Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS200770-0001
Title	A Phase I, Open-label, Uncontrolled, Multicenter, Dose--escalation Study of M3541 in Combination with Palliative Radiotherapy in Subjects with Solid Tumors
Trial Phase	I
Investigational Medicinal Product(s)	M3541
Clinical Trial Protocol Version	04 March 2019 / Version 5.0 Amendment 4.0

Integrated Analysis Plan Author

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

Integrated Analysis Plan Date and Version 04 October 2019 / Version 2.0

Integrated Analysis Plan Reviewers

Function	**Name**
Biostatistics, PPD	PPD
Drug Safety, Merck	PPD
Medical Responsible, Merck	PPD
Clinical Pharmacology, Merck	PPD
PPD , Merck	PPD
PPD Merck	PPD
PPD	PPD

Signature Page

Integrated Analysis Plan: MS200770-0001

A Phase I, Open-label, Uncontrolled, Multicenter, Dose-escalation Study of M3541 in Combination with Palliative Radiotherapy in Subjects with Solid Tumors

Merck responsible	Date	Signature
PPD, Coordinating Author	Via ELDORADO approval process	

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
ATM	Ataxia-Telangiectasia Mutated
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
$AUC_{extra\%}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{0-\infty}$ /Dose	Dose normalized $AUC_{0-\infty}$
AUC_{0-6h}	Area under the concentration-time curve from time zero to the 6 -hour post dose
AUC_{0-t}	Area under the concentration-time curve from time zero to the last quantifiable sampling time point
AUC_{0-t} /Dose	Dose normalized AUC_{0-t}
$AUC_{0-\tau}$	Area under the concentration-time curve during a dosing interval
BMK	Biomarker Analysis Set
BOR	Best Overall Response
BORc	Confirmed Best Overall Response
BPI-SF	Brief Pain Inventory – Short Form
C_{avg}	Average plasma concentration
CI	Confidence Interval
$CL/_f$	Oral clearance
$CL_{SS/f}$	Oral clearance at steady state (extravascular)
C_{max}	Maximum observed plasma concentration
C_{max}/Dose	Dose normalized C_{max}
C_{min}	Minimum observed plasma concentration
C_{trough}	Predose plasma concentration
$C_{2\ 25h}$	Concentration at 2.25 hours post dose
C_0	Initial concentration at time zero
CR	Complete Response
CSR	Clinical Study Report
CTC	Common Terminology Criteria

CTMS	Clinical Trial Management System
CTP	Clinical Trial Protocol
CV	Coefficient of variation
DLT	Dose Limiting Toxicity
EAS	Enrolled Analysis Set
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
FD	Fraction Day
GCP	Good Clinical Practice
GeoCV	Geometric coefficient of variation
GeoMean	Geometric mean
HIV	Human Immunodeficiency Virus
IAP	Integrated Analysis Plan
ICF	Informed Consent Form
ICH	International Council for Harmonization
ID	Identification
IMP	Investigational Medicinal Product
λ_z	Terminal elimination rate constant
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{ss}	Mean residence time at steady state
MTD	Maximum Tolerated Dose
N	Number of non-missing observations
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not Evaluable
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PKS	Pharmacokinetics Analysis Set
PR	Partial Response

PT	Preferred Term
PTD	Post-treatment day
QD	Once daily
QPD	Quantitative Pharmacology and Drug Disposition
QTcF	QT interval corrected based on Fridericia's formula
$R_{acc(AUC0-6h)}$	Accumulation ratio for the area under the concentration-time curve
$R_{acc(Cmax)}$	Accumulation ratio for maximum concentration
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II Dose
Rsq	Goodness of fit statistic for calculation of λ_z
RT	Radiotherapy
SDTM	Study Data Tabulation Model
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Stable Disease
SMC	Safety Monitoring Committee
SoLD	Sum of Lesion Diameter
SOC	System Organ Class
$t_{1/2}$	Apparent terminal half-life
TEAE	Treatment Emergent Adverse Event
t_{max}	Time to reach maximum concentration
t_{min}	Time to reach minimum observed concentration
ULOQ	Upper Limit of Quantification
ULN	Upper Limit of Normal
V_{ss}/f	Apparent volume of distribution at steady state (extravascular)
V_Z/f	Apparent volume of distribution during the terminal phase (extravascular)
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	01Dec2017	PPD	Not applicable since first version.
2.0	04Oct2019	PPD	• List of approvers and reviewers was updated • Few objectives and endpoints updated after new protocol amendment • Note on the fact that no subjects in intermittent M3541 schedules will be enrolled and hence no changes to the analysis • Clarification on DLT and biomarker analysis set definition • Clarification on precision of summary statistics used • Update of DLT evaluation period definition after new protocol amendment • Definition of time points used for ECG, immune system data and PD data analysis • Categories for exposure presentation updated • Clarification of subjects excluded from tumor analysis added • Details on last known alive date identification added • Laboratory parameters list updated according to data collected at site • Additional spider plot to investigate the effect of M3541 on selected laboratory parameters added • Details on ECG and biomarker analyses added Few typos corrected

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for all analyses of data collected for protocol MS200770-0001. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

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

5 Objectives and Endpoints

Table 1: Objectives and endpoints

	Objective	Endpoint	IAP section
Primary Objective	To determine the MTD and a RP2D for M3541 in combination with fractionated palliative RT	**Primary Endpoint:**	
		Occurrence of DLTs	15.1
Secondary Objective	To evaluate the safety profile and tolerability of M3541 in combination with fractionated palliative RT	**Secondary Endpoints:**	
		AE	15.2 and 15.3
		Lab values	15.4
		Vital sign	15.5
		ECG	15.7
	To explore the antitumor activity of M3541 in combination with fractionated palliative RT	**Secondary Endpoints**:	
		BOR	14.1
		PFS	14.2
	To assess the PK of M3541 in combination with fractionated palliative RT.	**Secondary Endpoints:**	
		Pharmacokinetics parameters	16.1
Exploratory Objective	To explore the antitumor activity of M3541 in combination with fractionated palliative RT	**Exploratory Endpoints:**	
		SoLD of the irradiated lesions	14.3
		Location of disease progression	14.4

	Objective	Endpoint	IAP section
	To assess treatment-related changes in pharmacodynamic markers of M3541 in combination with fractionated palliative RT	Pharmacodynamic markers concentration in blood	16.2
	CCI [redacted]		
	To explore the potential impact on the immune system of M3541 in combination with palliative RT	Immune system biomarkers concentration in blood	16.2
	CCI [redacted]		

6 Overview of Planned Analyses

Source of data is the electronic Case Report Form (eCRF). The data cut-off will be applied to SDTM datasets. Data collected until clinical cut-off dates, as described in Table 2 below, will be used to create ADaM data sets.

Table 2: Summary milestones and cut-off dates

Milestones	Cut-off date
SMC	Last subject of associated cohort has completed the DLT evaluation period
Primary analysis	Last subject in the last cohort has completed the Short-term Safety follow-up period
Final analysis	Last subject has completed one year survival follow-up period

6.1 Safety Monitoring Committee (SMC)

In this trial, the SMC will decide on Dose Limiting Toxicities (DLTs) relevant for the treatment and will be responsible to provide recommendations for dose-escalation / de-escalation decisions (such as adding new cohorts at different previously non-explored dose level) and may decide to enroll additional subjects at a previously explored dose level, which will be considered a new cohort at that dose level. The SMC may recommend to stop the study based on the observed safety profile.

The decision of the SMC will be guided by the result of the Bayesian 2-parameter logistic regression model with overdose control[1-3] provided by the sponsor to the committee.

The overdose control ensures that the risk of using a too toxic dose is limited. Overdose is defined as a toxicity rate of > 35%. For each dose level, the risk of overdose will be calculated, and only dose levels for which this risk is lower than 25% will be considered for suggestion by the model.

The following model is applied:

For a dose d_j

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

The relationship between dose and toxicity rate is described by this 2-parametric logistic model with parameters α and β, using the following parametrization:

- Prior for 1st cohort based on best knowledge
  - (α, β) = (-0.847,-0.279)
  - SD(α) = 1.007, SD(β) = 1.636, Cov(α, β) = 0
- Loss function used for the recommendation of the next dose level
  - [0, 0.2) weighted with 1 (too low)
  - (0.2, 0.35) weighted with 0 (in the right range)
  - (0.35, 0.6) weighted with 1.5 (too high)

- (0.6, 1.0) weighted with 2 (much too high).

- Overdose Control, i.e., risk to use a dose d_j with too high toxicity is limited to 25%:
  - Prob(DLT rate > 35% | d= d_j) < 25%.

A dedicated SAP (Addendum 1) provides complete details on decision criteria and on material used during the meeting.

6.2 Primary analysis

The primary analysis will be performed once all subjects have completed the Short-term Safety follow-up period.

Cut-off date:

The cut-off for the primary analysis will be triggered by the completion of the Short-term Safety follow-up period (Post-treatment Day [PTD] 30)by the last subject in the last cohort. For the primary analysis, all trial data will be entered in the clinical database and all data queries will be resolved for all subjects until cut-off date. Issues which cannot be resolved will be clearly documented.

6.3 Final analysis

Final analyses will be run when last subject has completed one year survival follow-up or discontinued from the trial with all data in-house, all data queries resolved, and the database locked. For final analysis the same analyses as planned for primary analysis will be provided based on the above data cut off.

Cut-off date:

The cut-off for the final analysis will be triggered by the completion of the one year survival follow-up period by the last subject in the last cohort.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

Summaries of pain- and interference related quality of life data are included but these are not explicitly mentioned in the protocol.

Statistical analyses and reporting of data for intermittent M3541 schedules (thrice and twice weekly) mentioned in the protocol are not described in this document since those were never explored in the trial.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

All important protocol deviations will be documented in SDTM datasets whether identified through site monitoring, medical review or programming and will be reported in the CSR.

8.2 Definition of Analysis Sets and Subgroups

Screened Analysis Set (SCR):

The SCR will include all the subjects who signed the informed consent form (ICF).

Safety Analysis Set (SAF):

The SAF will include all subjects who received at least 1 dose of M3541. Subjects will be analyzed according to the actual treatment (i.e., dose level as collected in the "Cohort" eCRF page) they received.

Dose Limiting Toxicity Analysis Set (DLT):

The DLT analysis set will include all subjects who received at least 1 dose of M3541 and meet at least 1 of the following criteria:

- Experienced at least 1 DLT during the DLT evaluation period as defined in section 9, regardless of the number of doses of M3541 administered
- Received at least 80% of planned dose of each treatment, i.e. 8 fractions of RT and 8 of 10 M3541 administrations, and completed the DLT evaluation period (i.e. provided at least one safety result on or after the end date of the period, as defined at section 9).

Pharmacokinetics Analysis Set (PKS):

The PKS analysis set will consist of all subjects who received at least one dose of M3541, and provided at least one quantifiable postdose concentration.
Postdose data for a fraction day from subjects with a vomiting episode within 2 times of t_{max} time of M3541 (vomiting at around 4 hours postdose) or any other significant event affecting PK may be excluded from final PK analysis on a case-by-case basis. Subjects will be analyzed according to the actual treatment (i.e., dose level as collected in the "Cohort" eCRF page) they received. All PK analyses will be based on this analysis set.

Biomarker Analysis Set (BMK):

The Biomarker (BMK) analysis set will consist of all subjects who received at least 1 dose of M3541 and have provided a quantifiable blood sample for pharmacodynamic/biomarker analysis prior to any M3541 treatment and at least 1 quantifiable post-treatment blood sample. Subjects will be analyzed according to the actual treatment (i.e., dose level as collected in the "Cohort"

eCRF page) they receive. All pharmacodynamics and biomarker analyses will be based on this analysis set.

Table 3: Summary of analyses and associated analysis set

Analyses	SCR	SAF	DLT	BMK	PKS
Dispositions and deaths	✓				
Baseline Assessments		✓			
Past and Concomitant Therapies		✓			
Compliance and Exposure		✓			
Primary endpoint: DLTs			✓		
Efficacy endpoints		✓			
Safety and tolerability		✓			
Biomarkers and pharmacodynamics				✓	
Pharmacokinetics					✓

9 General Specifications for Data Analyses

Posterior distribution and recommended next dose level will be calculated using EAST Version 6.4 or higher.

Non-compartmental computation of PK parameters will be performed using Phoenix WinNonlin Version 6.4, or higher.

All other statistical analyses will be performed using SAS Version 9.2 or higher, or R, Version 3.0.2 or higher.

Pharmacokinetic figures will be prepared using SigmaPlot Version 12.5 or higher or SAS Version 9.2 or higher.

Data handling after cut-off date for SMC and primary analyses:

Data after cut-off for SMC and primary analyses do not undergo the cleaning process. Hence data obtained after the cut-off will not be displayed in listings or used for summary statistics (e.g. laboratory values of samples taken after data cut-off, AE with onset date after data cut-off, etc.).

Presentation of continuous and qualitative variables:

Data will be presented by dose level and overall unless specified otherwise. The dose level will be defined by the planned dose of the corresponding cohort. If several cohorts have same dose level, they will be pooled together for all summary outputs.

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

- Number and percentage of subjects, number and percentage of subjects with missing values

- Mean, 95% confidence intervals (CI), as appropriate
- Standard deviation (SD)
- Median
- Q1, and Q3
- Minimum (Min), and maximum (Max)

Mean, median, Q1, Q3, Min, and Max will have the same precision as collected in SDTM datasets for non-derived data. Standard deviation will be presented with 1 digit more than the mean. For derived data, the number of decimal digits will be defined on a case-by-case basis.

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

Qualitative variables will be summarized by frequencies 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.

If there are no missing values, this should be indicated by a 0 (0.0).

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

Presentation of pharmacokinetic/biomarker concentration data

Pharmacokinetic/biomarker concentration data will be descriptively summarized per dose level using: number of non-missing observations (N), arithmetic mean (Mean), SD, coefficient of variation (CV%), Min, median, and Max.

Descriptive statistics of PK/biomarker 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/biomarker concentration data:

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

Presentation of pharmacokinetic parameter data

Pharmacokinetic parameter data will be descriptively summarized per dose level using: N, Mean, SD, CV%, Min, Median, Max, geometric mean (GeoMean), and the geometric coefficient of

variation (GeoCV) and the 95% CI for the GeoMean (lower CILCI 95% GeoMean, Upper CIGM, UCI 95% GeoMean).GM)

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

Definition of baseline:

The last non-missing measurement prior to first administration of M3541 will be used as the baseline measurement.

Definition of treatment day:

Treatment day 1 is defined as the date of first administration of M3541, the day before is defined as Treatment day –1 (no Treatment day 0 is defined).

Definition of fraction day:

Fraction days are defined as days of radiotherapy administration.

Definition of on-treatment period for safety analyses:

On-treatment period for safety analyses will be the time from the Treatment day 1 until the last M3541 administration date + 30 days (PTD 30), the earliest date of subsequent anticancer drug therapy minus 1 day or the clinical cut-off date (if the treatment is still ongoing), whichever occurs first.

Subsequent anticancer drug therapy date will be based on "Anti-cancer treatment after discontinuation", "Radiotherapy after discontinuation", and "Surgery after discontinuation" eCRF pages.

Definition of duration:

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

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

Definition of DLT evaluation period:

<u>For all subjects enrolled before protocol v5.0 (amendment 4.0):</u>

The DLT evaluation period will start on the day of the first administration of M3541 / RT and will end 23 days after the last administration of M3541 / RT (2-day M3541 / RT holiday after the last fraction day (FD) plus a 3-week DLT follow-up period that starts on the third day after the last administration of M3541 / RT). The end date of the period will be calculated as follows:

Date of last administration of M3541/RT + 23 days

The DLT evaluation period will be 5 weeks in duration, unless M3541 / RT has been interrupted for up to 3 days.

For all subjects enrolled under or after protocol v5.0 (amendment 4.0):

The DLT evaluation period will start on the day of the first administration of M3541 / RT and will end 14 days after the last administration of M3541 / RT (2-week radiotherapy treatment period plus a 2-week DLT follow-up period that starts on the day after the last administration of M3541 / RT). The end date of the period will be calculated as follows:

Date of last administration of M3541/RT + 14 days

The DLT evaluation period will be 4 weeks in duration, unless M3541 / RT has been interrupted and given over a period exceeding 2 weeks.

Definition of analysis time points

Actual time elapsed from first M3541 administration in hours will be derived as:

$$Actual\ time\ (hours) = \frac{Datetime\ of\ interest - Datetime\ first\ M3541\ dose}{3600}$$

Nominal time elapsed from first M3541 administration in hours will be derived according to the following rules:

- For results collected at screening, Nominal time = -1
- For results collected from fraction day 1 to fraction day 5:

$$Nominal\ time\text{Nominal time} = (X - 1) * 24 + Y$$

- For results collected from fraction day 6 to fraction day 10:

$$Nominal\ time\text{Nominal time} = (X + 1) * 24 + Y$$

With X = fraction day and Y = number of hours elapsed from M3541 administration on X. Y = 0 for predose samples.

Of note, the nominal time will not be derived for unscheduled samples.

The time points at which assessments are expected are reported below (distinguishing among subjects enrolled before protocol v5.0 (EARLY) and under it (LATE)):

Table 4: Nominal time points for ECG, pharmacodynamics and immune system sampling

X	Y	Nominal Time from first M3541 dose (in hours)	ECG		PD		IM	
			EARLY	LATE	EARLY	LATE	EARLY	LATE
SCREENING	-	-1	X					
FRACTION DAY 1	Predose	0	X	X	X	X	X	X
FRACTION DAY 1	0.5 hour postdose	0.5	X	X				
FRACTION DAY 1	1 hour postdose	1	X	X	X	X		
FRACTION DAY 1	1.5 hours postdose	1.5	X	X				
FRACTION DAY 1	2.25 hours postdose	2.25	X	X				
FRACTION DAY 1	3 hours postdose	3	X	X	X	X		
FRACTION DAY 1	4 hours postdose	4	X	X				
FRACTION DAY 1	6 hours postdose	6	X	X				
FRACTION DAY 1	8 hours postdose	8	X	X				
FRACTION DAY 1	12 hours postdose	12	X					
FRACTION DAY 2	Predose	24	X	X	X	X		
FRACTION DAY 2	2.25 hours postdose	26.25	X	X				
FRACTION DAY 3	Predose	48	X					
FRACTION DAY 3	2.25 hours postdose	50.25	X					
FRACTION DAY 4	Predose	72	X			X		
FRACTION DAY 4	2.25 hours postdose	74.25	X					
FRACTION DAY 5	Predose	96	X	X				
FRACTION DAY 5	2.25 hours postdose	98.25	X	X				
FRACTION DAY 6	Predose	168	X	X	X	X	X	X
FRACTION DAY 6	1 hour postdose	169			X	X		
FRACTION DAY 6	2.25 hours postdose	170.25	X	X				
FRACTION DAY 6	3 hours postdose	171			X	X		
FRACTION DAY 7	Predose	192		X		X		
FRACTION DAY 7	2.25 hours postdose	194.25		X				
FRACTION DAY 9	Predose	240	X		X	X	X	X

X	Y	Nominal Time from first M3541 dose (in hours)	ECG		PD		IM	
			EARLY	LATE	EARLY	LATE	EARLY	LATE
FRACTION DAY 9	0.5 hour postdose	240.5	X					
FRACTION DAY 9	1 hour postdose	241	X		X			
FRACTION DAY 9	1.5 hours postdose	241.5	X					
FRACTION DAY 9	2.25 hours postdose	242.25	X					
FRACTION DAY 9	3 hours postdose	243	X		X			
FRACTION DAY 9	4 hours postdose	244	X					
FRACTION DAY 9	6 hours postdose	246	X					
FRACTION DAY 10	Predose	264		X				
FRACTION DAY 10	0.5 hour postdose	264.5		X				
FRACTION DAY 10	1 hour postdose	265		X				
FRACTION DAY 10	1.5 hours postdose	265.5		X				
FRACTION DAY 10	2.25 hours postdose	266.25		X				
FRACTION DAY 10	3 hours postdose	267		X				
FRACTION DAY 10	4 hours postdose	268		X				
FRACTION DAY 10	6 hours postdose	270		X				
FRACTION DAY 9	72 hours postdose	312	X					
FRACTION DAY 10	72 hours postdose	336		X				
FRACTION DAY 9	240 hours postdose	480	X					
FRACTION DAY 10	240 hours postdose	504		X				

Table 4. ECG = Electrocardiogram, PD = Pharmacodynamic samples, IM = Immune system samples

Conversion factors:

The following conversion factors will be used:

- Age: to convert days into months or years: *1 month = 30.4375 days, 1 year = 365.25 days.*
- Height: to convert inches in centimeters: *1 inch = 2.54 cm*

- Weight: to convert pounds in kilograms: *1 lb. = 0.453592 kg*

Handling of missing data:

As a general rule, missing data will not be replaced.

For identification of treatment emergent AE, incomplete dates will be handled as follows:

- In case the onset date is completely missing or the onset is in the same year (if the onset year is available only) or the onset is in the same month and year (if the day is missing) as start of trial treatment then the onset date will be replaced by the minimum of start trial treatment and AE resolution date.
- In all other cases, the missing onset day or 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. If stop date of AE is after date of cut-off outcome of AE is ongoing at cut-off.
- In all other cases (i.e., if day and month are missing or if the stop date is completely missing), the incomplete stop date will not be imputed.

In data listings, the documented date as given in the eCRF will be reported (e.g. __May2013 in case of day missing, but month and year available).

For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Rules presented in Table 5 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

Table 5: Stopping rules for medication/procedure end dates

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

UNK = Unknown

Table 6: Rules to define previous and/or concomitant medications

Start date of medication/procedure			Stopping rule (see Table 4)	Medication/procedure
Day	**Month**	**Year**		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	<= Treatment start (year)	Before treatment start	Previous
UNK	UNK	<= Treatment start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Treatment start (year) and <= Treatment end + 30 days (year)	After treatment start	Concomitant
UNK	<= Treatment start (month and year)		Before treatment start	Previous
UNK	<= Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and <= Treatment end + 30 days (month and year)		After treatment start	Concomitant
<= Treatment start (date)			Before treatment start	Previous
<= Treatment start (date)			After treatment start	Previous and concomitant
> Treatment start (date) and <= Treatment end + 30 days (date)			After treatment start	Concomitant

UNK = Unknown

Handling of unscheduled and early termination visit assessments:

As a general rule, unscheduled assessments will always be included in the analysis.

Early termination visit assessments will be analyzed according to the treatment day of collection, as defined above.

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

All tables and listings related to disposition of subjects and discontinuations will be generated using SCR analysis set.

A primary table of Subject Disposition will provide the overall summary of the analysis sets by dose level and overall:

- Number of screened subjects*
- Number of subjects discontinued prior treatment start (overall and by reason)*
- Number of subjects who continued beyond screening
- Number of subjects who completed treatment with M3541 ("M3541 Termination" eCRF page)
- Number of subjects who completed treatment with RT ("Radiotherapy Termination" eCRF page)
- Number of subjects discontinued from M3541 overall and by reason ("M3541 Termination" eCRF page)
- Number of subjects discontinued from RT overall and by reason ("Radiotherapy Termination" eCRF page)
- Number of subjects who completed the trial ("Study Termination" eCRF page).
- Number of subjects discontinued from trial overall and by reason ("Study Termination" eCRF page).

A second summary table on analysis sets will be generated:

- Number of subjects in Screened Analysis Set*
- Number of subjects in DLT Analysis Set (Overall and per dose level)

- Number of subjects in SAF Analysis Set (Overall and per dose level)
- Number of subjects in PKS Analysis Set (Overall and per dose level)
- Number of subjects in BMK Analysis Set (Overall and per dose level)

*These will be reported in the overall column only.

A third summary table will display the number of subjects overall, in each country and in each site (per analysis set).

A listing of subject disposition will include the following information (as applicable): dose level, subject identification number (ID), date and version of ICF, protocol version, reason for screen failure, date of first and last dose of M3541 and RT, SAF analysis set, DLT analysis set, BMK analysis set and PKS analysis set.

A second listing will include the following trial discontinuation information: dose level, subject ID, end of trial status (completed, ongoing, discontinued), the reason for trial discontinuation, the last follow-up date on trial, and the date of first and last dose of M3541 and RT.

A third listing will include the following M3541 and RT discontinuation information: dose level, subject ID, end of treatment status (completed, ongoing, discontinued), the reason for M3541 and/or RT discontinuation, and the date of first and last dose of M3541 and RT.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

Listings of protocol deviations will be generated on the safety population by displaying following information:

- Listing of important protocol deviations: dose level, subject ID, deviation type and description as displayed in CTMS.

- Listing of deviations from treatment compliance (subjects with less than 80% of compliance): dose level, subject ID, compliance with M3541 (%), compliance with RT (%), first and last dose date for both M3541 and radiotherapy. Compliance will be derived using the algorithm reported in section 13.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

For subjects and data excluded from DLT, PKS, and BMK analysis sets, the reasons for exclusion will be listed.

11 Demographics and Other Baseline Characteristics

Population: SAF Analysis Set

All demographics and baseline characteristics will be listed and summarized by dose level and overall using SAF analysis set.

11.1 Demographics

The following demographic characteristics will be summarized using the information from the "Demographics" eCRF page.

- Sex: male, female
- Race: Black of African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, White, Other, Not collected at this site
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Age (years): summary statistics

Specifications for computation:

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

A listing of demographic data will include the following information: dose level, subject ID, sex, race, ethnicity, date of birth and age in years.

11.2 Medical History

Population: SAF analysis set

The medical history will be summarized from the "Medical History" eCRF page, using the most recent available version of MedDRA (version 20.0 or later) preferred term (PT) as event category and MedDRA system organ class (SOC) body term as body system category.

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

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

11.3 Other Baseline Characteristics

Population: SAF analysis set

The following baseline characteristics will be summarized using the information from the "Vital Signs" and "ECOG performance status" eCRF pages:

- Height (cm)
- Weight (kg)
- ECOG Performance status

A listing of baseline characteristics will include the following information: dose level, subject ID, height in cm, weight in kg, ECOG performance status, results for HIV, Hepatitis B and Hepatitis C virus test with methods used (from "Serology" eCRF page).

Additionally a listing of disease history will be provided including all relevant data from the "Disease History" eCRF page.

12 Previous or Concomitant Medications/Procedures

Population: SAF Analysis Set

12.1 Prior Anti-Cancer Treatments and procedures

The prior anti-cancer treatments and procedures are collected under the "Prior anti-cancer drug therapies", "Prior anti-cancer surgeries", and "Prior anti-cancer radiotherapy" eCRF pages.

The following listings of prior anti-cancer treatments and procedures will be provided:

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

These will include the subject ID, dose level and all the relevant collected data fields on the corresponding eCRF pages.

12.2 Previous Medications

Previous medications are medications, other than trial medications, which started before first administration of trial treatment.

Previous medications will be summarized from the "Concomitant medications" eCRF page. The Anatomical Therapeutic Chemical (ATC)-2nd level and PT will be tabulated as given from the

World Health Organization Drug Dictionary (most recent available version of WHO-DD, Sept. 2016 or later). In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting.

In case the date values will not allow to unequivocally allocate a medication to previous medication, the approach described at section 9 will be followed.

Previous medications will also be listed. The listing will include: subject ID, dose level and all corresponding collected data fields on the corresponding eCRF page.

12.3 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 M3541 treatment for each subject) or within 30 days after last dose of M3541 treatment (PTD 30). Medications started after 30 days will be presented and flagged in listings but will not be taken into account in summary tables. Medications started on treatment day 1 will only be considered concomitant.

Concomitant medications will be summarized from the "Concomitant medications" eCRF page. The ATC-2nd level and PT will be tabulated as given from the most recent available version of WHO-DD, Sept. 2016 or later. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting.

In case the date values will not allow to unequivocally allocate a medication to concomitant medication, the approach described at section 9 will be followed.

Concomitant medications will also be listed. The listing will include: dose level, subject ID and all corresponding collected data fields on the corresponding eCRF page.

12.4 Concomitant Procedures

Concomitant procedures are procedures which are undertaken any time on-trial. These will be listed according to the CRF page "Concomitant Procedures".

In case the date values will not allow to unequivocally allocate a procedure to concomitant procedure, the approach described at section 9 will be followed.

The listing will include: dose level, subject ID and all corresponding collected data fields on the corresponding eCRF page.

12.5 Pain Therapy

Pain therapy results will be listed according to the CRF page "Pain Therapy". The listing will include: subject ID, dose level, date and fraction day, medication change and flag for new therapy given.

12.6 Anti-cancer, radiotherapy and surgery post-treatment

Anti-cancer, radiotherapy and surgery post-treatment will be listed according to "Anti-cancer treatment after discontinuation", "Radiotherapy after discontinuation" and "Surgery after discontinuation" eCRF pages. The 3 listings will include: subject ID, dose level and all corresponding collected data fields on the corresponding eCRF page.

13 Treatment Compliance and Exposure

Population: SAF Analysis Set

Treatment compliance and exposure will be listed and summarized by dose level and overall using SAF analysis set.

All dosing calculations and summaries will be based on "M3541 Administration" and "Radiotherapy Administration" eCRF pages.

Subjects should receive treatment with M3541 at a starting dose of 50 mg QD, which should be given 1 hour and 45 minutes (+/- 15 minutes) before each RT fraction (3 Gy) for up to 10 fractions. Based on nonclinical assumptions, the pre-planned dose levels are 50, 100, 200, 300, 500, and 800 mg; however, the number of dose levels and the actual dose to be explored in each subsequent cohort remains to be determined.

Number of days of therapy

The number of fraction days of Radiotherapy treatment and the number of days of M3541 therapy will be summarized by dose level.

Additionally, number and percentage of subjects in the following exposure categories will be reported by dose level:

- [1 day – 4 days]
- [5 days - 7 days]
- [8 days - 9 days]
- 10 days
- > 10 days

Cumulative dose

The cumulative dose (mg) of M3541 will be calculated as the sum of the total daily doses that the subject received.

The cumulative dose (Gy) of RT will be calculated as the sum of the total daily doses that the subject received.

Compliance with treatment

The compliance with the treatment is defined as:

- For M3541:

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{cumulative dose (mg)}}{10 * \text{planned daily dose (mg)}} * 100\right)$$

- For RT:

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{cumulative dose (y)}}{10 * \text{planned daily dose (y)}} * 100\right)$$

The compliance with the treatments will display using the following categories:

- > 100%
- 100%
- [80% - 100%[%[
- [65% - 80% [
- [50% - 65% [
- < 50%

The following summary tables will be provided for M3541 and RT administrations by dose level:

- Number of fraction days for Radiotherapy and number of days of M3541 therapy
- Cumulative dose (mg for M3541 and Gy for RT) and relative dose intensity

The listing of exposure assessments for each M3541 and RT administration (including e.g. start and stop date and time of administration, dose, frequency, change in dose) will be provided by subject as recorded from the related eCRF pages.

14 Efficacy Analyses

Efficacy endpoints include Best Overall Response (BOR), Progression Free Survival (PFS), Sum of the Lesion Diameter (SoLD) for irradiated lesions, and location of disease progression.

14.1 Best Overall Response

Population: SAF Analysis Set

The tumor response assessment will be based on "Assessment of disease based on imaging (according to RECIST 1.1)" eCRF page.

The Best Overall Response (BOR) is defined as the best response across all time points evaluated per RECIST 1.1, assessed locally by the investigator every 6 weeks (starting on PTD 42) for the

first 6 months, then every 12 weeks thereafter until determination of Progressive Disease (PD), using the investigator-reported overall response per time point and excluding assessments after tumor surgery.

The order to obtain the BOR is the following: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE). 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.

To be considered the best response, SD must also meet the minimum 6 weeks (-7 days) from first day of treatment. If the minimum time is not met, the subject's best overall response depends on the subsequent assessments. For example, a subject who has SD at the first assessment, PD at the second assessment and does not meet the minimum duration for SD, will have a best overall response of PD. The same subject lost to follow-up after the first SD assessment would be considered NE for BOR.

If a subject has missing baseline tumor assessment and/or no tumor assessment on-treatment, BOR will be NE.

The confirmed BOR (BORc) will be also analyzed. In this case, CR and PR need to be confirmed at a subsequent assessment, at least 4 weeks after initial overall response assessment of CR/PR.

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

The Objective Response Rate (ORR) is defined as the proportion of subjects with BOR of PR or CR, and it will be tabulated for both confirmed and unconfirmed BOR by dose level, with 95% CI, calculated using the Clopper-Pearson method.

A spider graph will display the percentage change from baseline in tumor size, defined as sum of lesion diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions (as reported in the "Sum of diameters (according to RECIST 1.1)" eCRF page), against the treatment day for each subject per dose level. Subjects with no baseline tumor assessment or without any post-baseline tumor assessment will not be included.

In addition, waterfall plots with all subjects from all cohorts will be provided. Bar height will represent the best percentage change in tumor size from baseline per subject. The confirmed BOR will also be presented as an annotation on each vertical bar. Subjects with no baseline tumor assessment or without any post-baseline tumor assessment will not be included .

The listings of tumor assessments (including e.g. lesion number and site, type of lesion, imaging date and relative day, assessment method, size in mm) and tumor responses (including e.g. sum of diameter of target lesions, response for each lesion class, overall response) will be provided by subject as recorded from the "Target Lesions", "Sum of Diameters", "Non-Target Lesions", "Non-Target Lesions Summary", "New Lesions" and "Assessment of disease based on imaging" eCRF pages. Additionally, both will include: dose level, first/last M3541 dosing date, BOR (confirmed and unconfirmed), site of primary tumor and TNM status at study entry.

Finally, a listing reporting information on irradiated lesion location will be populated using information from "Irradiated Lesions Location" and "Radiotherapy" eCRF pages.

14.2 Progression Free Survival Time

Population: SAF Analysis Set

Progression Free Survival (PFS) time is defined as the time (in months) from first administration of trial treatment until the first date of PD or death due to any cause.

It will be based on "Assessment of disease based on imaging (according to RECIST 1.1)", "Survival follow-up / Progression disease", "Subject Status / Survival Follow-up", "Anti-cancer treatment after discontinuation", "Radiotherapy after discontinuation", "Surgery after discontinuation" and "Death" eCRF pages.

PFS will be censored in the following scenarios:

- Subjects who do not experience an event (PD or death) will be right-censored on the date of the last evaluable (non missing and non "Not Evaluable") tumor assessment.
- If an event (progression or death without previously documented PD) is observed after more than 2 missed study visits (using visit days as planned in the protocol for calculation) from last tumor assessment, the patient will be right-censored at the date of the last evaluable tumor assessment.
- Subjects who start new anti-cancer treatment prior to an event will be censored on the date of the last evaluable tumor assessment before anti-cancer therapy is given.
- Subjects who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the date of first dose unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

PFS = (date of PD or death/censoring – date of the first dose + 1)/ 30.4375(months).

The date of PFS event / censoring will be defined in Table 7.

Table 7 Progression-free Survival Event / Censoring

PFS Event Status		Censoring	Date of event / censoring
Progressed or died	Before any planned tumor assessment or within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD	Event	Minimum(Date of PD, Date of death)
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first dose, whatever is later

PFS Event Status	Censoring	Date of event / censoring
Neither progressed nor died	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first dose, whatever is later

PFS: progression-free survival, CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease.

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

For subjects alive, the last known alive date will be used to determine the end of follow-up and it will be derived using the following dates:

- Last known alive date collected in the "Subject Status / Survival Follow-Up" eCRF page (SSSTDTC variable from SS SDTM domain to be used)
- All patient assessment dates:
  - Laboratory assessments using information from "Serology", "Hematology", "Biochemistry", "Coagulation", "Urinalysis", "Microscopic analysis" and "Pregnancy test" eCRF pages (LBDTC variable from LB SDTM domain to be used)
  - Vital signs using information from "Vital signs" eCRF page (VSDTC variable from VS SDTM domain to be used)
  - Performance status using "ECOG Performance status" eCRF page (QSDTC variable from QS SDTM domain to be used)
  - ECG, using information from "Electrocardiogram" eCRF page (EGDTC variable from EG SDTM domain to be used)
  - Tumor assessments using "Tumor assessments" eCRF pages (TRDTC variable from TR SDTM domain to be used)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation using "Anti-cancer treatment after discontinuation", "Radiotherapy after discontinuation" and "Surgery after discontinuation" eCRF pages (CMSTDTC and CMENDTC variable from CM SDTM domain to be used)
- AE start and end dates using "Adverse events" eCRF page (AESTDTC and AEENDTC variables from AE SDTM domain to be used)
- Study treatment administration dates using "M3541 Administration" and "Radiotherapy Administration" eCRF pages (EXSTDTC variable from EX SDTM domain to be used)

A listing will provide the following information on PFS times: dose level, subject ID, date of first and last M3541 administration, date of event/censoring and relative day, event/censoring reason, time to event in months.

An additional listing on survival follow-up will contain all the fields from "Subject Status/Survival Follow-Up" and "Survival Follow-Up/Progression Disease" eCRF pages.

14.3 Sum of Lesion Diameter for Irradiated Lesions

Population: SAF Analysis Set

The sum of lesion diameters (longest for non-nodal lesions, short axis for nodal lesions) for all irradiated lesions will be calculated on the basis of "Tumor assessment (according to RECIST 1.1) - Target lesions" and "Irradiated lesions location" eCRF pages to investigate response of irradiated lesions.

A waterfall plot with all subjects from all cohorts will be provided. Bar height will represent the best percentage change from baseline in sum of diameters, calculated using irradiated lesions only. The confirmed BOR (based on all lesion, i.e. also taking non-irradiated lesions into account) will also be presented as an annotation on each vertical bar. Subjects with no baseline tumor assessment or without any post-baseline tumor assessment will not be included.

In addition, a spider graph to investigate the evolution in time of each target lesion will display the percentage change from baseline in lesion size against the treatment day. One graph per subject will be produced with one curve per lesion, clearly specifying lesion location and distinguishing irradiated from non-irradiated lesions. Subjects with no baseline tumor assessment or without any post-baseline tumor assessment will not be included.

14.4 Location of Disease Progression

Population: SAF Analysis Set

Location of disease progression will be defined as location where tumor size increase has been observed as well as the location of the newly observed lesions.

A listing including all subjects with progressive disease ('Overall Response' = 'Progressive disease' from "Assessment of disease" eCRF page) will be produced. For each subject, all locations for the following lesions will be included:

- Non-target lesions (from "Tumor assessment (according to RECIST 1.1) - Non-Target lesions" eCRF page)
- New lesions (from "Tumor assessment (according to RECIST 1.1) - New lesions" eCRF page)

Lesions within the irradiated field will be flagged. Specifically:

- Irradiated target and non-target lesions will be derived from "Irradiated lesions location" eCRF page;
- Irradiated new lesions will be derived using the free text lesion description reported in the "Tumor assessment (according to RECIST 1.1) - New lesions" eCRF page.

15 Safety Analyses

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

The primary endpoint of this trial is to evaluate the occurrence of DLTs. This endpoint is described in section 15.1.

Secondary safety endpoints are:

- Occurrence of treatment emergent adverse events (TEAEs), grade ≥3 AEs, SAEs, and deaths (graded according to the NCI CTCAE v4.03)
- Results of laboratory tests, physical examination (reported as AEs), vital signs, ECGs including QTcF.

All safety analyses will be performed on SAF Analysis Set and according to the as-treated principle.

15.1 Dose Limiting Toxicities (Primary Endpoint)

The primary endpoint is the occurrence of a DLT for a subject during the DLT evaluation period as defined in section 9.

Recommendations of the next dose level are based on a Bayesian dose escalation design using a two-parametric logistic regression model and final decision is made by the SMC. More details about the analyses to be provided to SMC members are presented in the dedicated SAP (Addendum 1).

15.1.1 Primary Objective: Analyses of Dose Limiting Toxicities

Population: DLT Analysis Set

The DLT information will be based on "Adverse Events" eCRF page with "Is the adverse event a dose limiting toxicity?" = Yes or with "Is the adverse event a dose limiting toxicity upon SMC review" = Yes.

A table with a summary DLTs during the DLT period will be provided for each dose level and overall with:

- Number of subjects with no DLT
- Number of subjects with DLT: one DLT, at least two DLTs

The listing of DLTs will also be provided.

15.2 Adverse Events (AEs)

All TEAEs will be summarized according to the following rules and definitions:

- TEAEs are all the adverse events with onset or worsening dates occurring during the on-treatment period for safety analyses (as defined in section 9)
- Events will be coded using the most recent available MedDRA version (20.0 or later)
- Unless otherwise stated events will be summarized using PT as event category and primary SOC term as Body Organ System category in alphabetical order.
- Events severity will be graded using National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 toxicity grades.
- If an event is reported for a given subject more than once during treatment, the worst severity and the worst relationship to trial treatment will be tabulated.
- Events related to trial treatment are those events with relationship missing, unknown or related to at least one treatment (M3541 or RT).
- Only subject counts will be summarized.
- In case a subject has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.
- For identification of TEAEs, incomplete dates will be handled using the rules presented in section 9.

Additionally, the following events will be listed even when occurred outside the on-treatment period for safety analyses:

- AEs that are reported as related to M3541 and / or RT by the Investigator;
- Serious AEs (SAEs) assessed as related to M3541 and / or RT by the Investigator.

15.2.1 All Adverse Events

Population: SAF analysis set

Frequency tables for AEs captured on the "Adverse Events" eCRF pages will be based on TEAEs (as defined above).

A first overview table of adverse events will be provided by dose level and overall by summarizing the number and percentage of patients with any:

- TEAE
- TEAE related to at least one trial treatment (at least M3541 or RT), M3541 , RT
- Serious TEAE
- Serious TEAE related to at least one trial treatment (at least M3541 or RT), M3541, RT
- TEAE with grade ≥ 3
- TEAE with grade ≥ 4

- TEAE with grade ≥ 3 related to at least one trial treatment (at least M3541 or RT), M3541, RT
- TEAE with grade ≥ 4 related to at least one trial treatment (at least M3541 or RT), M3541, RT
- TEAE leading to death
- TEAE leading to death related to at least one trial treatment (at least M3541 or RT), M3541, RT
- TEAE leading to trial discontinuation

In addition, frequency tables summarizing events in the following categories will be prepared by dose level and overall, SOC and PT:

- TEAE
- TEAE related to at least one trial treatment (at least M3541 or RT),
- TEAE related to M3541
- TEAE related to RT
- Serious TEAE
- Serious TEAE related to at least one trial treatment (at least M3541 or RT)
- Serious TEAE related to M3541
- Serious TEAE related to RT
- TEAE by worst CTCAE grade: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAE related to at least one trial treatment (at least M3541 or RT) by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAE related to M3541 by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAE related to RT by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAE leading to death
- TEAE related to at least one trial treatment (at least M3541 or RT) leading to death
- TEAE related to M3541 leading to death
- TEAE related to RT leading to death

All tables will be sorted by alphabetical order of SOC and PT.

The listing for all AEs (whether treatment-emergent or not) will include all the data fields as collected on the "Adverse Events" eCRF pages with the following items:

- Dose level
- Subject ID
- Age, sex and race
- First and last dose date and number of fraction days for M3541 and RT
- Reported Term with SOC and PT
- Start and end date with their corresponding treatment day
- Treatment Emergent Adverse Events flag (N/Y) and Serious Adverse Events flag (N/Y) with reason for seriousness
- Timing related to M3541/RT (if same day of treatment administration)
- Relationship to M3541/RT
- Causality factors other than study treatments
- DLT flag (Y/N) with source (investigator/SMC)
- CTCAE Grade
- Action taken with M3541, RT and other action taken
- Outcome of AE

Additionally, a listing for all TEAEs leading to death will be included, using the same layout.

CT.gov / EudraCT

Summary tables for non-serious adverse events excluding SAEs applying frequency threshold of 5% will be provided by dose level and overall, SOC and PT in alphabetical order.

15.2.2 Adverse Events Leading to Treatment Discontinuation

Population: SAF analysis set

An overview table of adverse events leading to discontinuation will be provided by dose level and overall by summarizing the number and percentage of patients with any:

- TEAE leading to temporary discontinuation of at least one trial treatment, of both trial treatments, of at least M3541, and of at least RT (corresponding to AEs with action taken = "Drug interrupted" for M3541 and/or "Drug interrupted" for Radiotherapy)

- TEAE leading to permanent discontinuation of at least one trial treatment, of both trial treatments, of at least M3541, and of at least RT (corresponding to AEs with action taken = "Drug withdrawn" for M3541 and/or "Drug withdrawn" for Radiotherapy)

The following frequency tables will be produced for each dose level and overall, by SOC and PT in alphabetical order:

- TEAEs leading to temporary discontinuation of at least one trial treatment
- TEAEs leading to temporary discontinuation of both M3541 and RT
- TEAEs leading to temporary discontinuation of at least M3541
- TEAEs leading to temporary discontinuation of at least RT
- TEAEs leading to permanent discontinuation of at least one trial treatment
- TEAEs leading to permanent discontinuation of both M3541 and RT
- TEAEs leading to permanent discontinuation of at least M3541
- TEAEs leading to permanent discontinuation of at least RT

The listings for all TEAEs leading to temporary and permanent discontinuation will also be included. A layout similar to the one described on section 15.2.1 will be used.

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

15.3.1 Deaths

Population: SAF analysis set

All deaths, deaths within 60 days after first dose, and deaths within 30 days after last dose of trial treatment, as well as reasons for deaths, will be tabulated based on all relevant information available in the "Death" eCRF page:

- Number of deaths
- Number of deaths within 30 days after last dose of M3541
- Number of deaths within 60 days after first dose of M3541
- Primary reason of death

In addition, date and cause of death will be provided in an individual subject data listing together with selected dosing information for M3541 and radiotherapy (date of first / last administration, dose and number of doses).

Subject listing of deaths includes columns for:

- AEs with fatal outcome (list PTs of AEs with outcome=fatal),
- flag for death within 30 days of last dose of M3541
- flag for death within 60 days of first dose of M3541

15.3.2 Serious Adverse Events

Population: SAF analysis set

SAEs will be summarized for each dose level and overall, by SOC and PT in alphabetical order, as described at section 15.2.1.

In addition, subject listings of SAEs will be provided (refer to section 15.2.1 for items to be listed).

15.4 Clinical Laboratory Evaluation

Population: SAF analysis set

Local laboratory values captured on the "Hematology" and "Biochemistry" eCRF pages will be used for summary statistics and shift tables.

Laboratory results (including corresponding normal ranges) will be classified according to the NCI-CTCAE version 4.03 and distinguished between Common Terminology Criteria (CTC) gradable and non-CTC gradable parameters.

Common Terminology Criteria (CTC) gradable parameters

In this trial, CTC gradable parameters are the following:

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Name in NCI-CTC	Direction of abnormality
	Biochemistry			
Electrolytes	Calcium	CA	Hypocalcemia/Hypercalcemia	Low/High
Electrolytes	Magnesium	MG	Hypomagnesemia/Hypermagnesemia	Low/High
Electrolytes	Phosphorus (Phosphate)	PHOS	Hypophosphatemia	Low
Electrolytes	Potassium	K	Hypokalemia/Hyperkalemia	Low/High
Electrolytes	Sodium	SODIUM	Hyponatremia/Hypernatremia	Low/High
Enzymes/cardiac	Creatinine Phosphokinase	CK	CPK increased	High
Enzymes/liver	Alanine Aminotransferase	ALT	Alanine Aminotransferase increased	High
Enzymes/liver	Alkaline Phosphatase	ALP	Alkaline Phosphatase increased	High
Enzymes/liver	Aspartate Aminotransferase	AST	Aspartate Aminotransferase increased	High
Enzymes/liver	Gamma-glutamyltransferase	GGT	GGT increased	High
Enzymes/liver	Total bilirubin	BILI	Blood bilirubin increased	High
Enzymes/pancreas	Lipase	LIPASET	Lipase increased	High
Enzymes/pancreas	Serum amylase	AMYLASE	Serum amylase increased	High
Metabolism	Glucose	GLUC	Hypoglycemia/Hyperglycemia	Low/High
Metabolism	Uric acid[(1)]	URATE	Hyperuricemia	High
Plasma proteins	Albumin	ALB	Hypoalbuminemia	Low
Renal/kidney	Creatinine	CREAT	Creatinine increased	High
Renal/kidney	Creatinine Clearance	CREATCLR	part of Chronic kidney disease	Low
	Hematology			
Platelets	Platelets Count	PLAT	Platelet count decreased	Low
Red blood cells	Hemoglobin	HGB	Anemia/Hemoglobin increased	Low/High

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Name in NCI-CTC	Direction of abnormality
White blood cells/differential	White Blood Cell Count	WBC	White blood cell decreased/Leukocytosis	Low/High
White blood cells/differential	Absolute Lymphocytes Count	LYM	Lymphocyte count decreased/increased	Low/High
White blood cells/differential	Absolute Neutrophils Count	NEUT	Neutrophil count decreased	Low

(1) According to CTCAE grade, if uric acid value is between ULN and 590 µmol/L it should be graded as following:

- Grade 1 if there are no physiologic consequences
- Grade 3 if there are physiologic consequences

For a programming perspective, values between ULN and 590 µmol/L will all be graded as Grade 1 (if any physiologic consequences are observed, it should be completed as an adverse event).

For all CTC gradable parameters, shift tables from baseline to worst grade during the on-treatment period (as defined in section 9) will be produced. The worst grade per subject will be defined as the highest CTC grade among the on-treatment evaluations. If there is no on-treatment evaluation, then the worst grade will be set to 'Missing'. Parameters will be grouped by category.

Non-CTC gradable parameters

In this trial, non-CTC gradable parameters are displayed in table below:

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Direction of abnormality
	Biochemistry		
Electrolytes	Chloride	CL	High/Low
Enzymes/cardiac	Lactate dehydrogenase	LDH	High
Enzymes/liver	Direct bilirubin	BILDIR	High
Plasma proteins	Total protein	PROT	Low
Renal/kidney	Blood Urea Nitrogen	UREANUREAN	High
Renal/kidney	Urea	UREA	High
	Hematology		
Red blood cells	Red blood cells (Erythrocytes)	RBC	High/Low
Red blood cells	Reticulocytes/Erythrocytes	RETIRBC	High/Low
Red blood cells	Reticulocytes	RETI	High/Low
White blood cells/differential	Lymphocytes/Leukocytes	LYMLE	High/Low
White blood cells/differential	Neutrophils/Leukocytes	NEUTLE	High/Low
White blood cells/differential	Basophils/Leukocytes	BASOLE	High
White blood cells/differential	Basophils	BASO	High
White blood cells/differential	Eosinophils/Leukocytes	EOSLE	High
White blood cells/differential	Eosinophils	EOS	High
White blood cells/differential	Monocytes/Leukocytes	MONOLE	High/Low
White blood cells/differential	Monocytes	MONO	High/Low

Shift tables based on the normal range from baseline (as defined in section 9) to worst on-treatment value will be produced with the following categories for all hematology and blood chemistry parameters (CTC gradable and non-CTC gradable):

- Baseline: Low/Normal/High/Missing/Total
- Worst On-treatment: Low/Normal/High/Missing/Total

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

Only subjects with post baseline laboratory values will be included in these analyses.

In addition, a spider graph to investigate the evolution in time of some specific hematology and biochemistry parameters will display the observed value against thetreatment day. One graph per dose level will be produced for the following parameters:

- Hematology: all parameters within "White blood cells/differential" category
- Biochemistry: AST, ALT and Albumin

All CTC gradable and non-CTC gradable parameters will be listed for each measurement (pre-treatment, on-treatment and post-treatment). Parameters will be grouped by category.

Listings will include at least the following items:

- Dose Level
- Subject ID
- First / last M3541 / RT administration date and number of fraction days
- Age, sex and race
- Category
- Parameter (SI unit)
- Visit
- Date of collection (relative day)
- Observed value
- Change from baseline
- Reference range and normal range indicator (Low, Normal, High)
- NCI CTCAE grade
- Baseline flag
- Worst value on-treatment flag (Min/Max)

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

Coagulation parameters

All coagulation parameters captured on the "Coagulation" eCRF page will be listed for each measurement (pre-treatment, on-treatment and post-treatment).

Urinalysis

A listing of urinalysis and microscopic analysis captured on the "Urinalysis" and "Urinalysis Microscopic Evaluation" eCRF pages will be provided.

15.5 Vital Signs

Population: SAF analysis set

The following vital signs parameters data from "Vital Signs" eCRF pages will be considered:

- Systolic and diastolic blood pressure
- Pulse rate
- Body temperature
- Respiratory rate
- Weight

One figure for each dose level will be produced, with six spider plots (one for each parameter) in the same page using panel layout. On each plot, one curve per subject will display the absolute value against the treatment day.

Additionally, a listing will be produced, including: dose level, subject ID, age, sex, race, first and last M3541/RT administration date and number of fraction days, parameter (unit), visit, date of collection and relative day, value, details of collection method, change from baseline and baseline flag.

15.6 ECOG Performance Status

Population: SAF analysis set

The listing will include all the data from the "ECOG Performance Status" eCRF section.

Additionally, one spaghetti plot per dose level will be produced, using different colors per patient.

15.7 ECG and QT/QTc evaluations

Population: SAF analysis set

Electrocardiogram values based on "Electrocardiogram" eCRF page will be used for summary statistics and shift tables.

Time of ECG collection will be expressed both as actual and nominal (i.e. expected) time elapsed from first M3541 administration in hours, derived as defined at section 9.The following spider graphs will be produced separately using actual and nominal times for QTcF, as collected in the eCRF. Three. Three plots per dose level will be produced, with one curve per subject according to the specifications below:

1. Overall: Time point (in hours) on the x-axis (From -1 to 250) vs. QTcF observed value on the y-axis (i.e. results collected 72 and 240 hours post fraction 9 dose will not be presented)
2. Fraction Day 1: Time point (in hours) on the x-axis (From -1 to 12) vs. QTcF observed value on the y-axis
3. Fraction Day 9: Time point (in hours) on the x-axis (From 240 to 250) vs. QTcF observed value on the y-axis.

ECG parameters on-treatment will be presented by the following frequency table (by dose level and overall):

- Shift from normal baseline result to any abnormal post-baseline result (i.e. maximal on-treatment value)
- Worst absolute QTcF interval post-baseline
    - > 450 ms and ≤ 480 ms
    - > 480 ms and ≤ 500 ms
    - > 500 ms
- Worst QTcF increase from baseline
    - > 30 ms and ≤ 60 ms
    - > 60 ms

Two listings will display all the results as presented in "ECG" eCRF page, one on Qualitative Results (rhythm and ECG interpretation) and another one on Quantitative Results (heart rate, PQ/PR duration, RR duration, QRS duration, QT duration, QTcF). All visits and time points will be included in listings.

One additional listing will contain all the information from the "Continuous Holter" eCRF page.

15.8 Pregnancy Test

Pregnancy testing (serum β-HCG) will be performed at screening and 30 days post-treatment. A listing will display all the results as presented in "Pregnancy Test" eCRF page.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

16.1.1 General Considerations

Population: PK analysis set

Pharmacokinetic parameters will be calculated using actual collection time data where available. There will be no rounding of actual time values, and full precision values will be used as calculated from eCRF data. In the case that the actual time is not available, the scheduled time will be used. Predose samples that occur before drug administration will be assigned a time of 0 hours for that FD, as if the sample had been taken simultaneously with the study drug administration.

Values below the lower limit of quantitation 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 quantitation (ULOQ) the numeric value of the actual ULOQ of the bioanalytical assay may be used for preliminary, draft PK evaluations only. For final evaluations >ULOQ values are not accepted and should be replaced by valid numeric values from dilution measurement.

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

Pharmacokinetic concentrations which are erroneous due to a protocol violation, as defined in the clinical trial protocol (CTP), documented handling error or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed upon with sponsor PK analyst/clinical pharmacologist prior to performing the statistical analysis. Any PK concentrations excluded from the PK analysis set will be listed and flagged, and the rationale for exclusion will be listed and provided in the CSR. Any other PK concentrations that appear implausible to the Pharmacokineticist must not be excluded from the analysis. Any implausible data will be discussed in the CSR.

Individual PK concentrations in plasma for M3541 will be listed and summarized by dose and fraction day using standard descriptive statistics. A listing of PK blood sample collection times as well as derived sampling time deviations will also be provided.

Pharmacokinetic parameters for M3541 will be listed and summarized by dose and fraction day using standard descriptive statistics (see TFLs for further information). PK parameters derived with inclusion of flagged concentrations will not be used in the descriptive statistics.

Dose proportionality will be presented graphically as follows:

- Scatter Plot of individual and geometric mean AUC and C_{max} versus Dose on a linear scale, using $AUC_{0-\infty}$, $AUC_{(0-t)}$, $AUC_{0-\infty}$ and C_{max} derived from FD1 and using $AUC_{(0-t)}$, and C_{max} derived from FD9.

Individual concentration-time profiles by subject will be created using the actual time points and the numeric concentration data. Arithmetic mean concentration-time profiles by dose and fraction day 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 SD error bars when plotted on a linear scale. Additional plot presenting overlay of the arithmetic mean concentrations for each dose level will be provided on a semi-log scale (see TFLs for further information).

The trough concentrations (C_{trough}) will be listed and summarized by dose, using standard descriptive statistics. Individual C_{trough} values will be plotted against actual fraction day on a linear scale, for all subjects by dose. Arithmetic mean C_{trough} ±SD will also be plotted by dose, on a linear scale.

16.1.2 Estimation of Individual Pharmacokinetic Parameters

Population: PK analysis set

The final analysis will be performed IQVIA and reviewed by the Clinical PK/PD Group of quantitative pharmacology (QP), Merck, Darmstadt, Germany. Standard non-compartmental methods will be used to calculate PK parameters using the actual administered dose and 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 or dose is missing, calculations will be performed using the scheduled time or dose level. Otherwise, there will be no further imputation of missing data. The following PK parameters will be calculated for the determination of the PK profile of M3541, where appropriate for Fraction Day 1, 2 to 6, or 9:

Symbol	Definition
AUC_{0-6h}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the 6-hour sampling time. Calculated using the mixed log linear trapezoidal rule (linear up, log down). (FD 1 and 9 only)
AUC_{0-t}	The AUC from time zero (= dosing time) to the last quantifiable 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) (FD 1 and 9 only).

Symbol	Definition
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, using the formula AUC_{0-t} /Dose. (FD 1 and 9 only)
$AUC_{0-\infty}$	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. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\ \lambda_z$. (FD 1 only)
$AUC_{0-\infty}$ /Dose	The Dose normalized AUC from time zero extrapolated to infinity. Normalized using actual dose, using the formula $AUC_{0-\infty}$ /Dose. Predicted $AUC_{0-\infty}$ should be used. (FD 1 only)
$AUC_{0-\tau}$	The AUC from time zero (dosing time) extrapolated to the end of the dosing interval (24 h). (FD 9 only)
$CL_{/f}$	The apparent total body clearance of drug following extravascular administration, taking into account the fraction of dose absorbed. CL/f = Dose /$AUC_{0-\infty}$. Predicted $AUC_{0-\infty}$ should be used. (FD 1 only)
$CL_{SS/f}$	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 / $AUC_{0-\tau}$ where $AUC_{0-\tau}$= AUC extrapolated to 24h (FD 9 only)
C_{max}	Maximum observed concentration for each fraction day. (FD 1 and 9 only)
C_{max} /Dose	The dose normalized maximum concentration. Normalized using the actual dose, and the formula C_{max} /Dose. (FD 1 and 9 only).
C_{trough}	The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing). (FD 2 to 6 and FD 9)
$C_{2.25h}$	The concentration observed at 2.25 h post dose. (FD 1-6 and 9)
C_{min}	Minimum observed plasma concentration collected during a dosing interval. (FD 9 only)
C_{avg}	Average plasma concentration during a dosing interval. C_{avg} = $AUC_{0-\tau}$ /τ. (FD 1 and 9 only)

Symbol	Definition
$R_{acc(AUC0-6h)}$	The accumulation ratio to assess the increase in exposure via AUC_{0-6h}. $R_{acc(AUC0-6h)}$= (AUC_{0-6h} after multiple dose) / (AUC_{0-6h} after single dose). (FD 9 only)
$R_{acc(Cmax)}$	The accumulation ratio to assess the increase in maximum concentration with multiple dosing. $R_{acc(Cmax)}$ = (C_{max} after multiple dose)/ (C_{max} after single dose) (FD 9 only)
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$. (FD 1 only)
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the first occurrence in case of multiple/identical C_{max} values). (FD 1 and 9 only)
t_{min}	The time to reach the minimum observed concentration collected during a dosing interval. (FD 9 only)
V_Z/f	The predicted 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. (FD 1 only)
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. (FD 1 only)

FD 9 parameters should only be included in descriptive statistics if 4 consecutive days of treatment with no interruption were given to the patient. PK parameters not included in descriptive statistics will be flagged. Any flags should be included in the study specific SDTM/ADaM.

The following PK parameters will be calculated for diagnostic purposes (Fraction Day 1 only) 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,adj) for calculation of λ_z.

The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$ AUCextra% = (extrapolated area/$AUC_{0-\infty}$)*100 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.

AUCextra% should be < 20%, the coefficient of correlation (Rsq, adj) should be ≥0.8 and the observation period over which the regression line is estimated should be at least two-fold 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/ADaM.

Partial areas $AUC_{0\text{-}6h}$ should be calculated using the scheduled dosing interval, as defined in the CTP. The actual dosing interval calculated from eCRF time data should not be used. The following rules apply when calculating the partial area $AUC_{0\text{-}6h}$ within the observed time interval fromT_1 to T_2:

- 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 data point and initial concentration at time zero (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.

Potential drug accumulation will be evaluated by individual accumulation ratios for $AUC_{0\text{-}6h}$, C_{max}, $R_{acc(AUC0\text{-}6h)}$ and $R_{acc(Cmax)}$ (that will be calculated by dividing the values obtained after multiple dose (e.g., on Fraction Day 9) by the values obtained after single dose (e.g., Fraction Day 1) and summarized descriptively for each dose level.

Concentrations below LLOQ, which are before the last quantifiable data point, will be taken as zero for calculating the AUC. Unless otherwise specified in the CTP, 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 same applies to the very first predose sample of a multiple-dose study.

16.2 Biomarkers

Population: BMK Analysis Set

All statistical analyses and descriptive summaries of pharmacodynamic biomarker and immune system biomarkers will be performed on the BMK Analysis Set. All pharmacodynamic biomarker data not included in the Pharmacodynamic Biomarker analysis set will be listed and flagged.

The following parameters will be analyzed:

Pharmacodynamic Biomarkers			
		Parameter	
		Phospho ATM/Total ATM ratio	
Immune System Biomarkers			
Panel	**Cell Type**	**Parameter**	**Units**
Q-TBNK assay	T Cells	$CD3^+$ %	%%
		$CD3^+$ ABS	Cells/µL
		$CD3^+$ $CD4^+$ %	%%
		$CD3^+$ $CD4^+$ ABS	Cells/µL
		$CD3^+$ $CD8^+$ %	%%
		$CD3^+$ $CD8^+$ ABS	Cells/µL
	B Cells	$CD3^-$ $CD19^+$ %	%%
		$CD3^-$ $CD19^+$ ABS	Cells/µL
	NK Cells	$CD3^-$ $CD56^+$ / $CD16^+$ %	%%
		$CD3^-$ $CD56^+$ / $CD16^+$ ABS	Cells/µL
	Monocytes	$CD14^+$ %	%%
		$CD14^+$ ABS	Cells/µL
TReg (FoxP3/CD45RA) Assay		CD3+CD4+CD25+CD127-/loFoxP3+ %	%
		CD3+CD4+CD25+CD127-/loFoxP3+ ABS	Cells/µL
		CD3+CD4+CD25+CD127-/loFoxP3+CD45RA+ %	%
		CD3+CD4+CD25+CD127-/loFoxP3+CD45RA+ ABS	Cells/µL
		CD3+CD4+CD25+CD127-/loFoxP3+CD45RA- %	%
		CD3+CD4+CD25+CD127-/loFoxP3+CD45RA- ABS	Cells/µL
T Cell Subsets (Th1, 2, T17/CD45RA/CCR7) Assay	Naïve CD4+ T Cell	CD4+CD45RA+CD197+ %(CD4)	%
		CD4+CD45RA+CD197+ ABS	Cells/µL
	Central Memory CD4+ T Cell	CD4+CD45RA-CD197+ %(CD4)	%
		CD4+CD45RA-CD197+ ABS	Cells/µL
	Effector Memory CD4+ T Cell	CD4+CD45RA-CD197- %(CD4)	%
		CD4+CD45RA-CD197- ABS	Cells/µL
	Naïve CD8+ T Cell	CD8+CD45RA+CD197+ %(CD8)	%
		CD8+CD45RA+CD197+ ABS	Cells/µL
	Central Memory CD8+ T Cell	CD8+CD45RA-CD197+ %(CD8)	%
		CD8+CD45RA-CD197+ ABS	Cells/µL
	Effector Memory CD8+ T Cell	CD8+CD45RA-CD197- %(CD8)	%
		CD8+CD45RA-CD197- ABS	Cells/µL
	Effector CD8+ T Cell	CD8+CD45RA+CD197- %(CD8)	%
		CD8+CD45RA+CD197- ABS	Cells/µL

	Th1 Cells	CD4+CD45RA-CD183+CD196- %(CD4)	%
		CD4+CD45RA-CD183+CD196- ABS	Cells/µL
	Th2 Cells	CD4+CD45RA-CD183-CD196- %(CD4)	%
		CD4+CD45RA-CD183-CD196- ABS	Cells/µL
	Th17 Cells	CD4+CD45RA-CD183-CD196+ %(CD4)	%
		CD4+CD45RA-CD183-CD196+ ABS	Cells/µL
	Th1/Th17 Cells	CD4+CD45RA-CD183+CD196+ %(CD4)	%
		CD4+CD45RA-CD183+CD196+ ABS	Cells/µL

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 same applies to the very first predose sample of a multiple-dose study.

Biomarker concentrations which are erroneous due to a protocol violation (as defined in the CTP), documented handling error or analytical error (as documented in the bioanalytical report) may be excluded from the biomarker analysis if agreed upon prior to performing a statistical analysis. In this case the rationale for exclusion must be provided in the CSR. Any other biomarker concentrations/effects that appear implausible to the analyst must not be excluded from the analysis. Any implausible data will be documented in the CSR.

Pharmacodynamic biomarker and immune system biomarkers data in each matrix will be listed and summarized by dose and fraction day using standard descriptive statistics for observed and change from baseline data. Individual biomarker data-time profiles will be created usingobserved concentration data. Nominal (i.e. expected) time elapsed from first M3541 administration in hours, according to the derivation defined at section 9 will be used.

Arithmetic (±SD) mean concentration-time profiles by dose will be provided using scheduled (nominal) time points and the numeric data. All biomarker plots will be presented on a linear scale and SD bars extending below 0 will be set to 0.

16.3 Patient-Reported Outcomes

Population: SAF Analysis Set

The Brief Pain Inventory - Short Form (BPI-SF) is a 9-item self-administered questionnaire used to evaluate the severity of the subject's pain and the impact of the pain on daily functioning. The subject is asked to rate their worst, least, average, and current pain intensity, and list current treatments and their perceived effectiveness. The subject is also asked to rate on a 1 to 10 scale the degree to which the pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life.

Analyses of BPI-SF questionnaire will be based on "Quality of life questionnaire - BPI-SF" eCRF page. Questionnaire data refer only to areas being irradiated as part of the experimental treatment.

Questionnaire results collected on FD 1 prior to any other study-related assessments will be used as baseline. Only subjects with cancer pain at baseline will be included in the analysis.

As suggested in the user guide[5] provided by questionnaire developers, only the following 5 items will be summarized:

3 - Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

4 - Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

5 - Please rate your pain by marking the box beside the number that best describes your pain on the **average**.

6 - Please rate your pain by marking the box beside the number that tells how much pain you have **right now**.

9 - Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your: general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life.

Absolute values answered to questions 3 to 6 will be used for graphical representation. BPI pain interference (question 9) will be evaluated following two complementary approaches:

- Overall: it will be scored as the mean of the seven interference items. This mean will be used only if more than 50%, or four out of seven, of the total items have been completed on a given administration day, otherwise it will be set to missing.

- Sub scores: activity-related sub score will be derived as the mean of general activity, walking, work and sleep items, and a mood-related sub score will be derived as the mean of mood, relations with other people, sleep and enjoyment of life items. Please consider that the sleep item is included in the calculation of both sub scores. Sub score means will be used only if more than 50%, or three out of four, of the total items have been completed on a given administration day, otherwise it will be set to missing.

Two figures (one for pain and one for interference questions) for each dose level will be produced.

- Pain figure: it will include four spider plots (one for each question) in the same page using panel layout. On each plot, one curve per subject will display the absolute value against the treatment day. Pain therapy increase and decrease derived from "Pain therapy" eCRF page, will be reported in each plot.

- Interference plot: it will include three spider plots (for overall score, activity and mood-related sub scores) in the same page using panel layout. On each plot, one curve per subject will display the mean value against the treatment day. Pain therapy increase and decrease derived from "Pain therapy" eCRF page, will be reported in each plot.

The listing of BPI-SF questionnaire results will include: dose level, subject ID, question 1, questions from 3 to 6, received treatment for pain, percentage of relief from pain and interference of pain with different activities (see section 18.1 for questionnaire text).

17 References

1. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: Efficient dose escalation with overdose control. Stat Med 1998;17(10):1103-20.

2. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to Phase I cancer trials. Stat Med 2008;27(13):2420-39.

3. Sweeting M, Mander A, Sabin T. Bayesian Continual Reassessment Method Designs for Phase I Dose-Finding Trials. J Stat Softw 2013;54:1-26.

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

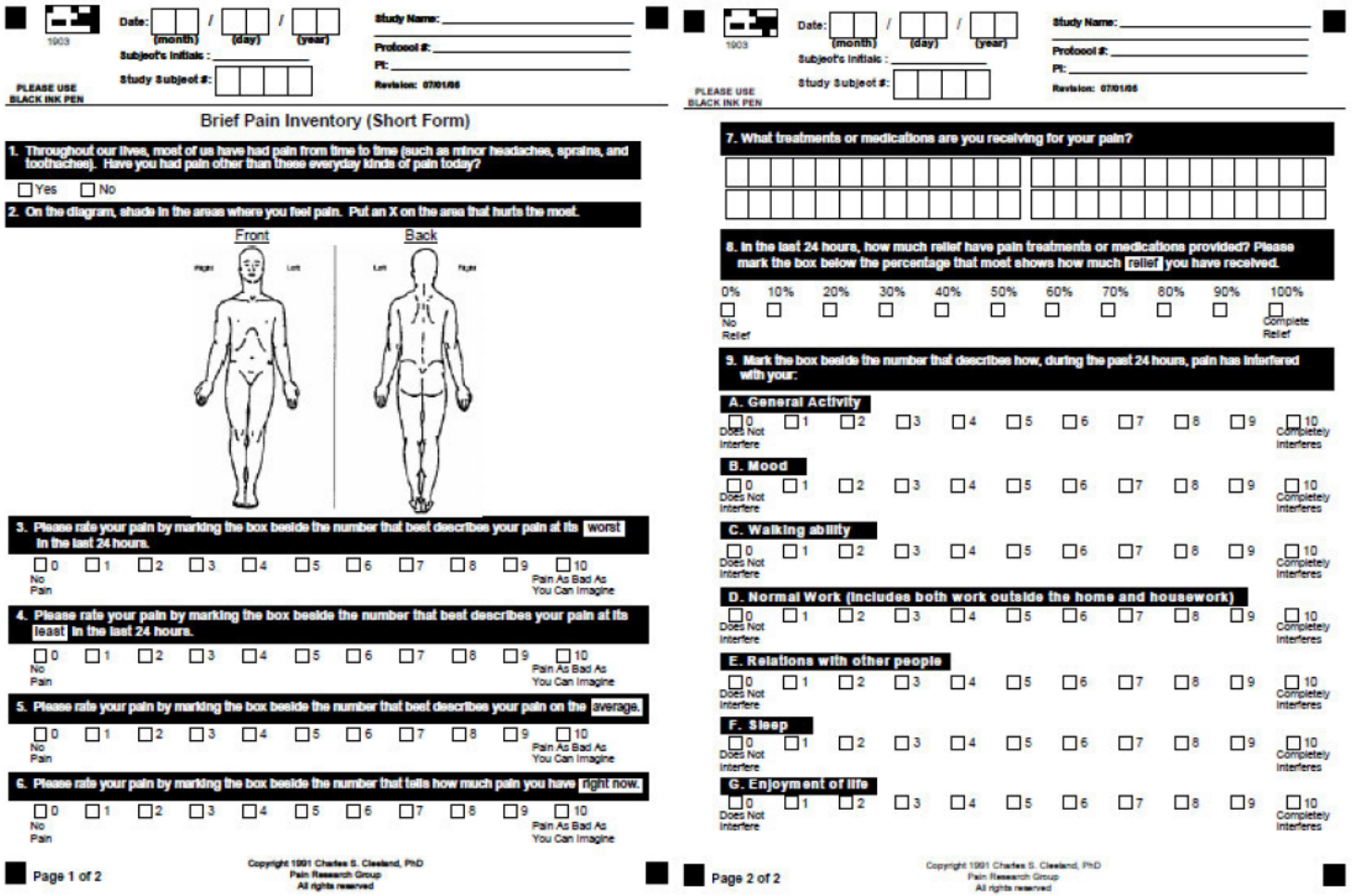
5. Cleeland CS, The Brief Pain Inventory - User Guide, 2009

18 Appendices

Specifications for the tables, listings and figures (TLFs) reside in a separate document. In a companion table of content it is clarified the output to be included as in-text tables in the CSR and the output that is planned for Section 15 in the CSR.

Since more than one batch of test drug/investigational product will be used, patients receiving each batch should be identified and listed in section 16.1.6, in line with ICH E3 requirements.

18.1 Brief Pain Inventory (Short Form)



Brief Pain Inventory (Short Form)

Date: (month) / (day) / (year)
Subject's initials:
Study Subject #:
Study Name:
Protocol #:
Pt:
Revision: 07/01/05
PLEASE USE BLACK INK PEN

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.
Front Back

3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Date: (month) / (day) / (year)
Subject's initials:
Study Subject #:
Study Name:
Protocol #:
Pt:
Revision: 07/01/05
PLEASE USE BLACK INK PEN

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
No Relief — Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Does Not Interfere — Completely Interferes

B. Mood
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Does Not Interfere — Completely Interferes

C. Walking ability
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Does Not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Does Not Interfere — Completely Interferes

E. Relations with other people
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Does Not Interfere — Completely Interferes

F. Sleep
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Does Not Interfere — Completely Interferes

G. Enjoyment of life
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Does Not Interfere — Completely Interferes

Page 2 of 2

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Taken from Cleeland CS, The Brief Pain Inventory - User Guide, 2009.