4112 as single agent (Part IA only) CCI [redacted] The target population for Part I (Dose Escalation) comprises of subjects with advanced or metastatic solid malignancies for whom no effective standard therapy exists or has failed or subjects who are intolerant to established therapy known to provide clinical benefit for their condition.

Part IA CCI [redacted] Dose Escalation

A broad dose range in monotherapy will be investigated to determine the safety profile, tolerability, PK, and PD markers and to explore signs of antitumor activity in subjects with advanced solid tumors.

Subjects will receive M4112 at the starting dose of 100 mg BID (100 mg BID which equals to 200 mg total daily dose) at least 1 h prior to a meal and at least 2 h after a meal. Cohorts will consist of 3 subjects each, if not decided differently by the SMC. The first subject of each dose level will be observed for at least 5 days before the second subject can be treated. Subsequent subjects may receive first dosing at no less than 48 h intervals between subjects for the first 2 cohorts of mono and combination therapy. If the safety profile is acceptable and agreed by the SMC, the 48 h observation after Subject 2 may be removed). The safety and tolerability data and available PK and PD data (as minimum Day 1 and Day 15 PK and PD data from

previous cohort and all available PK and PD data from the current cohort) will be reviewed by the SMC at the end of each cohort. In cases where enrollment of 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 Cycle 1. The SMC will be assisted in their dosing and regimen (administration schedule) decisions by PK, PD, and a Bayesian 2-parameter logistic regression model modeling dose-limiting toxicity (DLT) rate with overdose control. The model incorporates nonclinical toxicity data in the prior and DLTs observed until the SMC to provide a recommended dose for the next cohort. During the dose escalation part of the study, the SMC will advise, primarily based on safety (DLTs) and additional data relevant for the treatment, on dose escalation, dose de-escalation, dose level expansion or regimen change, or it may recommend suspension of enrollment, with the final decision being a Sponsor decision. The SMC may also recommend a cohort size different from 3 subjects as the Bayesian design allows dose recommendation based on less or more than 3 subjects.

Prespecified ascending doses of 100, 200, 400, 600, 800, and 900 mg BID (means respectively, 100 mg BID for 200 mg total daily dose, 200 mg BID for 400 mg total daily dose, 400 mg BID for 800 mg total daily dose, 600 mg BID for 1,200 mg total daily dose, 800 mg BID for 1,600 mg total daily dose, 900 mg BID for 1,800 mg total daily dose) as single agent in 28-day cycles are foreseen. Dose escalation decisions will be driven primarily by DLT, safety, and tolerability. CCI

CCI

A BID dosing regimen will be followed, based on PK modelling, to achieve the target C_{min} over the dosing interval at a lower total daily dose and thereby reducing C_{max} and AUC over the day to potentially improve safety and tolerability when compared to once daily (QD) dosing. Based on PK data from subjects, the SMC will evaluate whether this regimen can be sustained or needs to be changed.

In principle, dose escalation of single agent M4112 (Part IA) will proceed according to the recommendation of the SMC to at least the upper end of the above given dose range, unless the MTD has been reached or there is excess of PK nonlinearity, or the SMC recommends to end dose escalation following review of safety, tolerability, PK and PD results. Depending on the observed toxicity profile and available PK and PD, a dose regimen different to or dose(s) higher/lower than the prespecified doses may be tested.

The following criteria will be applied to define the RP2D of M4112 as single agent:

- CCI
- CCI

This dose level will then be studied in ≤ 6 evaluable subjects to establish safety, tolerability, PK, and PD and will be defined as the RP2D of M4112 as single agent.

CCI

- CCI

The starting dose of M4112 CCI will be dependent on the observed safety, tolerability, and PK/PD profile during dose escalation in the single agent cohort (Part IA) and will lag at least 1 dose level behind the last completed safe dose level of M4112 as single agent, which was confirmed as safe by the SMC. CCI

Separate Bayesian logistic regression models will be used for guidance of dose escalation for each of the combinations.

Dose escalation will proceed until the OBD of M4112 CCI is reached or dose escalation ends due to occurrence of DLTs establishing MTD or the SMC recommends to end dose escalation following review of safety, tolerability, PK and PD results whatever occurs first. CCI

CCI

CCI

- CCI [redacted]
- CCI [redacted]

Once safety and PD effects are confirmed in ≤ 6 additional subjects, these dose levels will be used as the RP2D of the respective combination therapies.

DLT Definition

DLTs will be used to determine dose escalation, dose de-escalation, and the MTD (if reached), using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03). DLTs are defined in the clinical study protocol.

CCI [redacted]

Subjects with nausea and vomiting will maintain normal schedule without re-dosing.

The MTD is defined by the SMC. An MTD is suggested from the Bayesian logistic regression model with target toxicity of 30%.

Subjects who tolerate M4112 and their combination partner without significant clinically relevant toxicities will continue to receive their assigned dose until discontinuation criteria are met, withdrawal of consent or the study ends, whatever occurs first.

Follow-up Period:

The Safety Follow-up Visit is scheduled 30 ± 3 days CCI [redacted] after the last dose of M4112 CCI [redacted] or until resolution of AEs to Grade 1, before start of any new anticancer therapy, whatever comes first.

Subjects who discontinue treatment must be followed on study until resolution of toxicity or until confirmed disease progression.

Planned number of subjects:

Part I (A CCI Dose Escalation): Monotherapy escalation A: Approximately 24 subjects, CCI [redacted]

Primary endpoints:

Part IA (Dose Escalation – M4112 as Single Agent)

- Occurrence of DLTs in subjects receiving M4112 as single agent during the first 4 weeks (Day 1 to Day 28 of Cycle 1) of treatment
- Occurrence of treatment-emergent adverse events (TEAEs) and TRAEs according to NCI-CTCAE 4.03 (including deaths) in subjects receiving M4112 as single agent from start of treatment up to the last Safety Follow-up Visit
- Treatment-emergent changes from baseline in clinical laboratory measures, vital signs, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and physical examination findings in subjects receiving M4112 as single agent up to the last Safety Follow-up Visit.

CCI

CCI

- CCI

Secondary endpoints:

Part IA (Dose Escalation – M4112 as Single Agent)

- Plasma PK parameters for M4112: AUC_{0-8}, C_{max}, t_{max}, $AUC_{0-8/dose}$, $C_{max/dose}$, (Days 1 and 15), $R_{acc(AUC0-8)}$ and $R_{acc(Cmax)}$ (Day 15), C_{min}, and $C_{min/dose}$ (Days 8 and 15 of Cycle 1 and Day 1 of Cycle 2)
- Slope of concentration-QTc (cQTc) regression based on time-matched electrocardiogram (ECG) readings (3 or more replicates) and PK samples during Cycle 1 at Day 1 and Day 15, central tendency and outlier analyses for absolute QTcF, and delta QTc
- BOR, DOR, DCR, time to tumor response, and PFS using RECIST 1.1, up to confirmed tumor progression.

CCI

CCI

- CCI

Concentration-QTc and safety ECG:

Time-matched ECG readings (3 or more replicates) will be collected at -45, -30, and -15 min predose and at 0.5, 1, 2, 3, 4, 6, and 8 h postdose, just prior to PK sample collections during Cycle 1 at Day 1 and Day 15 during Part IA (M4112 monotherapy).

CCI

- **Pharmacokinetics:**

- Pharmacokinetic parameters for M4112 will be based on plasma concentrations collected predose and at 0.5, 1, 2, 3, 4, 6 and 8 h postdosing on Days 1 and 15 of Cycle 1. Predose concentrations on Day 8, Cycle 1 and predose and 2 h postdose on Day 1, Cycle 2 will be assessed.

[redacted]

- [redacted]

Safety assessments:

The safety profile of M4112 will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), adverse events of special interest (AESIs), DLTs in Cycle 1 and any treatment-emergent immune-related AE observed in subsequent cycle (Cycle 2) that in the opinion of the SMC needs to be taken into account for safety and proposal of dose escalation, physical examination findings including vital signs, laboratory tests (chemistry, hematology, and coagulation), ECOG PS, and a 12-lead ECG in triplicate from the date of signature of first informed consent until the either until the 30 ± 3 days Safety Follow-up Visit, [redacted] or before the start of any anticancer therapy, whatever comes first.

7 Sample Size/Randomization

As inherent in dose escalation studies, the sample size cannot be prespecified. The planned size of each dosing cohort is 3 subjects; however, based on the results of a Bayesian two-parameter logistic model, the SMC may elect to change the size of future cohorts.

8 Overview of Planned Analyses

The following analyses requiring an SAP/iAP are planned for this trial:

- SMC analyses (this iAP)
- End of monotherapy dose escalation analysis (separate iAP)
- Primary analysis of escalation part of the trial (separate iAP)

Patient Profiles based on the raw data will also be produced for SMCs, and no separate iAP is needed for this deliverable.

Cut-off date:

SMCs are usually planned after the last subject of each cohort has finished the DLT assessment period of 28 days or dropped out of the study. 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 set an earlier data cut-off, except the first SMC which needs all three subjects have finished the DLT period. For each SMC, a two-parameter logistic Bayesian model will be updated with the observed safety data based observed DLTs to help the SMC in its dosing decision.

When monotherapy and combination therapy cohorts are open at the same time, efforts will be made to have a joint SMC with a data cut-off at the end of the DLT period for the last subject to be included in the joint SMC.

8.1 Sequence of Analysis

Summary TLFs based upon cumulative data within each treatment arm will be created upon availability of data of ≥ 6 treated subjects in the respective treatment arm. Analyses and decisions will be made separately for each treatment arm.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

There are no changes to the planned analyses.

10 Analysis Sets

Analysis sets relevant to SMCs are defined in Table 1.

Table 1 Analysis Sets

Population	Description
Screening	All participants who sign informed consent.
Dose Escalation	All subjects treated in dose escalation cohorts who do not miss > 5 planned total daily doses of M4112 CCI in the first cycle (first 28 days) of the dose escalation part for other than DLT. The latter only applies to subjects in the combination dose escalation.
Safety	The Safety Analysis Set will include all subjects who receive at least 1 dose of study treatment. In case of combination treatment, study treatment includes also the combination agents.
M4112 Pharmacokinetic	All subjects from the Safety Analysis Set without major protocol deviations/violations or events that would affect PK. Subjects in the PK Analysis Set must have received at least 1 dose of M4112 and must have sufficient M4112 plasma concentration data to enable the calculation of at least 1 PK parameter. Sufficient concentration data is defined as at least 3 valid, postdose concentration points in the PK profile to obtain any PK parameter.
Pharmacodynamics	All subjects who received at least 1 dose of M4112 and provide the predose and at least 1 postdose sample for PD assessment.

ADA = anti-drug antibody; cQTc = concentration-corrected QT interval (QTc); DLT = dose-limiting toxicities; ECG = electrocardiogram; PD = pharmacodynamics; PK = pharmacokinetic.

11 General Specifications for Statistical Analyses

All analyses will be separate for each treatment arm (M4112 monotherapy, CCI CCI CCI CCI and so will decisions by the SMC.

Significance level:

There will be no statistical tests performed in these 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 subjects (N), number of subjects 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.

Definition of baseline:

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

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 randomization + 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 (Section 13, 15, 16 and 17), missing data will not be replaced.

In all listings, 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.

Treatment day is defined relative to the date of first study drug administration. Treatment Day 1 is treatment start date of first administration of any of the following study drugs (M4112, CCI , CCI ; the day before is defined as Treatment Day -1 (no Treatment Day 0 is defined).

All analyses (except calculations of posterior distributions, recommended next dose and associated outputs) will be performed using SAS® Software version 9.2 or higher. For the outputs of the Bayesian two-parameter logistic model updates, East® 6.0 or R (version 3.1.2 or higher [Core Team, 2014]) and the R package bcrm [Sweeting, 2013] or crmpack will be used.

12 Trial Subjects

Only displayed in Patient Profiles.

13 Demographics and Other Baseline Characteristics

Only displayed in Patient Profiles.

14 Previous or Concomitant Medications/Procedures

Only displayed in Patient Profiles.

15 Treatment Compliance and Exposure

Only displayed in Patient Profiles.

16 Endpoint Evaluation

16.1 Primary Endpoint Analyses

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. The primary analysis of DLTs is performed using a Bayesian two-parameter logistic modeling approach 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.

The SMC will receive patient profiles containing:

- Subject disposition (still in trial, or withdrawn with reason for withdrawal)
- Demographics and baseline characteristics (e.g., cancer diagnosis, staging)
- 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, dose completion, and dose adjustment
- All serious and non-serious AEs, including but not limited to:
  - DLTs
  - 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, including change from baseline in QTc interval
- Vital signs

Patient profiles will be provided for the current cohorts under review and updated patient profiles will be provided for the previous cohorts (i.e. the cohorts of the last previous SMC in same study part).

In addition, a DLT profile plot of all subjects in the SAF Analysis Set will be produced. This will show an open square for all subjects who did not have a DLT during Cycle 1, a closed square for those who experienced a DLT during Cycle 1, and an open circle for those who were excluded from the DE Analysis Set. This plot will have Cohort Number on the x-axis and dose level (mg) on the y-axis.

Bayesian two-parameter logistic model

Upon completion of the DLT observation period of each cohort, summary statistics of the posterior probability distribution of the true DLT rate (2.5%, 25%, 50%, 75%, and 97.5% quantiles) for each predefined dose level will be updated and estimated according to the logistic model. Using data from all subjects completing the DLT period or experiencing a DLT during this period at the completion of a new cohort (and data from all previous cohorts: DE analysis set), the Bayesian logistic model provides a recommended dose level for the next cohort.

Recommendation is based on a loss function (probabilities of being in 1 of the 4 intervals will be multiplied with a loss term as follows:

0 * P(target dosing (estimated DLT rate in (0.17-0.35])) + 1 * P(for over dosing (estimated DLT rate in (0.35-0.67]) or under dosing (estimated DLT rate in [0-0.17])) + 2 * P(excessive dosing (estimated DLT rate in (0.67-1])).

In addition, only doses with estimated probability of $\leq$ 25% that the true DLT rate is more than 35% (overdose control) will be recommended by the model. The recommended dose level resulting from the model for the next cohort is the dose with the lowest loss function from all doses fulfilling the overdose control rule. This Bayesian escalation approach will be used to assist the SMC to select the next dose from a predicted set of acceptable doses, i.e., 100 mg, 200 mg, 400 mg, 600 mg, 800 mg and 900 mg BID. It is possible to choose a dose(s) not within the pre-specified dose-escalation plan. Using a Bayesian model-based design aids the SMC in dosing decisions by providing more information compared to a 3+3 design (e.g., an estimated dose-toxicity curve with confidence information utilizing data on all subjects in DE analysis set at time of analysis).

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 Bayes theorem.

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

The prior distribution is set-up as follows:

The relationship between dose and toxicity rate is defined by

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

Where $d_j \in \{100\text{ mg}, 200\text{ mg}, 400\text{ mg}, 600\text{ mg}, 800\text{ mg}, 900\text{ mg}\}$ (or different) and (α,β) are bivariate normally distributed.

Assuming a target toxicity rate of 31 % at a reference dose of 900 mg and a toxicity of 11% at a dose of 400 mg the following could be derived:

$E(\alpha)=\log(0.31/0.69) = -0.8001$

$E(\beta)= \log((\log(0.11/0.89)-\log(0.31/0.69))/\log(400/900))=0.4647$

Variances are chosen as follows: $Var(\alpha)=1.5^2$, $Var(\beta)=1.5^2$, $Cov(\alpha, \beta)=0$

The prior distribution has not been changed compared to the protocol defined.

Exemplary code for the update of the prior in R using package bcrm:

```
library(bcrm)

## Pre-defined doses
dose<-c(100,200,400,600,800,900)

## Target toxicity level
target.tox<-0.30

## Toxicity cut-points
tox.cutpoints<-c(0.17,0.35,0.67)

## Losses associated with toxicity intervals [0,0.17]=1, (0.17,0.35]=0, (0.35,0.67]=1, (0.67,1]=2
loss<-c(1,0,1,2)

## definition of prior ####;
sdose<-log(dose/900)
mu<-c(log(0.31/0.69),log((log(0.11/0.89)-log(0.31/0.69))/log(400/900)))

Sigma<-rbind(c(1.5^2,0),c(0,1.5^2))
```

```
###following lines: example input of observed data, line needs adjustment according to subject number,
doses and DLTs observed, I put example scenarios ####;
data1<-data.frame(patient=1:3,dose=c(rep(1,3)),tox=c(rep(0,3)))
data2<-data.frame(patient=1:6,dose=c(rep(1,3),rep(2,3)),tox=c(rep(0,6)))
data3<-data.frame(patient=1:6,dose=c(rep(1,3),rep(2,3)),tox=c(rep(0,5),1))
data4<-data.frame(patient=1:9,dose=c(rep(1,3),rep(2,3),rep(3,3)), tox=c(rep(0,9)))

#### example modeling step, nmax needs adjustment ####;
TwoPLogistic.tox.intervals.bcrm<-
bcrm(stop=list(nmax=3),data=data1,sdose=sdose,dose=dose,ff="logit2",prior.alpha=list(4,mu,Sigma),targ
et.tox=target.tox,constrain=FALSE,tox.cutpoints=tox.cutpoints,loss=loss,method="rjags",burnin.itr=10000
00,production.itr=1000000)
print(TwoPLogistic.tox.intervals.bcrm)
plot(TwoPLogistic.tox.intervals.bcrm)

TwoPLogistic.tox.intervals.bcrm<-
bcrm(stop=list(nmax=6),data=data2,sdose=sdose,dose=dose,ff="logit2",prior.alpha=list(4,mu,Sigma),targ
et.tox=target.tox,constrain=FALSE,tox.cutpoints=tox.cutpoints,loss=loss,method="rjags",burnin.itr=10000
00,production.itr=1000000)
print(TwoPLogistic.tox.intervals.bcrm)
plot(TwoPLogistic.tox.intervals.bcrm)

TwoPLogistic.tox.intervals.bcrm<-
bcrm(stop=list(nmax=6),data=data3,sdose=sdose,dose=dose,ff="logit2",prior.alpha=list(4,mu,Sigma),targ
et.tox=target.tox,constrain=FALSE,tox.cutpoints=tox.cutpoints,loss=loss,method="rjags",burnin.itr=10000
00,production.itr=1000000)
print(TwoPLogistic.tox.intervals.bcrm)
plot(TwoPLogistic.tox.intervals.bcrm)

TwoPLogistic.tox.intervals.bcrm<-
bcrm(stop=list(nmax=9),data=data4,sdose=sdose,dose=dose,ff="logit2",prior.alpha=list(4,mu,Sigma),targ
et.tox=target.tox,constrain=FALSE,tox.cutpoints=tox.cutpoints,loss=loss,method="rjags",burnin.itr=10000
00,production.itr=1000000)
print(TwoPLogistic.tox.intervals.bcrm)
plot(TwoPLogistic.tox.intervals.bcrm)

sessionInfo()
```

Analyses done with R package bcrm (reference to Sweeting, 2013 to be included) or package crmpack will be repeated with East for validation of results.

16.2 Secondary Endpoint Analyses

16.2.1 M4112 Concentration and Pharmacokinetic Analyses

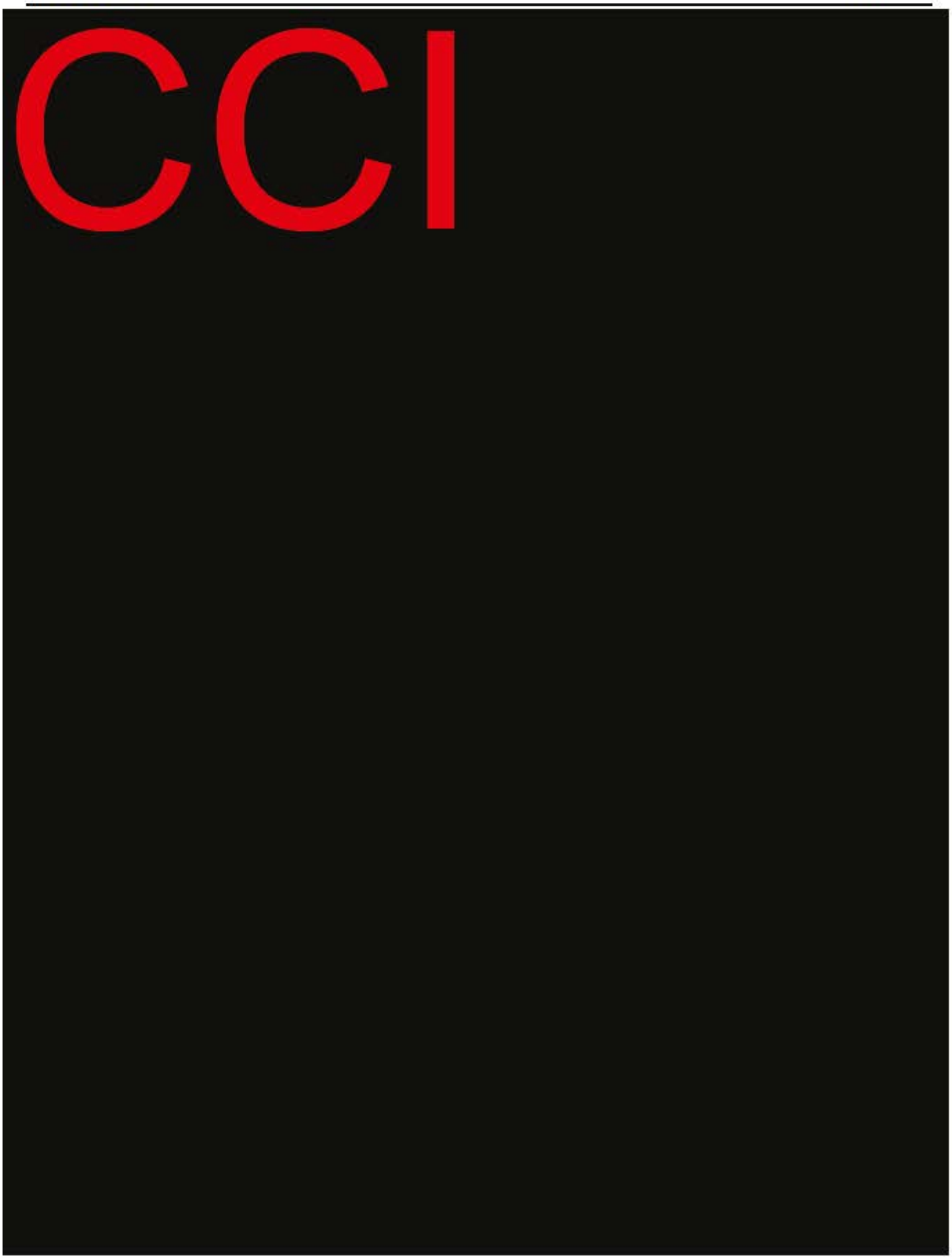
Available individual M4112 plasma concentrations will be summarized by dose, study day and collection time and presented as summary tables, including summary statistics where data allows. Individual as well as mean concentration-time profiles will be plotted on linear and log scales.

For M4112, PK parameters, as described in the protocol, will be calculated using commercial software (Phoenix® WinNonlin®) following global Merck standard procedures. Nominal collection times may be used for PK determinations in support of the SMC review. Key PK

parameters (Cmax, AUC0-8, Cmin [predose on Day 8, Day 15 and/or Day 1, Cycle 2 as available], and corresponding dose-normalized parameters) will be plotted by dose and study day (individual and mean)

16.3 Other Endpoint Analyses

CCI


CCI

CCI

17 Safety Evaluation

The primary endpoints of this trial are safety-related, and analyses are described in section 16.1.

Safety analyses will be performed on the SAF Analysis Set (unless otherwise specified). All safety parameters will be summarized, by dose level and overall within each treatment arm, unless otherwise stated.

17.1 Adverse Events

The severity of adverse events will be graded using the NCI-CTCAE version 4.03, 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.

- **Related Adverse Events**: AEs with relationship to study treatment of 'Related' reported by the investigator, as well as those of unknown relationship (i.e., no answer to the question, 'Relationship with study treatment'). Relationship is judged separately for M4112, CCI

- **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'). Treatment discontinuation is recorded separately for M4112, CCI CCI .

- **AEs Leading to Death**: AEs leading to death (as recorded on the AE eCRF page, Outcome = 'Fatal').

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.

Incomplete AE-related dates will be handled as follows:

- If the onset date is missing completely or missing partially – but the onset month and year, or year, are equal to that of the study treatment start – then the onset date will be replaced by the minimum of the start of study treatment and the AE resolution date.
- In all other cases, the missing onset day or month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if only day is missing), if not resulting in a date later than the date of subject's death or data cut-off. In the latter case, the date of death or data cut-off will be used to complete the stop date.
- In all other cases the incomplete stop date will not be imputed. If the stop date of an AE is after the date of cut-off, the outcome of the AE is ongoing at cut-off.
- Further information after cut-off (such as fatal outcome) might be taken from the Safety database and reported separately.

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

17.1.1 All Adverse Events

All AEs will be tabulated in an overall summary table for each treatment arm, to include:

- Any TEAE
- TEAEs leading to death
- Serious TEAEs
- TEAEs, grade ≥ 3
- TEAEs leading to permanent treatment discontinuation of M4112
- TEAEs leading to dose reduction of M4112
- AESIs
- Related to M4112 TEAEs
- Related to M4112 TEAEs, grade ≥ 3
- Related to M4112 serious TEAEs
- Related to M4112 TEAEs leading to death
- Related to M4112 TEAEs leading to permanent treatment discontinuation of M4112

- Related to M4112 TEAEs leading to dose reduction of M4112

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

A listing of all TEAEs will be provided, split into those occurring within the first and after the first cycle. This listing will be sorted by dose level and subject. This listing will additionally contain SOC, PT, grade, SAE (yes/no), DLT (yes/no), relatedness to M4112 (yes/no), CCI (yes/no), to CCI (yes/no), start date (+treatment day), stop date (+treatment day), and outcome. This listing is to be produced on the current cut-off in JReview.

Additionally, a listing of all adverse events grade >=3 will be provided, sorted by SOC and PT within each dose level and subject. These will also include seriousness, dose level, time since last and since first administration of study drug, age, sex, and race of the subject) and relatedness to M4112 (yes/no), CCI (yes/no), to CCI (yes/no). This listing is to be produced on the current cut-off in JReview.

17.1.2 Adverse Events Leading to Treatment Discontinuation

A listing of TEAEs leading to treatment discontinuation, interruption, or dose reduction of each study drug will be provided. This listing, sorted by SOC and PT, will include: AE, SOC, PT, relationship to M4112, CCI, and CCI (as applicable), seriousness, treatment discontinuation for M4112, CCI, and CCI (as applicable), dosing cohort, time since last and since first administration of M4112, and subject's age, sex, and race.

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

17.2.1 Serious Adverse Events

A listing of all SAEs will be provided, sorted by SOC and PT, including: AE, SOC, PT, relationship to M4112, CCI and CCI (as applicable), dosing cohort, time since last and since first administration of M4112, and subject's age, sex, and race.

17.2.2 Adverse Events of Special Interest

A listing of all AESIs will be provided, sorted by SOC and PT, including: AE, SOC, PT, relationship to M4112, CCI and CCI (as applicable), dosing cohort, time since last and since first administration of M4112, and subject's age, sex, and race.

17.3 Clinical Laboratory Evaluation

The severity of laboratory results for hematology and chemistry parameters will be graded according to the NCI-CTCAE version 4.03.

All clinical laboratory analyses will be performed on the SAF Analysis Set.

Hepatotoxicity assessment

A plot of peak ALT versus peak total bilirubin, both relative to the ULN, will be provided. This eDISH (evaluation of drug-induced serious hepatotoxicity) plot will have reference lines at 3xULN for ALT and 2xULN for total bilirubin. Each subject will get a special character/color combination; the color will represent dose level, and the characters within each color will be used to distinguish the subjects from one another, with ID numbers presented in a legend (sorted by dose level and subject ID number).

17.4 Vital Signs

Vital signs will only be presented in the Patient Profiles.

17.5 Other Safety or Tolerability Evaluations

ECG results will only be presented in the Patient Profiles.

18 Benefit Risk Assessment

Not applicable.

19 References

R Core Team R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2014, URL http://www.R-project.org/.

Sweeting M, Mander A, Sabin T. bcrm: Bayesian Continual Reassessment Method Designs for Phase I Dose-Finding Trials. J Statist Software 2013;54(13):1-26. URL http://www.jstatsoft.org/article/view/v054i13

ELECTRONIC SIGNATURES

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Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Technical Approval	02/11/2019 17:26:12
PPD	Task Completed (Approval eSign): Approved	Technical Approval	02/11/2019 20:09:34
PPD	Task Completed (Approval eSign): Approved	Business Approval	02/11/2019 21:11:25
PPD	Task Completed (Approval eSign): Approved	Technical Approval	02/12/2019 12:55:29