Integrated Analysis Plan

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Title	Open-label, Phase I, Dose Escalation Trial of Methionine Aminopeptidase 2 Inhibitor M8891 in Subjects with Advanced Solid Tumors
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Signature Page

Integrated Analysis Plan for end of monotherapy dose escalation: MS 100015-0019
An Open-label, Phase I, Dose Escalation Trial of Methionine Aminopeptidase 2 Inhibitor M8891 in Subjects with Advanced 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.

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2 List of Abbreviations and Definition of Terms

CCI [redacted]	
AE	Adverse Event
Ae_{τ}	Cumulative amount excreted during a complete dose interval at steady state
Ae_{0-t}	Cumulative percentage of dose excreted from time zero (= dosing time) to the end of the current collection interval after dosing
$Ae_{0-\infty}$	Cumulative amount excreted from time zero (dosing time) to infinity
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	Area under the concentration-time curve from time zero to last sampling time
$AUC_{0-\tau}$	Area under the concentration-time curve from zero to τ
$AUC_{0-\infty}$	Area under the concentration-time curve from zero extrapolated to infinity
$AUC_{extra\%}$	AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$
BID	Twice Daily
BLM	Bayesian Logistic Model
CCI [redacted]	
BMI	Body Mass Index
BOR	Best Overall Reponse
CI	Confidence Interval
cIPD	Clinically Important Protocol Deviation
C_{max}	Maximum observed concentration
$CL_{/f}$	Apparent total body clearance of drug following extravascular administration
$CL_{ss/f}$	Apparent body clearance of drug following extravascular administration at steady state
CR	Complete Response
CRF	Case Report Form
cs	Clinically significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for AEs
CTP	Clinical Trial Protocol
CV%	Coefficient of Variation
DLT	Dose Limiting Toxicity
DRM	Data Review Meeting
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status

EOT	End of Treatment
FU	Follow-up
GCP	Good Clinical Practice
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
IAP	Integrated Analysis Plan
ICARS	International Cooperative Ataxia Rating Scale
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IPD	Important Protocol Deviation
λ_z	Terminal first order (elimination) constant
LCI	Lower limit of confidence interval
LLOQ	Lower limit of quantification
Max	Maximum
Mean	Arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
CCI	[redacted]
CCI	[redacted]
Min	Minimum
MMSE	Mini-Mental State Examination
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
nc	Non-clinically relevant
ORR	Objective Response Rate
PCSA	Potentially Clinically Significant Abnormalities
PD	Progressive Disease
CCI	[redacted]
PFS	Progression-free Survival
PK	Pharmacokinetics
PopPK	Population Pharmacokinetics
PR	Partial Response
PT	Preferred Term
QCD	Quantitative Clinical Development
QD	Once daily
QTcF	QT interval corrected for heart rate according to Fridericia
$R_{acc(AUC\tau)}$	Accumulation factor to assess increase in exposure until steady state is reached

$R_{acc(Cmax)}$	Accumulation factor to asses increase in maximum concentration until steady state is reached
RECIST	Response Evaluation Criteria In Solid Tumours
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
Sd	Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
$t_{1/2}$	Apparent terminal half-life
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures
UCI	Upper limit of confidence interval
ULOQ	Upper limit of quantification
t_{max}	Time to reach maximum observed concentration
$V_{Z/f}$	Apparent volume of distribution during the terminal phase
WBC	White blood cells
WHO-DD	Word Health Organization – Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	20 Apr 2018	PPD PPD PPD PPD PPD	Initial version

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP, referred to as Statistical Analysis Plan in protocol version 2.0 of this study) is to document technical and detailed specifications for the final analysis of data collected for protocol MS1000015-0019. Results of the analyses described in this IAP will partly be included in a Clinical Study Report (CSR) or a separate report (e.g. PopPK analysis). 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 a CSR but not identified in this prospective IAP will be clearly identified as such in the CSR.

This IAP does not describe the analyses done for the Safety Monitoring Committee (SMC) meetings. Instead, details can be found in SMC IAP, version 1.0 dated Oct 2017.

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

5 Objectives and Endpoints

	Objective	Endpoint	IAP Section
Primary Objective	• To determine the maximum tolerated dose (MTD) of M8891 as a single agent in subjects with solid tumors.	• Dose limiting toxicities (DLTs) during the first 21-day treatment cycle, based on a pre-defined set of adverse events (AEs), to determine the MTD.	• 15.1
Secondary Objectives	• To evaluate the safety profile and tolerability of M8891 as a single agent • To investigate the pharmacokinetic (PK) profile of M8891 as single agent	• Incidence and severity of treatment-emergent adverse events (TEAEs), and deaths, including cause of death, from screening up to the End of Treatment visit (EOT). • Changes in clinical laboratory measures, electrocardiogram (ECG) measures, vital signs, Eastern Cooperative Oncology Group Performance status (ECOG PS). • PK parameters of M8891 after QD and BID dosing, as applicable: Cmax, tmax, AUC0-t, AUC0-∞, AUC0-τ, t1/2, λ_z, CL/F, CLss/F, V_z/F, Racc(AUC$_\tau$) and Racc(Cma$_x$)	• 14 • 15 • 16.1

	Objective	Endpoint	IAP Section
	• To assess the antitumor activity of M8891 as single agent according to RECIST v1.1 • To determine the recommend Phase II dose (RP2D) as single agent.	• Best overall response (BOR: complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD]) according to RECIST v 1.1. criteria as assessed by investigators • Clinical benefit defined as CR, PR, and SD for ≥ 12 weeks • PFS (progression-free survival) defined as the time from first study drug administration to either first observation of PD (as assessed by RECIST v 1.1) or occurrence of death due to any cause, whichever occurs first	

CCI [redacted]

CCI [redacted]

The analyses of the endpoints will be described in the respective sections for efficacy, safety or other endpoints, regardless if the endpoint is a primary endpoint or not.

6 Overview of Planned Analyses

During the study, tables, listings and figures (TLFs) and dosing recommendations based on the Bayesian Logistic Model (BLM) will be provided to the SMC. These analyses are described in the separate SMC IAP.

Unless there is a protocol amendment to include more than monotherapy dose escalation in this study, there won't be a further interim analysis, and the main statistical analysis for the monotherapy dose escalation of the study is described within this IAP. This analysis will take place when dose escalation is completed (data cutoff see Section 9); after study completion (i.e. after last subject last visit, when all subjects terminated treatment) an update of the analysis will be provided. If combination dose escalation or expansion parts are added to the study after completion of the dose escalation part, this IAP will be amended.

A data review meeting (DRM) 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 Trial Protocol

In protocol Section 8.5.3.3, estimation of posterior probabilities for clinical benefit and disease control rate are mentioned. These analyses are only applicable for expansion cohorts, and may be performed accordingly at a later time point. For the end of monotherapy dose escalation, only confidence intervals will be presented for the clinical benefit rate.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

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

IPDs include:

- Subjects that are dosed on the study despite not satisfying the inclusion criteria;
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn;
- Subjects that receive the wrong treatment or an incorrect dose;
- Deviation from Good Clinical Practice (GCP)
- Missed safety assessments

IPDs are clinically important if they lead to the exclusion of a subject from an analysis set, or if they could impact the key objectives of the study (see Section 10.2).

A list of IPDs can be found in Appendix 18.1, including possible consequences for assignment to analysis sets; clinically important protocol deviations (cIPDs) are highlighted accordingly. The final assessment of whether these protocol deviations lead to exclusion from an analysis population will be made at the DRM.

8.2 Definition of Analysis Sets and Subgroups

For purposes of analysis, the following populations 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 did not miss >4 cumulative days planned doses of M8891 in the first cycle of the dose escalation part for other than safety reasons
Safety	The Safety Analysis Set will include all subjects who receive at least one dose of trial treatment.
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 M8891 and have sufficient M8891 plasma concentration data to enable the calculation of at least one PK parameter. Sufficient concentration data is defined as at least 3 valid, post-dose concentration points in the PK profile to obtain any PK parameter.
CCI	
CCI	

PK Pharmacokinetic; WBC White blood cell.

9 General Specifications for Data Analyses

All tables and listings (and titles and footnotes for figures) will be produced using the Courier New font with a font size of 10 points. A font size of 9 points will be acceptable in cases where a font size of 10 points does not fit.

All TLFs will be produced using a paper size of US letter in landscape with 1 inch margins on all four sides.

Significance level:

There is no formal significance level for this trial and all analyses are considered descriptive. If confidence intervals or credibility intervals are mentioned, the level will be 95% unless otherwise specified.

Cutoff

For the analysis after the end of dose escalation for monotherapy, the cutoff will be 22 days after the first treatment day of the last subject enrolled into the monotherapy dose escalation cohort.

Pooling of centers:

Because of the anticipated small number of subjects enrolled in each center data will be pooled across centers, and the factor center will not be considered in statistical models or for subgroup analyses.

Definition of baseline:

In general, the last non-missing measurement prior to first trial drug administration will be used as the baseline measurement, unless otherwise specified (e.g. Section 15.7).

Definition of duration:

Duration in days will be calculated by the difference of start and stop date + 1 day (e.g. survival time (days) = date of death – date of first treatment + 1).

In case smaller units are of interest, duration will be calculated as stop date and time – start date and time.

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 (e.g. Section 11.3, 15, 16.1), missing data will not be replaced.

In all listings imputed information will be flagged accordingly.

Days in Trial and on Treatment:

The first study day is the day of informed consent. The first treatment day is the day of first administration of Investigational Medicinal Product (IMP). The day before the first treatment/study day will be labelled as study/treatment day -1; there will be no study/treatment day 0.

9.1 Listings

All original and derived parameters relevant to the study endpoints as well as demographic and disposition data will be listed, including repeated and unscheduled measurements.

All dates and times will be presented in the format ‘DDMMMYYYY’ and ‘HH:MM’, respectively. Data will be listed with the same number of decimal places as in the original data.

Subjects will be identified in listings by theirSubject ID.

9.2 Tables

Presentation of continuous and categorical variables

The following summary statistics will be used to summarize the trial data (other than PK concentration and PK parameters) per dose group (as defined by both dosing level and frequency) unless otherwise specified:

- Continuous variables: number of non-missing observations, number of missing observations, arithmetic mean (Mean), standard deviation (Sd), median (Median), minimum (Min), and maximum (Max) (in case less than 5 individual values are present: only mean, min and max will be given)
- Categorical variables: frequencies and percentages.

The following conventions are applied for reporting descriptive statistics of all continuous data (n refers to the number of decimal places reported for the original data):

Mean, Median	n decimal digits
Sd	n + 1 decimal digits
Min, Max	n decimal digits
Confidence Intervals (CIs)	n decimal digits
Credibility Intervals	n decimal digits

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.

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

All tables will be sorted by scheduled time point in chronological order, unless otherwise specified.

Unscheduled measurement will not be used for summary tables or statistical analysis, unless it was a repeated measurement, performed due to technical reason or unreliable values for a planned assessment.

Should a repeated measurement occur prior to IMP administration, the last obtained reliable value prior to dosing will be used as baseline, unless otherwise specified.

Should a repeated measurement occur after IMP administration, then the measurement closest to the scheduled time will be used in the descriptive statistics and for changes from baseline. In case this rule does not identify a unique measurement to use, the earliest one among those

identified will be used. Again, this rule should be used unless otherwise specified (see e.g. Section 15.7).

Presentation of PK concentration data

M8891 concentration data will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (Sd), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max). If there are fewer than 3 observations, only N, Min, and Max will be reported.

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

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

Presentation of PK parameter data

Pharmacokinetic parameter data will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (Sd), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM). For time to reach maximum observed concentration (t_{max}), only N, Min, Median and Max will be reported.

The PK parameter maximum observed plasma concentration (C_{max}) will be reported with the same precision as the source data and t_{max} will be reported to 2 decimal places. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the Study Data Tabulation Model (SDTM) PP domain, PK parameters will be provided with full precision, and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

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

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

9.3 Software

Pharmacokinetic parameters will be derived using PPD Version 6.4 or higher. All other statistical analyses will be performed using PPD version 9.3 or higher or R and

packages PPD or higher, or East version 6.4 or higher. PK figures and tables may be prepared using PPD version 9.3 or higher .

10 Trial Subjects

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

10.1 Disposition of Subjects and Discontinuations

Subject disposition will be presented using the screening population and will be summarized (n and percentages) by dose group (including dosing frequency) and overall. Subject disposition will also be summarized by site. The following information will be included:

- Total number of subjects screened (i.e. subjects who gave informed consent)
- Number of subjects who discontinued from trial prior to treatment, overall and grouped by main reason (e.g. the failed specific inclusion or exclusion criteria, withdraw of consent)
- Number of treated subjects
- Number of subjects that discontinued the treatment, overall and grouped by main reason
    - For the first cycle (frequencies calculated using number of subjects treated):
        - Number of subjects treated in the cycle
        - Number of subjects that discontinued the treatment, overall and grouped by main reason
        - Number of subjects who completed the cycle
    - For cycles after the first:
        - Number of subjects treated in the cycle who completed the previous cycle (denominator for frequency is the number of subjects who completed the previous cycle)
        - Number of subjects that did not continue treatment in the cycle (but were treated in the previous cycle), overall and grouped by main reason (denominator for frequency is the number of subjects who completed the previous cycle)
        - Number of subjects that discontinued the treatment during the cycle after first dose, overall and grouped by main reason (denominator for frequency is the number of subjects treated in cycle)
        - Number of subjects who completed the cycle (denominator for frequency is the number of subjects treated in cycle)
- Number of treated subjects who terminated the study, overall and 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 non-inclusion:
    - Subject did not meet all eligibility criteria (as specified in ClinBase, including the description of the violated criteria)
    - Subject withdrew informed consent
    - Other reasons (specified in ClinBase)

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 IPDs will be provided (separately for pre-/post inclusion deviations), based on the safety population:

- Frequency table of IPDs by classification and description
- Listing of IPDs (sorted by dose group and subject ID), indicating whether it was a cIPD

The frequency table will be by dose group and overall.

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

11.1 Demographics

Demographic characteristics will be listed (sorted by dose group and subject ID) and summarized by dose group and overall, based on the safety population, showing the following:

- Demographic characteristics
  - Gender: male, female
  - Race: White, Black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Other
  - Ethnicity: Hispanic or Latino, Not Hispanic or Latino
  - Age (years), calculated as (date of informed consent – date of birth + 1) / 365.25
  - Age categories: <65, 65-74, 75-84, ≥85 years
  - Weight (kg)
  - Height (cm)
  - Body Mass Index (BMI), calculated as (weight in kg) / (height in meters)^2 (kg/m^2)
- Center

11.2 Medical History

The medical history will be coded with the most recent Medical Dictionary for Regulatory Activities (MedDRA®) version, Version 20.1 or later.

Medical history will be listed by subject, based on the safety population, and will include the following information:

- Description of medical condition
- System Organ Class (SOC)
- MedDRA Preferred Term (PT)
- Start/End Date (or ongoing, if applicable)
- Toxicity grade (if applicable)
- Relation to study condition

11.3 Disease History and Prior Anti-Cancer Therapies

The safety population will be used for all disease history and prior anti-cancer therapy related outputs.

Disease history will be listed including the following information:

- Site of primary tumor
- Sub Sites
- Date of initial cancer diagnosis
- Date of documented locally advanced, inoperable or metastatic disease (if applicable)
- Histopathological classification
- T, N and M classification at initial diagnosis
- T, N and M classification at study entry

The disease history will be summarized by dose group and overall using the safety population for the following categorical variables:

- T, N and M stages at study entry
- Time since initial diagnosis (months)
- Time since documentation of locally advanced, inoperable or metastatic disease (months)
- Histopathological classification

Incomplete dates for disease history (initial diagnosis date, date of documented locally advanced, inoperable or metastatic disease) will be imputed as follows:

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

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.

12 Previous or Concomitant Medications/Procedures

The safety population will be used to list and summarize previous and concomitant medications.

Concomitant treatments are medications, other than trial medications, which are taken by subjects any time on-trial (on or after the first day of trial drug treatment for each subject) or within 28 days after last dose of trial drug. In case the date values will not allow to unequivocally allocate a medication to concomitant medication, the medication will be considered as concomitant medication.

Previous medications are medications, other than trial medications and pre-medications for trial drug, which started before first administration of trial drug. In case the date values will not allow to unequivocally allocate a medication to previous medication, the medication will be considered as previous medication.

All medication will be coded with the most current World Health Organization – Drug Dictionary (WHO-DD) version September 2017 or later.

Both previous and concomitant medication will be listed including the following information:

- Name of medication
- Anatomical Therapeutic Chemical (ATC) 2nd level and Preferred Term (PT)
- Start and end date
- Dose and frequency
- Route of administration
- Reason for medication

All concomitant medication will be summarized by dose group and overall, ATC 2nd level and PT.

In case multiple ATC's are assigned to a drug, all ATC 2nd level will be used for reporting.

All **concomitant procedures**, which were undertaken any time on trial, will be listed, showing the following information:

- Name of procedure
- Start and end date
- Reason for procedure

13 Treatment Compliance and Exposure

Exposure to the IMP will be listed using the safety population, showing the following information:

- 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)

Using the safety population, compliance and exposure will be summarized by dose group and overall, including duration of therapy (weeks), number of times dose missed (overall and by reason) and number of times dose was adjusted (overall and by reason).

14 Efficacy Analyses

14.1 Analysis of Best Overall Response, Clinical Benefit and Progression-free Survival Time

All efficacy endpoints will be listed and summarized descriptively as described in Section 9.2. The following categorical variables will be included:

- Best overall response (BOR: complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD] according to RECIST v 1.1; objective response rate [ORR=CR+PR].)
- Clinical benefit (CR, PR and SD for ≥ 12 weeks: yes/no)

In addition, 95% exact Clopper Pearson Confidence intervals will be calculated for the overall clinical benefit rate and the ORR (regardless of dose level).

Furthermore, the following variable will be analyzed:

- Progression-free survival time (PFS)

PFS time is defined as the time from start of treatment to the date of the first documentation of objective progression of disease (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) at data cutoff, or for patients with an event after two or more subsequent missing response assessments (i.e. 2 times the scheduled time interval between two subsequent response assessments, plus 1 week time window). Patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored at start of treatment unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

The date of the overall response assessment is the earliest date of imaging of target, non-target and new lesions of images taken at that response assessment.

	Status	Censoring	Date of event / censoring
Progressed or died	*Within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD or treatment start*	*Event*	*Minimum(Date of PD, Date of death)*
	Otherwise	*Censored*	*Date of last tumor assessment with outcome CR, PR or SD or date of treatment start, whatever is later*
Neither progressed nor died		*Censored*	*Date of last tumor assessment with outcome CR, PR or SD or date of treatment start, whatever is later*

The censored values will be presented descriptively. Number of and reason (PD/Death after two or more subsequent missing response assessments, censored at treatment start, lost to follow-up / withdrew consent, due to data cutoff (administrative censoring)) for censored values will be displayed, including percentages.

In the listing censored values will be flagged and the reason for censoring will be displayed.

Kaplan-Meier estimates (product-limit estimates) will be presented for the analysis of PFS together with a summary of associated statistics (median survival time, 6-, 12-, 18-, 24-month survival rate estimates and estimates for every 6 months thereafter if applicable) including the corresponding two-sided 95% confidence intervals, presented overall, and for daily dose ≤/> median daily dose.

The confidence intervals for the median will be calculated according to Brookmeyer and Crowley (1982) and confidence intervals for the survival function estimates at above defined time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980). The estimate of the standard error will be computed using Greenwood's formula.

The safety population will be used for the analysis of efficacy.

14.2 Analysis of Response Evaluation Criteria in Solid Tumors (RECIST)

The results of the RECIST evaluation will be listed using the safety population and will contain the following information:

- Designation of lesion (target/non-target/new)
- Lesion number
- Site
- Assessment Method
- Imaging Date
- Type of lesion (primary, node or metastasis)
- Size (longest diameter for non-nodal, short axis for nodal)
- Sum of longest diameters of target lesions (mm, per assessment)
- PET result

The list will be sorted by dose group, subject, designation, number of lesion and date.

Overall disease assessment based on imaging (RECIST 1.1) will be listed, including the following information:

- Date of overall response assessment (as defined in Section 14.1)
- Time from start of treatment (months)

- Response target lesions
- Response non-target lesions
- New lesions
- Overall response

The percent change from baseline in sum of longest diameters (mm) for target lesions will be summarized by dose group and overall, and by time point.

Spider plots per dose group and overall will be produced. For each subject a different combination of color and line type will be used; all subjects in the same dose group will be presented using the same color.

14.3 Eastern Cooperative Oncology Group Performance Status (ECOG PS)

The ECOG PS assessments will be listed using the safety population, including date of assessment and performance status.

The shift from baseline to best and worst on-treatment ECOG PS, respectively, will be summarized by dose group based on the safety population. The missing category will be included and the number of subjects in each cohort will be used as the denominator. Also, the number of subjects with increase, decrease, as well as no change in ECOG PS compared to baseline during treatment, respectively, will be summarized.

15 Safety Analyses

15.1 Analyses of Dose Limiting Toxicities (Primary Endpoint)

The dose escalation set will be used for all analyses related to the primary endpoint. The frequency and percentage of subjects experiencing a dose limiting toxicity (DLT) will be summarized by dose group and overall. A listing will be provided as well (details on presented information, see Section 15.2).

In addition, the following will be presented:

- Quantiles (2.5%, 25%, 50%, 75% and 97.5%) for the posterior probability of a subject experiencing a DLT at each of the dose levels used in the study according to the same Bayesian Logistic Model (BLM) as descripted in the SMC IAP, Section 14:

Bayesian two-parameter logistic model:

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 suggested $d_j \in \{7\text{ mg}, 12\text{ mg}, 20\text{ mg}, 35\text{ mg}, 60\text{ mg}, 100\text{ mg}, 150\text{ mg}, 210\text{ mg}\}$ for QD (and (α, β)aere bivariate normally distributed. CCI [redacted] the following is be derived:

E(α)=log(0.8/0.2) =1.386

E(β)= log((log(0.33/0.67)-log(0.8/0.2))/log(210/340))=1.469

Variances are chosen as follows: Var(α)=2², Var(β)=2², Cov(α, β)=0.2.

MTD suggestion from the BL model

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

1) The BLM will be updated with all DLT data from the dose escalation.
2) Estimated E(α), E(β), Var(α), Var (β) and Cov(α, β) as well as the estimated curve will be provided.
3) The dose with targeted toxicity probability of 30% will be identified using the curve.
4) The next lower tested dose will be selected.
5) It will be checked whether this dose fulfills the overdose control.

   The credibility interval will be provided.

This information will be forwarded to the SMC that will decide on the determination of the MTD. Additionally, the SMC will receive the estimated DLT probability and associated probability quantiles for all other doses tested.

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

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

2) Steps 3) and 4) of the first approach will be followed.

3) The confidence interval for the DLT probability will be provided.

There will also be a plot showing both the observed percentage of DLTs and the 75% quantile for the predicted probability according to the BLM over dose. If the SMC decides to switch from QD to BID dosing, there will be a figure for QD and a figure for BID dosing.

Additionally, the posterior probability of toxicity will be plotted versus the dose, using East.

15.2 Adverse Events

All adverse events analyses will be based on the safety population.

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of an IMP, whether considered related to the IMP or not. All AEs will be coded using the most recent Medical Dictionary for Regulatory Activities MedDRA version, Version 20.1 or later.

A treatment emergent adverse event (TEAE) is defined as an AE that begins or worsens after at least one dose of the IMP has been administered. AEs that started before administration of IMP or more than 30 days after last dose of IMP will not be considered TEAEs.

Every AE listing will include the following information:

- System organ class (SOC) and preferred term (PT)
- Start and end date/time
- Days under treatment
- Duration
- Seriousness criteria
- Relationship with M8891
- Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade
- Other causality factors
- Action taken with M8891
- Other actions taken
- Outcome
- Whether AE is dose-limiting toxicity

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

The following summaries will be presented by dose group and overall using the safety population:

- Number of subjects with the following kinds of TEAEs:
    - Any TEAE
    - Related TEAEs
    - TEAEs leading to withdrawal of trial drug
    - TEAEs leading to death (overall and by reason for death)
    - Serious TEAEs
    - Related serious TEAEs
    - TEAEs with CTCAE grade ≥ 3
    - Related TEAEs with CTCAE grade ≥ 3
    - TEAEs leading to dose reduction
    - TEAEs leading to temporary interruptions of trial drug
- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- TEAEs leading to withdrawal of trial drug, dose reduction, temporary interruptions of trial drug, and death
- Non-serious TEAEs occurring with incidence in PT greater than 5% in at least one dose group, by SOC and PT

AEs will be summarized by worst severity per subject, using the MedDRA PT as event category and MedDRA primary SOC as Body System category.

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

AEs with missing classifications regarding relationship to study treatment and start date greater or equal to start of study treatment will be considered as related to study treatment.

Incomplete AE-related dates will be handled as follows:

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

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

Listings will be presented for the following types of AEs:

- TEAEs leading to death, including flags for death within 30 days of last dose of IMP
- TEAES with CTCAE grade ≥ 3
- Serious TEAEs
- TEAEs leading to withdrawal, dose interruption or dose reduction of trial drug

15.3.1 Deaths

Deaths will be listed using the Safety Analysis Set, displaying by dose group the following:

- Deaths by primary reason of death
- Flags for death within 30 days of last dose of IMP.

15.4 Clinical Laboratory Evaluation

The safety population will be used for all clinical laboratory evaluations.

All laboratory results (biochemistry, hematology, coagulation, urinalysis, pregnancy test), will be listed by subject and time point. The following information will be included in the listing:

- Sex of subject
- Date/time of sample
- Treatment day
- Result
- Reference range (for continuous variables)
- Flag for values above (“H”) or below (“L”) the reference range (for continuous variables)
- Change from baseline (for continuous variables)
- NCI-CTCAE grade
- Flag for value with worst-on trial grade (“Y”)

All continuous laboratory results will be summarized by dose and time point, including absolute values and change from baseline.

Laboratory results will also be classified by Grade according to NCI-CTCAE. The worst post-baseline on-trial Grades will be summarized, as well as the worst post-baseline Grades within the first cycle. Shifts in toxicity grading from first treatment to highest Grade will be displayed: number of subjects with shift to any higher grade, to higher grade 3 or 4, to higher grade 4.

Results for variables that are not part of NCI-CTCAE will be presented as below, within, or above normal limits. Only subjects with post-baseline laboratory values will be included in these analyses.

D-dimer results will be listed with biochemistry.

15.5 Vital Signs

The safety population will be used for all vital sign evaluation. Vital signs will be listed, including the following information:

- Date/Time of assessment
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Position in which blood pressure was taken
- Heart rate (bpm)
- Temperature
- Respiratory rate (breaths/minute)
- Change from baseline for continuous variables
- Weight

All continuous variables will be summarized descriptively by dose group and time point, including absolute values and change from baseline.

15.6 Lower Extremity Doppler Ultrasonography

The results of the lower extremity Doppler Ultrasonography will be listed by dose group and time point using the safety population and include the following information:

- Date/Time of assessment
- Whether deep vein thrombosis (DVT) was detected
- Location of DVT
- Size of DVT (cm)

15.7 ECG

All analysis of electrocardiogram (ECG) data will be based on the safety population.

Triplicate values will be handled as follows: listings will contain the individual triplicates and the aggregated results. Summaries will only use the aggregated values. The aggregation of triplicate ECGs will be performed using the arithmetic mean for all parameters at each time point. The aggregated values of the last triplicate ECG measurement prior to first trial drug administration will be used as the baseline measurement.

Results will be listed, including the following information:

- Time point
- Time of measurement
- Position
- Heart rate (beats/min)
- PQ/PR duration (ms)
- RR duration (ms)
- QRS duration (ms)
- QT corrected using Fridericia's formula: $\mathrm{QTcF} = \mathrm{QT}/\sqrt[3]{RR}$ (ms)
- Rhythm evaluation
- Whether ECG is abnormal
- Clinical significance if ECG is abnormal

Potentially clinically significant abnormal values of ECG will be flagged according to the following criteria:

Parameter	Potentially Clinically Significant Abnormalities (PCSA) Criteria
Heart rate	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
PQ/PR	≥ 220 ms and increase from baseline ≥ 20 ms
QRS	≥ 120 ms
QTcF absolute	Prolonged: >450 ms (Male), >470 ms (Female) Potentially significant abnormality: ≥ 500 ms
QTcF change from baseline	Prolonged: Increase from baseline > 60 ms

Only the aggregated measurement will be flagged as described. The flagging of the aggregated measurement will be performed by applying the above rules directly on the averaged ECG parameters.

For display of overall assessment of the result of the ECG as normal, abnormal not clinically significant, and abnormal clinically significant, the worst result of the triplicates will be considered for the analysis of the aggregated measurements.

The ECG parameters will be summarized by descriptive statistics per time point including absolute values and change from baseline. Number and percentages for subjects meeting the PCSA Criteria will also be provided. For the investigator's overall ECG assessment, a shift table from baseline to the worst on-treatment result will be created.

Data will be further analyzed using concentration effect modeling for baseline corrected QTcF values.Change from baseline (QTcF) will be modelled using a linear mixed model, with baseline QTcF value and drug concentration as continuous covariates, and subject as a random factor, using data from the first cycle, and additionally using all data until cut-off. One model will be run using an unstructured covariance matrix, another one using the compound-symmetry structure. The estimate for the concentration coefficient will be reported, including standard error, degrees of freedom and 95% confidence interval for the coefficient. The concentration effect model will be fit using the PK analysis set. The SAS code for this analysis can be found in the TFL shells.

15.8 Physical Examination

Physical examination (including neurologic examinations) will be listed using the safety population and include the following information:

- Date
- Neurological examination:
    - Mental Status (Normal/Abnormal)
    - Cranial Nerves (Normal/Abnormal)
    - Motor System (Normal/Abnormal)
    - Muscle Strength (Normal/Abnormal)
    - Gait, stance and coordination (Normal/Abnormal)
    - Sensation (Normal/Abnormal)
    - Reflexes (Normal/Abnormal)
    - Autonomic Nervous System (Normal/Abnormal)
- Mini-Mental State Examination (MMSE):
    - Result (Normal/Abnormal)
    - Score

- International Cooperative Ataxia Rating Scale (ICARS):
    - Postural and Gait Disturbance
    - Limb Ataxia
    - Dysarthria
    - Oculomotor disorders
    - Total score

The results will be summarized by dose group and using the safety population, displaying counts and percentages for abnormal results and summary statistics for scores (considered as continuous, see Section 9.2 for details).

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

16.1.1 Analysis of PK Concentrations

All individual pharmacokinetic (PK) plasma concentrations of M8891 will be listed by time point using the safety population. Subjects that are not included in the PK analysis set will be flagged, and the list will be sorted so that they are at the bottom of the list.

The listing for the plasma concentration of M8891 will include the following:

- Scheduled and actual date/time
- Concentration
- Time relative to scheduled time (HH:MM:SS)

The PK plasma concentrations will also be summarized descriptively using the PK Analysis Set by dose and time point using the PK analysis set. Values below the lower limit of quantification (LLOQ) will be taken as zero for descriptive statistics of concentrations.

Individual plasma concentration-time profiles (linear and semi-logarithmic scale) will be plotted using the safety population. Subjects that are not part of the PK analysis set will be flagged in the plot.

Mean plasma concentrations per dose group and day will be plotted using scheduled time points on the linear (± Sd) and semi-logarithmic scale. If mean minus Sd is negative, Sd will be truncated at 0. In case PK blood samples were not performed within the time window specified in the protocol, these calculations and plots will be repeated excluding the respective plasma concentrations. The PK analysis set will be used for these figures.

The following tables and figures will be provided:

Tables

- Individual Plasma Concentrations of M8891 and Descriptive Statistics by Scheduled Time for Each Dose Group after Single Dosing (Cycle 1 Day 1)
- Individual Plasma Concentrations of M8891 and Descriptive Statistics by Scheduled Time for Each Dose Group after Multiple Dosing (Cycle 1 Day 15)
- Individual Trough Plasma Concentrations of M8891 and Descriptive Statistics by Scheduled Time and Dose Group

Figures

- Individual M8891 Plasma Concentration-Time Profiles by Dose Group and Day, Linear Scale
- Individual M8891 Plasma Concentration-Time Profiles by Dose Group and Day, Semi-Logarithmic Scale
- Mean (±Sd) M8891 Plasma Concentration-Time Profiles by Dose Group and Day, Linear Scale
- Mean M8891 Plasma Concentration-Time Profiles by Dose Group and Day, Semi-Logarithmic Scale
- Individual M8891 Plasma Concentration-Time Profiles for Single and Multiple Dose Overlaid, Linear Scale. (Overlaid means that the x-axis is hours post dosing on the same day.)
- Individual M8891 Plasma Concentration-Time Profiles for Single and Multiple Dose Overlaid, Semi-Logarithmic Scale
- Mean (±Sd) M8891 Plasma Concentration-Time Profiles by Dose Group, for Single and Multiple Dose Overlaid, Linear Scale
- Mean M8891 Plasma Concentration-Time Profiles by Dose Group, for Single and Multiple Dose Overlaid, Semi-Logarithmic Scale

Results of the PK urine sampling will be listed using the safety population, including the following information:

- Time of last urination before start of dosing (HH:MM)
- Collection start and end date/time
- Volume collected
- Any comment recorded in the CRF
- Concentration of M8891
- Total amount of M8891 (calculated as volume x concentration)

Subjects that are not included in the PK analysis set will be flagged, and the list will be sorted so that they are at the bottom of the list. The urine PK values (volume, concentration and amount) will also be summarized by dose group and study day for the scheduled measurements using the PK analysis set.

Volume and amount will be added for multiple voidings and concentration will be calculated used an average weighted by volume.

16.1.2 Estimation of Individual PK Parameters

Pharmacokinetic parameters will be calculated by the PK/CCI Merck, Darmstadt, Germany, using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time and flagged in listings. For AUC_{0-24}, if the actual sampling time at 24 hours is not equal to the scheduled observation time, AUC_{0-24} will be calculated based on estimated concentration at the scheduled time and not the concentration at the actual observation time.

The following plasma PK parameters of M8891 will be calculated, when reliable on Day 1 and Day 15:

C_{max}	Maximum observed concentration
C_{max}/Dose	The Dose normalized maximum observed concentration. Normalized using the actual dose, and the formula C_{max} /Dose.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log linear trapezoidal rule (linear up, log down).
AUC_{0-t}/Dose	The Dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Normalized using the actual dose, and the formula AUC_{0-t} /Dose.
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last} , as estimated using the linear regression from λ_z determination. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\ \lambda_z$

$AUC_{0-\infty}$/Dose	The Dose normalized AUC from time zero extrapolated to infinity. Normalised using actual dose, using the formula $AUC_{0-\infty}$ /Dose.
AUC_{τ}	The area under the concentration-time curve (AUC) over the dosing interval from T_1=0 h to T_2=τ h. Calculated using the mixed log linear trapezoidal rule (linear up, log down). For single dose, AUCτ is calculated as a partial area with the defined time range. In multiple dose profiles AUC_{τ} is calculated at steady state from one pre-dose time point to the dosing interval time. In cases where the actual observation time is not equal to the scheduled observation time AUC_{τ} will be calculated based on the estimated concentration at τ hours, and not the concentration at the actual observation time.
AUC_{τ}/Dose	The Dose normalized AUC over the interval from T_1=0 h to T_2=τ h. Normalized using actual dose, using the formula AUC_{τ} /Dose.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$)*100 = (1−[AUC_{0-t}/$AUC_{0-\infty}$])*100.
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$
$CL_{/f}$	The apparent total body clearance of drug following extravascular administration, taking into account the fraction of dose absorbed. CL/f = Dose $_{p.o.}$ /$AUC_{0-\infty}$.
$CL_{SS/f}$	The apparent total body clearance of drug at steady state following extravascular administration, taking into account the fraction of dose absorbed. $CL_{SS/f}$ = Dose $_{p.o.}$ / AUC_{τ}
CL_R	The renal clearance of drug. $CL_R = Ae_{0-\infty}$ /$AUC_{0-\infty}$ or Ae_{0-t} /AUC_{0-t}
$V_{Z/f}$	The apparent volume of distribution during the terminal phase following extravascular administration, based on the fraction of dose absorbed. $V_{z/f}$ = Dose/($AUC_{0-\infty}$*λ_z) following single dose. $V_{z/f}$ = Dose/(AUC_{τ}*λ_z) following multiple dose.
$R_{acc(AUC)}$	The accumulation factor to assess the increase in exposure until steady state is reached. $R_{acc(AUC)}$= (AUC_{τ} after multiple dose (at steady state)) / ($AUC_{0-\infty}$ after single dose)

$R_{acc(Cmax)}$	The accumulation factor to assess the increase in maximum concentration until steady state is reached. $R_{acc(Cmax)}$ = (C_{max} after multiple dose (at steady state))/(C_{max} after single dose) = $C_{max\ D15}/C_{max\ D1}$

The following urine PK parameters of M8891 will be calculated, when reliable, for the QD and BID dosing, on Day 1 and Day 15:

Ae_{τ}	The cumulative amount excreted during a complete dose interval at steady state. Amount_Recovered = Σ(Concentration * Volume) from T_1 to T_2, where T_1 and T_2 denote the start and end time of the dose interval at steady state respectively.
Ae_{τ}%	The cumulative percentage of dose excreted during a complete dose interval at steady state. Percent_Recovered = 100*Amount_Recovered/Dose.
Ae_{0-t}	The cumulative amount excreted from time zero (= dosing time) to the end of the current collection interval after dosing. Amount_Recovered = Σ(Concentration * Volume)
Ae_{0-t}%	The cumulative percentage of dose excreted from time zero (= dosing time) to the end of the current collection interval after dosing. Percent_Recovered = 100*Amount_Recovered/Dose
$Ae_{0-\infty}$	The cumulative amount excreted from time zero (dosing time) to infinity. $Ae_{0-\infty}=Ae_{0-t}+((Ae_{0-(t-1)}-Ae_{0-t})/(t_{last-1}-t_{last}))/\lambda_z$ where λ_z is the excretion rate or $Ae_{0-\infty}$ = (Ae_{0-t} / AUC_{0-t}) * $AUC_{0-\infty}$
$Ae_{0-\infty}$%	The cumulative percentage of the dose that is excreted from time zero (= dosing time) to infinity. Percent_Recovered = 100*Amount_Recovered/Dose

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

- The time interval (h) of the log-linear regression ($\lambda_{z\ low}$, $\lambda_{z\ upp}$) to determine λ_z.
- Number of data points (N_{λ}) included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (Rsq) for calculation of λ_z.

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin best fit methodology will be used as standard. The last quantifiable concentration

should always be included in the regression analysis, while the concentration at t_{max} and any concentrations <LLOQ which occur after the last quantifiable data point should not be used. $AUC_{extra\%}$ should be less than 20%. If $AUC_{extra\%}$ is greater than 20%, all parameters derived using λ_z (i.e. λ_z, $t_{1/2}$, $AUC_{0-\infty}$ $AUC_{extra\%}$, V_z, CL) will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags should be included in the study specific SDTM.

The coefficient of correlation (R^2) should be ≥0.8 and the observation period over which the regression line is estimated should be at least twofold the resulting $t_{1/2}$ itself. If these criteria are not met, then the rate constants and all derived parameters (e.g.CL, and Vz etc.) will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags should be included in the study specific SDTM.

Partial areas AUC_τ should be calculated using the scheduled dosing interval, as defined in the CTP. The actual dosing interval calculated from CRF time data should not be used. The following rules apply when calculating the partial area AUC_τ within the observed time interval from T1 to T2:

- If the start time of the interval (T_1) occurs before the first observation, the observation at T_1 will be estimated using the linear interpolant between the first datapoint and C0. For single dose data C0= 0 when the drug was administered via an extravascular route or via infusion, and C0 is the estimated dosing time intercept when the drug was administered as an IV bolus. For steady state models, C0 is the minimum concentration value occurring within the time interval T_1 to T_2.
- If either T_1 or T_2 falls within the time range in which samples were taken, but does not coincide with an observed data point, then a linear or logarithmic interpolation is performed to estimate the corresponding concentration value. Whether a linear or logarithmic interpolation is used will depend on the method of AUC calculation e.g. linear up log down.
- If the end time of the interval (T_2) occurs after the last measurable concentration and the terminal regression (λ_z) is estimable, then λ_z is used to estimate the concentration at time T_2. The log trapezoidal rule will be used to calculate the area from the last observation time to the end time of the partial area (T_2). If λ_z cannot be estimated the partial area will not be calculated.

Concentrations below the lower limit of quantification (<LLOQ), which are before the last quantifiable data point, will be taken as zero for calculating the AUC. Unless otherwise specified in the CTP, pre-dose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration. The same applies to the very first pre-dose sample of a multiple dose study.

Dose dependent parameters (e.g. CL, Vz) will not be calculated for metabolites.

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

16.1.3 Analysis of PK Parameters

All PK parameters will be listed using the safety population. Subjects that are not included in the PK analysis set will be flagged, and the list will be sorted so that they are at the bottom of the list.

The PK parameters will also be summarized descriptively per day by dose group using the PK analysis set.

The following tables and figures will be provided:

Tables

Individual Pharmacokinetic Parameters of M8891 in Plasma and Descriptive Statistics by Treatment after Single Dosing (Cycle 1 Day 1)

Individual Pharmacokinetic Parameters of M8891 in Plasma and Descriptive Statistics by Treatment after Multiple Dosing (Cycle 1 Day 15)

Individual Accumulation Ratios of AUC, Ae and Cmax in Plasma and Descriptive Statistics by Treatment

Individual Dose Normalized Pharmacokinetic Parameters of M8891 in Plasma and Descriptive Statistics after Single Dosing (Cycle 1 Day 1)

Individual Dose Normalized Pharmacokinetic Parameters of M8891 in Plasma and Descriptive Statistics after Multiple Dosing (Cycle 1 Day 15)

Figures

Scatter Plots: M8891 Dose-normalized PK Parameter (eg, AUC0-t, AUC0-∞ and Cmax) versus Treatment, Single Dose (with linear regression)

Box Plots: M8891 Dose-normalized PK Parameter (eg, AUC0-t, AUC0-∞-, and Cmax) versus Treatment, Single Dose

Scatter Plots: M8891 Dose-normalized PK Parameter (eg, AUC, and Cmax) versus Treatment, Multiple Dose (with linear regression)

Box Plots: M8891 Dose-normalized PK Parameter (eg, AUC, and Cmax) versus dose

16.1.4 Analysis of Dose Proportionality

For the assessment of dose proportionality, the PK endpoints, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}\tau}$ and C_{max} of M8891 will be compared between dose levels for Day 1 and Day 15 separately.

The PK parameters will be dose normalized

The dose normalized parameters and the overall mean (y-axis) will be plotted over the dose (x-axis) on the linear scale and logarithmic (both axes) scale using the PK analysis set. The overall mean will be calculated on the scale that is used for the plot.

Modeling on the log transformed scale will be applied to the dose normalized parameters including dose as covariate. Dose proportionality will also be checked using the power model, if appropriate. The relationship between the PK parameter y and the actual total dose is defined as follows:

$$y = \alpha \, dose^{\beta}$$

On the log transformed scale this becomes a linear relationship to which a linear regression approach can be applied:

$$\log(y) = \log(\alpha) + \beta * \log(dose)$$

The estimate of β and 95% confidence intervals will be computed to quantify dose proportionality. If dose proportionality is given, β in theory is equal to 1 and the estimate of the model should not deviate strongly from 1. This linear regression will be calculated using the PK analysis set.

The SAS code for this analysis can be found in the TLF shells.

16.1.5 Population Pharmacokinetic Analysis

The PK and covariate data from this study may be analyzed jointly with data from other studies by nonlinear mixed effect approach, in order to describe the PK concentration time profile; to identify covariates explaining (part of) the between subject PK variability; and to estimate the residual PK variability. No standalone PopPK analysis on this trial is planned. For a combined PopPK analysis with other studies, more details will be given in a separate Data Analysis Plan for Population Pharmacokinetic Analysis. The results will be reported separately.

CCI [redacted]

CCI [redacted]

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[redacted]

17 References

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18 Appendices

18.1 Important Protocol Deviations

PD REF ID	Category (DVCAT)	Classification (DVDECOD)	Type of Deviation Observable/ Programmable (Data Driven)	PD (DVTERM	PD Identification Method Options	clPD ?
100	Important	Informed Consent	Observable	Subject has study-specific assessment performed prior to informed consent.	Source Data Review	
CCI [redacted]						
102	Important	Informed Consent	Observable	Improper Informed Consent - Subject was not consented properly prior to screening procedures commencing (No consent, missing date, incorrect name)	Source Data Review	
200	Important	Inc/Excl Criteria	Observable	Subject does not have Histologically confirmed advanced solid tumors with no clear curative treatment options available after at least 1 prior systemic anticancer therapy, however subject is included in the trial.	Source Data Review	
201	Important	Inc/Excl Criteria	Observable	Missing tumor accessible for biopsies and agreement to conduct pre-dose and post-dose fresh tumor biopsies, however subject is included in the trial.	Source Data Review	
202	Important	Inc/Excl Criteria	Observable	Bone marrow impairment as evidenced by hemoglobin < 9.0 g/dL, neutrophil count < 1.5 x 109/L, platelets < 100 x 109/L. Transfusion is not allowed within 3 weeks before first dose, however subject is included in the trial.	Source Data Review	Yes

PD REF ID	Category (DVCAT)	Classification (DVDECOD)	Type of Deviation Observable/ Programmable (Data Driven)	PD (DVTERM	PD Identification Method Options	clPD ?
203	Important	Inc/Excl Criteria	Observable	Renal impairment as evidenced by calculated creatinine clearance < 60 mL/min (according to the Cockcroft-Gault formula), however subject is included in the trial.	Source Data Review	Yes
204	Important	Inc/Excl Criteria	Observable	Liver function abnormality as defined by total bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN, for subjects with liver involvement AST/ALT > 5 x ULN, however subject is included in the trial.	Source Data Review	Yes
205	Important	Inc/Excl Criteria	Observable	Extensive prior radiotherapy to more than 30% of bone marrow reserves, or prior bone marrow/stem cell transplantation within 5 years of study start, however subject is included in the trial.	Source Data Review	Yes
206	Important	Inc/Excl Criteria	Observable	Clinically significant cardiac conduction abnormalities, including QTc prolongation of > 480 msec and/or pacemaker or impaired cardiovascular function such as New York Heart Association classification score > 2, however subject is included in the trial.	Source Data Review	Yes
207	Important	Inc/Excl Criteria	Observable	Any other severe clinical condition that in the opinion of the treating physician may compromise the trial participation, however subject is included in the trial.	Source Data Review	Yes
208	Important	Inc/Excl Criteria	Observable	Participation in another clinical trial within the past 28 days, however subject is included in the trial.	Source Data Review	

PD REF ID	Category (DVCAT)	Classification (DVDECOD)	Type of Deviation Observable/ Programmable (Data Driven)	PD (DVTERM	PD Identification Method Options	clPD ?
209	Important	Inc/Excl Criteria	Observable	History of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease or conditions that may hamper compliance and/or absorption of the investigational drugs, however subject is included in the trial.	Source Data Review	
210	Important	Inc/Excl Criteria	Observable	Life expectancy < 3 months, however subject is included in the trial.	Source Data Review	
211	Important	Inc/Excl Criteria	Observable	Known hypersensitivity to the trial treatment or to one or more of the excipients used, however subject is included in the trial.	Source Data Review	
212	Important	Inc/Excl Criteria	Observable	Legal incapacity or limited legal capacity, however subject is included in the trial.	Source Data Review	
213	Important	Inc/Excl Criteria	Observable	The subject is a female of childbearing potential who is pregnant, breastfeeding or who did not agree to use effective contraceptive measures from time of informed consent through 92 days after last dose of study drug.	Source Data Review	
214	Important	Inc/Excl Criteria	Observable	The subject is male with partners of childbearing potential that did not use barrier contraception and did not have their partners use another method of contraception from the time of informed consent through 92 days after last dose of study drug.	Source Data Review	
215	Important	Inc/Excl Criteria	Programmable	Eastern Cooperative Oncology Group Performance Status (ECOG PS) is not <2 however subject is included in study	On-Line Check	

PD REF ID	Category (DVCAT)	Classification (DVDECOD)	Type of Deviation Observable/ Programmable (Data Driven)	PD (DVTERM	PD Identification Method Options	clPD ?
216	Important	Inc/Excl Criteria	Observable	History of stroke, heart attack, thrombosis (e.g. deep vein thrombosis and pulmonary embolism) or genetically-determined hypercoagulopathy within 6 months	Source Data Review	
217	Important	Inc/Excl Criteria	Observable	Patient did not receive at least 1 prior systemic anticancer therapy prior to enrolling in study.	Source Data Review	
218	Important	Inc/Excl Criteria	Observable	Subject received blood product transfusion 3 weeks prior to first dose of M8891.	Source Data Review	
222	Important	Visit Schedule	Programmable	Any abnormal complete neurologic examination test detected during treatment but Mini Mental Exam not done.	On-Line Check	
223	Important	Visit Schedule	Programmable	Any abnormal complete neurologic examination test during treatment but International Cooperative Group for Ataxia Rating Scale (ICARS) not done.	On-Line Check	
300	Important	Withdrawal Criteria	Observable	Patient met withdrawal criteria during the study but is still on study	Source Data Review	
301	Important	Withdrawal Criteria	Observable	Subject withdrew consent, and was not withdrawn from the trial therapy.	Source Data Review	

PD REF ID	Category (DVCAT)	Classification (DVDECOD)	Type of Deviation Observable/ Programmable (Data Driven)	PD (DVTERM	PD Identification Method Options	clPD ?
302	Important	Withdrawal Criteria	Observable	Progressive neoplastic disease per RECIST v1.1 and the exceptions in protocol, a growth of the target lesions of less than 35% from baseline and no new lesions, or new lesion(s) smaller than 1 cm; bone metastatic lesions or lesions treatable with local radiotherapy would also fall in the same category), but the subject performance status is the same as baseline and there are no safety concerns, i.e. no ongoing symptomatic events Grade 2 or higher in severity, treatment may be continued for another 2 cycles to the next tumor evaluation, are not fulfilled but patient still on study	Source Data Review	
303	Important	Withdrawal Criteria	Observable	Subject requires more than 2 dose reductions but is still on study	Source Data Review	
304	Important	Withdrawal Criteria	Observable	Patient with treatment-emergent AE attributable to study drug and judged as clinical significance and deemed necessary to reduce the dose as per protocol but continued on study therapy at same dose administered when treatment-emergent AE occurred	Source Data Review	
305	Important	Withdrawal Criteria	Observable	Patient with evidence of treatment related hepatocellular injury but continued on study therapy at same dose administered when DLT occurred.	Source Data Review	

PD REF ID	Category (DVCAT)	Classification (DVDECOD)	Type of Deviation Observable/ Programmable (Data Driven)	PD (DVTERM	PD Identification Method Options	clPD ?
306	Important	Withdrawal Criteria	Observable	Patient with any Grade 4 liver enzyme elevation tha tis possibly drug related but continued on study therapy at same dose administered when DLT occurred.	Source Data Review	
307	Important	Withdrawal Criteria	Observable	Patient with Grade 4 neutropenia lasting >5 days or Grade ≥3 neutropenia with fever but continued on study therapy at same dose administered when DLT occurred.	Source Data Review	
308	Important	Withdrawal Criteria	Observable	Patient with Grade 4 thrombocytopenia lasting >5 days or Grade ≥3 thrombocytopenia with bleeding but continued on study therapy at same dose administered when DLT occurred.	Source Data Review	
309	Important	Withdrawal Criteria	Observable	Patient with any treatment interruption >7 days or >30% of total dose in Cycle 1 due to Aes not related to the underlying disease or concomitant medication but continued on study therapy at same dose administered when DLT occurred.	Source Data Review	
310	Important	Withdrawal Criteria	Observable	Patient with any Grade ≥3 non-hematologic toxicity (excluding Grade 3 nausea or vomiting that lasts <48 hours, Grade 3 fatigue <5 days, Grade 3 HTN in the absence of maximal medical therapy, Grade 3 rash <5 days, Grade 3 electrolyte abnormality that lasts <72 hours and is not clinically complicated) but continued on study therapy at same dose administered when DLT occurred.	Source Data Review	

PD REF ID	Category (DVCAT)	Classification (DVDECOD)	Type of Deviation Observable/ Programmable (Data Driven)	PD (DVTERM	PD Identification Method Options	clPD ?
311	Important	Withdrawal Criteria	Observable	Discontinuation of M8891 is desired or considered necessary by the Investigator and/or the subject (if applicable) due to occurrence of > Grade 2 AEs for more than 6 days but subject not withdrawn from M8891 treatment	Source Data Review	
312	Important	Withdrawal Criteria	Observable	Subject experienced a DLT and was not withdrawn from the trial therapy.	Source Data Review	
313	Important	Withdrawal Criteria	Programmable	Occurrence of pregnancy but subject was not removed from the trial therapy	Off-Line Manual Listing	
400	Important	AE/SAE	Observable	Safety Reports (SAE, IND) not reported to IRB as required.	Source Data Review	
401	Important	AE/SAE	Observable	Safety Reports (SAE, IND) not reported to EMD-GPS within 24 hours of event.	Source Data Review	
402	Important	AE/SAE	Observable	Pregnancies considered by the Investigator to be related to trial treatment resulting from a drug interaction with a contraceptive medication are not reported as an AEs.	Source Data Review	
500	Important	Visit Schedule	Programmable	Missing data for Physical Examination.	On-Line Check Off-Line Manual Listing	
501	Important	Visit Schedule	Programmable	Missing data for Vital signs.	Off-Line Manual Listing	
503	Important	Visit Schedule	Programmable	Missing data for pregnancy testing for Female subjects of Childbearing potential.	On-Line Check	
505	Important	Visit Schedule	Programmable	Missing data for Pharmacokinetic Blood sampling.	On-Line Check	Yes
531	Important	Visit Schedule	Programmable	ECG assessment is missing for "/timepoint/, /record #/".	Off-Line Manual Listing	

PD REF ID	Category (DVCAT)	Classification (DVDECOD)	Type of Deviation Observable/ Programmable (Data Driven)	PD (DVTERM	PD Identification Method Options	clPD ?
554	Important	Visit Schedule	Observable	A minimum of 7 days laps not achieved between dosing of subject 1 and subsequent subject in each cohort without SMC approval.	Source Data Review	
547	Important	Visit Schedule	Observable	Screening assessment dates are not within 28 Days prior to informed consent for a subject that has been re-screened.	Source Data Review	
600	Important	IP Admin/Study Treat	Observable	Subject received / has taken wrong dose / treatment schedule of M8891 different from the planned for the subject.	Source Data Review	
601	Important	IP Admin/Study Treat	Observable	Noncompliance that is deemed by the Investigator or the Sponsor to compromise the patient's safety or trial integrity" but subject was not withdrawn	Source Data Review	
548	Important	Visit Schedule	Programmable	Missing data for safety (hematology, biochemistry, coagulation).	Off-Line Manual Listing	
700	Important	Disallowed Medications	Observable	Subjects taken potent combined inhibitors of CYP3A4, CYP2C9 and CYP2C19 (i.e. fluconazole and voriconazole) during treatment of M8891.	Source Data Review	Yes
549	Important	Visit Schedule	Programmable	End of Treatment Visit not performed.	Off-Line Manual Listing	
604	Important	IP Admin/Study Treat	Programmable	>4 missed administration in Cycle 1 and subject did not have a DLT	Off-Line Manual Listing	Yes
219	Important	Inc/Excl Criteria	Observable	Subjects is not refractory to or intolerant of existing cancer therapy(ies) known to provide clinical benefit	Source Data Review	

PD REF ID	Category (DVCAT)	Classification (DVDECOD)	Type of Deviation Observable/ Programmable (Data Driven)	PD (DVTERM	PD Identification Method Options	clPD ?
220	Important	Inc/Excl Criteria	Observable	Protocol version 1.0: Presence of deep vein thrombosis based on screening lower extremity Doppler ultrasonography, or elevated D-dimer (> 0.5µg/mL) but subject enrolled in the study.	Source Data Review	
224	Important	Inc/Excl Criteria	Observable	Protocol version 2.0: Presence of deep vein thrombosis based on screening lower extremity Doppler ultrasonography but subject enrolled in the study.	Source Data Review	
221	Important	Inc/Excl Criteria	Observable	Missing data for complete neurologic examination	Source Data Review	
553	Important	Visit Schedule	Observable	A whole visit at the site is not performed	Source Data Review	

Integrated Analysis Plan for end of monotherapy dose escalation - Main Text Body

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Business Approval	PPD
PPD	Business Approval	PPD
PPD	Business Approval	PPD
PPD	Business Approval	PPD
PPD	Technical Approval	PPD
PPD	Technical Approval	PPD
PPD	Technical Approval	PPD