Boehringer Ingelheim

Trial Statistical Analysis Plan

c02246780-02

BI Trial No.:	1280.15
Title:	An open-label phase I dose escalation trial of weekly intravenous administrations of BI 836845 in Japanese patients with advanced solid tumours
Test Substance	Xentuzumab, BI 836845
Responsible trial statistician:	[redacted] Phone: [redacted], Fax: [redacted]
Date of statistical analysis plan:	10 DEC 2018 SIGNED
Version:	Revised

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2 LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of Special Interest
ATC	Anatomical, Therapeutic, Chemical
AUC	Area under the curve
BI	Boehringer Ingelheim
BMI	Body mass index
BSA	Body surface area
CR	Complete response
CRF	Care report form
CT	Concomitant therapies
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ENR	Enrolled set
EOT	End of treatment
IGF	Insulin-like growth factor
iPDs	Important protocol deviations
LLT	Lowest Level Term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MQRMs	Medical Quality Review Meetings
MRI	Magnetic Resonance Imaging
MS	MTD set
MTD	Maximum tolerated dose
NE	Not evaluable

P25	25th percentile
P75	75th percentile
PD	Progressive disease
PK	Pharmacokinetics
PKS	Pharmacokinetics Set
PPS	Per Protocol Set
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria In Solid Tumours
REP	Residual effect period
RPM	Report planning meeting
SAE	Serious adverse event
SD	Stable disease
SOC	System organ class
SOP	Standard Operating Procedures
TCM	Trial clinical monitor
TS	Treated set
TSAP	Trial statistical analysis plan
WHO DD	World Health Organisation – Drug Dictionary

3 INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP (see in section “Statistical Methods and Determination of Sample Size”). Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation. This TSAP follows Boehringer Ingelheims (BI) internal reference (1).

In general, study or trial medication refers to Xentuzumab.

SAS Version 9.4 or later version will be used for all analyses unless otherwise specified.

4 CHANGE IN THE PLANNED ANALYSIS OF THE STUDY

4.1 ADDITIONS/NEW ANALYSES

[redacted]

Dose proportionality analysis and attainment of steady state analysis for some PK parameters will be conducted.

4.2 CHANGES

As a change from planned pharmacokinetic analysis, the following PK parameters will not be calculated:

$AUC_{0-\infty}$, $t_{1/2}$, MRT, CL, Vz, Vss

Exploratory PK analyses during the dose escalation phase of study 1280.1 (with qw dosing) and 1280.2 (q3w dosing) have revealed that the qw dosing schedule does not allow to describe the elimination phase of Xentuzumab accurately. Therefore, all PK parameters related to the elimination phase will not be calculated in study 1280.15.

To align with BI standard definition, duration of disease control is defined as the time from first treatment administration until the earliest of disease progression or death, among patients with disease control.

A Clinical Trial Report (CTR) may be written before all patients have discontinued trial medication to document the results of the primary endpoint analysis. If written, subsequent data collected up to the point of trial completion will be reported in a revision to this CTR.

4.3 CLARIFICATIONS

The following points warrant further clarification:

- The terms “progression”, “progressive disease” (PD) and “disease progression” will be used interchangeably within this document.
- The terms “treatment cycle” or “treatment course” will be used interchangeably throughout this document.
- The terms “study medication” and “trial medication” will be used interchangeably throughout this document.

5 ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint is the maximum tolerated dose (MTD) of trial medication based on the occurrence of dose limiting toxicity (DLT) during the first treatment course. The planned treatment course consists of 21 days.

MTD:

MTD is defined as the highest dose level examined of trial medication, at which no more than 1 out of 6 patients experienced a DLT during the MTD evaluation period. The MTD evaluation period is defined as the time from the first administration of Xentuzumab up to start of cycle 2. That means that the exact duration of this period will be derived for each patient. If the patient does not start cycle 2, a fixed duration of 21 days will be used.

In case the MTD will not be reached until 1400 mg, it will be deemed as a sufficient tolerability in Japanese patients with advanced solid tumours at 1400 mg.

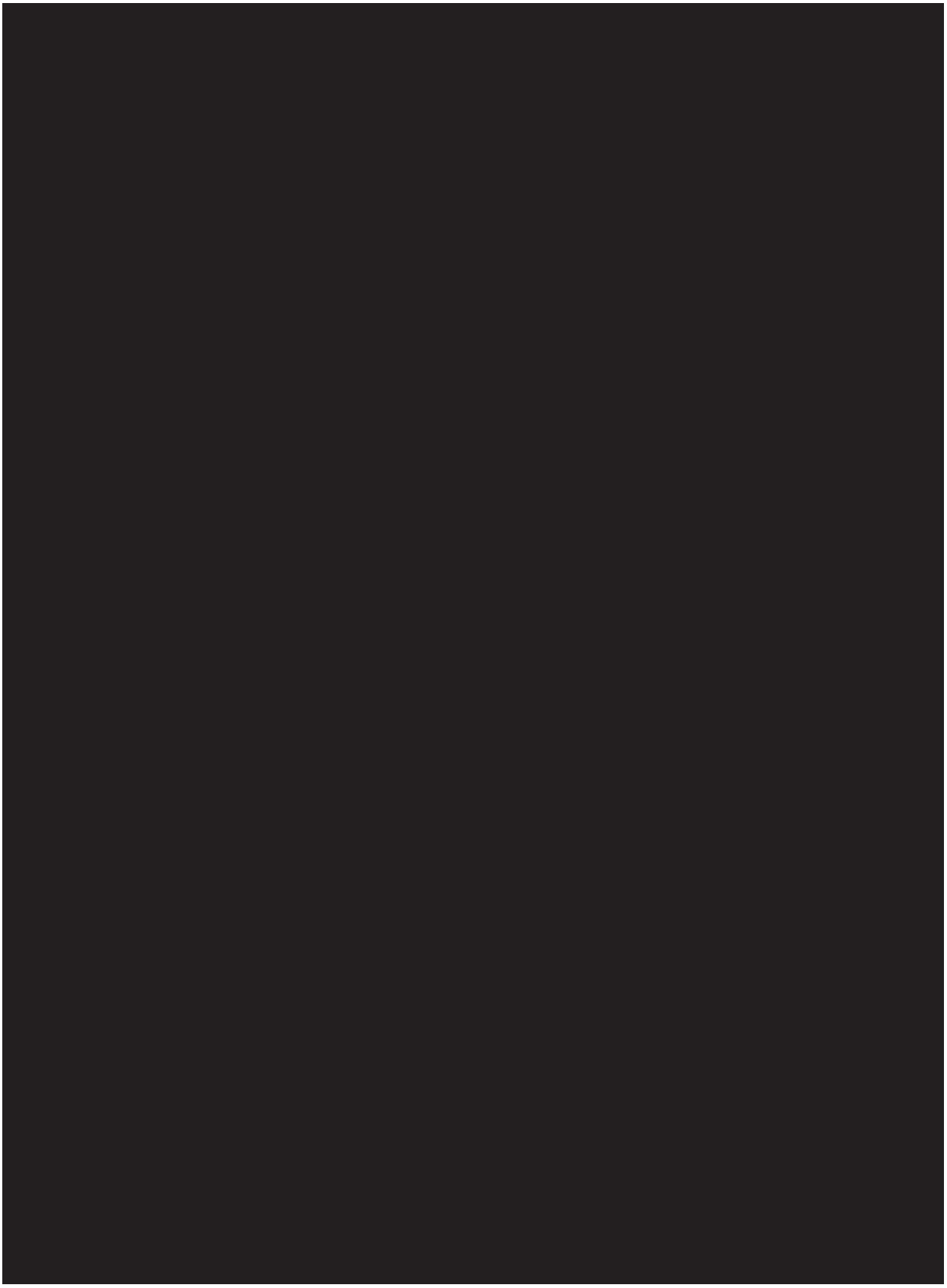
5.2 SECONDARY ENDPOINTS

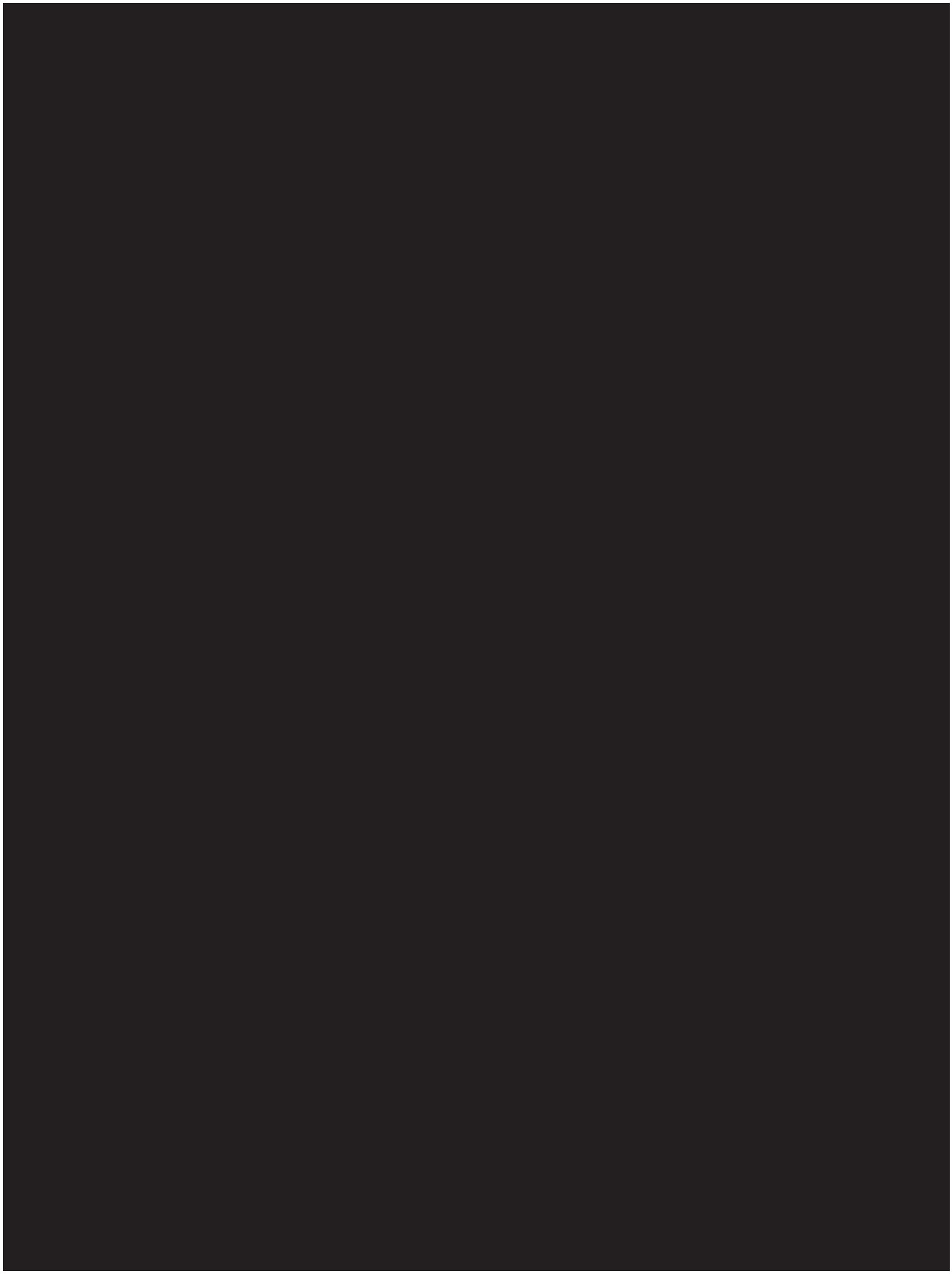
5.2.1 Key secondary endpoints

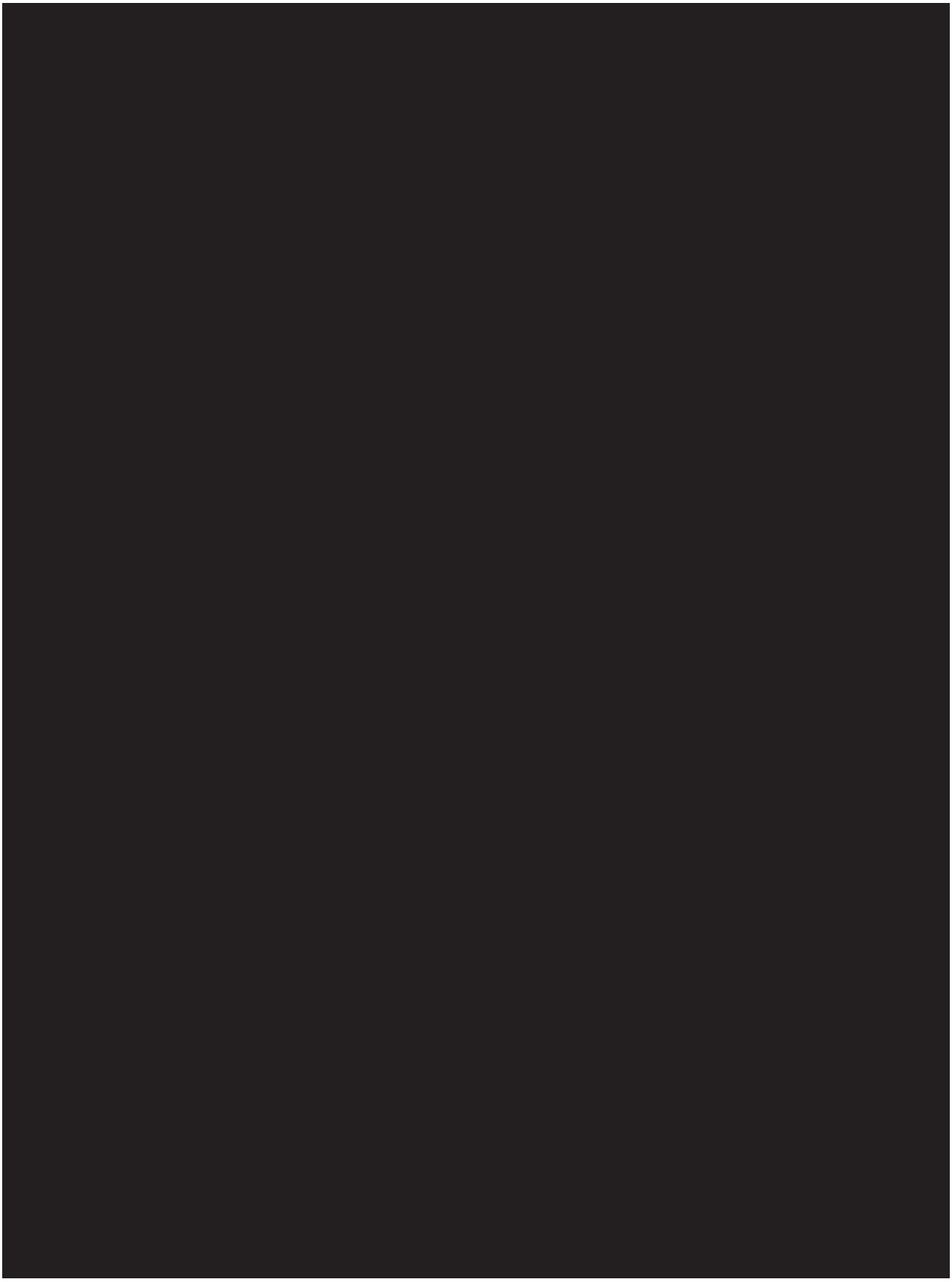
Not applicable.

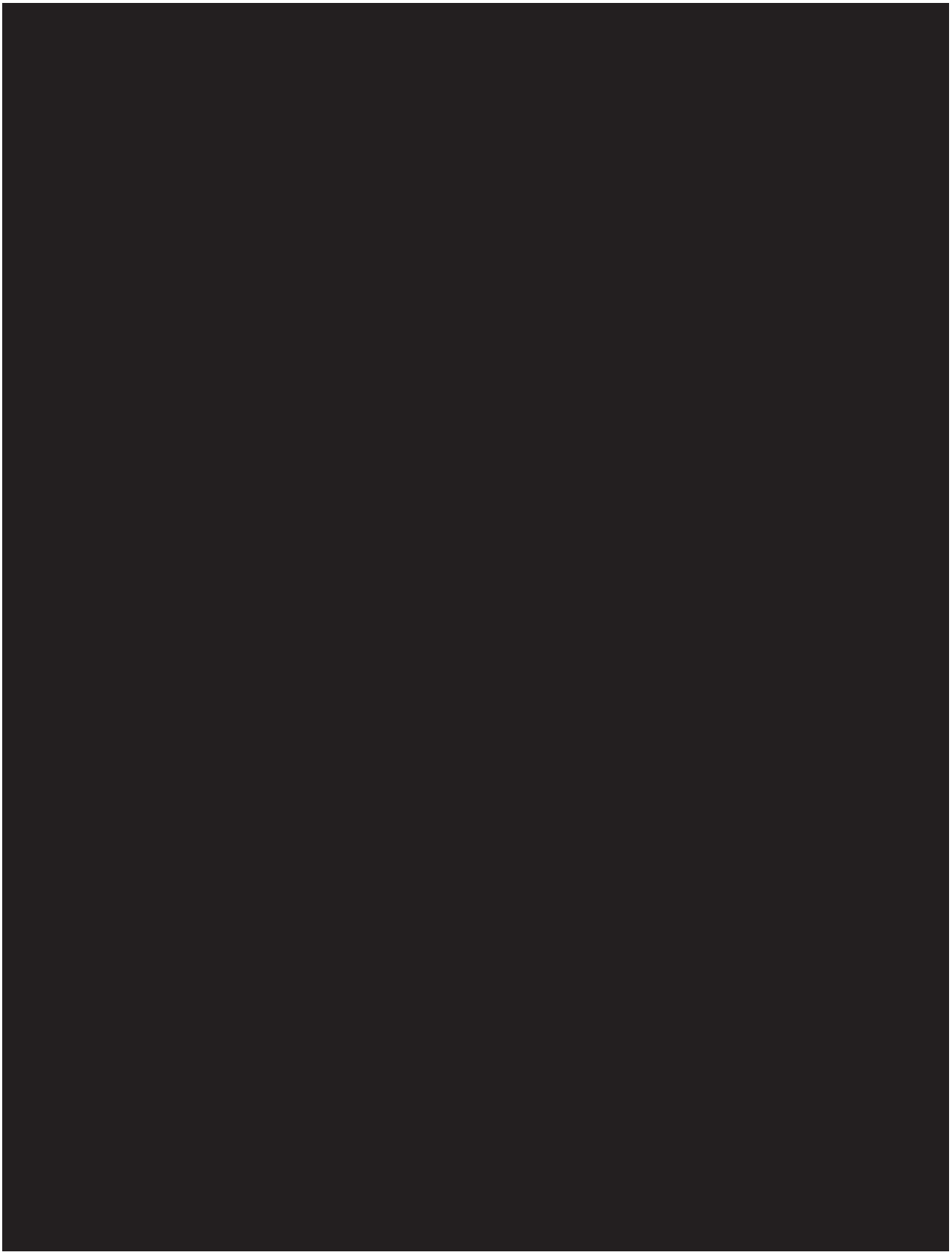
5.2.2 Other secondary endpoints

There are no secondary endpoints.









6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Patients will be analysed according to the cohort initially assigned. All planned analyses will be presented by this cohort, unless specified otherwise. Handling of patients where cohort assignment has not been followed will be handled on a case-by-case basis, to be agreed at report planning meetings or DBL meeting (but prior to database lock).

For safety summaries data recorded during the Residual Effect Period (REP) will be considered as on-treatment. For this trial, the length of the REP is 42 days.

The actual study periods and treatment codes are defined in a document entitled “8-7-other-sdtm-trial-arms-trial-elements”, which can be found in Data Management and Statistics (DMS) folder, Section 8, within BIRDS.

6.2 IMPORTANT PROTOCOL DEVIATIONS

No per protocol set (PPS) analysis will be performed for this study, hence, no patient will be excluded from the analyses. However patients with potentially important protocol deviations (iPDs) will be documented. The following list in Table 6.2: 1 of potentially IPDs will be used; note that this is a working list and may not be finalised until the final Report Planning Meeting (RPM) prior to database lock for the primary analysis. Potentially important protocol deviations will be handled according to BI standards (9).

During the study conduct, protocol deviation should be monitored and guidance for improving / teaching the respective sites should be discussed during the study Medical Quality Review Meetings (MQRMs).

Table 6.2:1 Important protocol deviations

Category/ Code		**Description**	**Requirements**	**Excluded from**
A [1]		**Entrance criteria not met**		
	A1	Diagnosis of trial disease questionable	Inclusion criteria IN1 not met	None
	A2	Prohibited baseline condition, diagnosis or treatment	Inclusion criteria IN3 not met or Exclusion criteria EX1, 3-12, EX14-15 or EX17-19	None
	A3	Laboratory result indicating inadequate organ function at screening	Exclusion criteria EX2	None

Table 6.2:1 (continued) Important protocol deviations

Category/ Code		Description	Requirements	Excluded from
	A4	Adequate archival tumour tissue not available	Exclusion criteria EX13	None
B [1]		**Legal Criteria**		
	B1	Informed consent not available / not done	Informed consent date missing or Inclusion criteria IN4 not met	All
	B2	Informed consent too late	Informed consent date was after Screening Visit date	None
	B3	Age limit for patient inclusion not adhered to	Inclusion criteria IN2 are not met or, Calculate age given the date of birth and date of informed consent: patients must be ≥ 20 years old	All
C [2]		**Trial medication and randomisation**		
	C1	Time window deviation for procedures performed at screening	Assessment at screening not within 28 days prior to first treatment	None
	C2	Trial medication not given according to protocol	Dose reduction scheme not followed description in section 4.1.3.6 in CTP.	None
	C3	Infusion time for the investigational treatment outside of CTP specific boundaries	Check medical review of administration data. Total infusion time (allowing for interruptions) < 60 minutes See the section 4.3 in CTP.	None
	C4	Patient assignment not followed	Patients do not receive the initial treatment they were allocated to	None

Table 6.2:1 (continued) Important protocol deviations

Category/ Code		Description	Requirements	Excluded from
D [2]		**Concomitant medication**		
	D1	Prohibited treatment during trial conduct phase	Indicated by medical review of concomitant therapy use during study treatment according to section 4.2.2.1 in CTP. Discuss the list which is given by TCM during MQRM.	None
E [2]		**Missing Data**		
	E1	Imaging assessments not done according to CTP instructions	Imaging assessment should be performed at Screening and several time points thereafter (see table 6.7.2: 1).	None
	E2	Pregnancy test not done according to CTP instructions	Exclusion criteria EX16 or Pregnancy test missing.	None
F [2]		**Trial Specific protocol deviations**		
	F1	Other protocol deviations affecting patient rights or safety	Manual PVs can be collectively captured	None

[1] iPD will be derived automatically
[2] iPD will be identified via individual review at MQRM/RPM/DBL.

6.3 PATIENTS SETS ANALYSED

The following analysis sets will be defined for this trial:

- Enrolled set (ENR)

This patient set includes all patients with informed consent given. The enrolled set will be used for patient disposition tables.

- Treated set (TS)

This patient set includes all patients who are documented to have received and taken at least one dose of study medication during the treatment cycles (from day 1).

The TS will be used for all planned safety and efficacy analyses.

- MTD Set (MS)

The MTD set defines the set of patients that are fully evaluable for the MTD in the first treatment course. The MTD set will be used for some safety analyses, this is specified in the technical TSAP.

Patients in the TS who were replaced within the MTD period of the trial will be excluded from the determination of the MTD. Patients in the TS who entered in an expansion cohort will be also excluded from the determination of the MTD. Replacement of patients of the study is defined in Section 3.3.5 of the CTP. The final list of replaced patients is supplied by the Trial Clinical Monitor (TCM) no later than the last report planning meeting before the database lock for the safety analysis.

- Pharmacokinetic set (PKS)

This patient set includes all patients in the treated set who have at least one valid drug plasma concentration available. The decision whether a concentration is considered valid or not will in general be made at the RPM before Database Lock (DBL). The PKS will be used for the PK analyses of the trial.

No per protocol population will be used for analyses.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because there are no inferential statistics, and therefore there is no statistical model in which centre/country can be included.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, missing data will not be imputed, unless required for the following analyses and definitions. Then the rules as described below apply.

Missing dates that affect the evaluation of endpoints specified in relevant sections of this TSAP will be imputed utilising a “worst case” approach, which will be applied on a case-by-case basis (depending on the affected endpoint) and agreed to by the trial team members at the final RPM before database lock at the latest. The agreements are implemented in the technical TSAP.

6.6.1 Adverse events

Missing or incomplete AE dates are imputed according to BI standards (2).

6.6.2 Laboratory values at baseline

For missing laboratory data at Visit 1 (before the very first administration of study medication) data from preceding visits will be used if not obtained longer than 2 days before the very first treatment with study medication.

6.6.3 PK parameters

[redacted]

6.7 BASELINE, TIME WINDOWS, AND CALCULATED VISITS

6.7.1 Baseline

The last measurement observed prior to start of trial medication will be assigned to baseline. Note that for some trial procedures (for example body weight, vital signs, laboratory tests) this may be the value measured on the same day trial medication was started. In these cases it will be assumed that the measurements were taken prior to the intake of any study medication. For tumour assessment, baseline evaluations must be based on Magnetic Resonance Imaging (MRI) or Computed Tomography scans performed no more than 28 days prior to start of trial medication.

Study days and visits will be labelled according to the flow chart of the CTP.

Unless otherwise specified, baseline is defined as the latest time-point before the very first administration of any study medication. If this criterion is not fulfilled then no baseline will be derived .

Laboratory values:

Baseline is defined as the latest time-point before the very first administration of any study medication. For laboratory values where not only the examination date but also time are recorded, examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first study drug administration is considered as baseline value if and only if the recording time was before or the same as the time of first study drug administration.

If any of these times are missing and the date of laboratory value is equal to the date of first study drug administration, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

6.7.2 Time windows for every RECIST assessment

In order to identify whether consecutive imaging time-points are missing for a given patient, a nominal time point [6, 12, 18 weeks and every 9 weeks thereafter] will be assigned to each and every image. This is achieved by creating windows for every RECIST assessment. The windows are defined in Table 6.7.2: 1 below.

Table 6.7.2: 1 Nominal time-points and windows for imaging

Nominal time-point [weeks from start of therapy]	**Due date of scans [days]**	**Window [days]**
6	43	1 to =< 64
12	85	65 to =< 106

Table 6.7.2: 1(continued) Nominal time-points and windows for imaging

Nominal time-point [weeks from start of therapy]	**Due date of scans [days]**	**Window [days]**
18	127	107 to =< 158
27	190	159 to =< 221
Every 9 weeks interval	*	*

*Due date of imaging = (nominal time point * 7) + 1. To calculate the lower bound of the window, use the middle point between the due date of the previous time point and the current due date+1. To calculate the upper bound of the window, use the middle point between the due date of the next time point and the current due date.

If a patient does not have an image in one of the windows described above, he/she will be said to have 'missed an assessment' for that time-point. In case a patient has more than one assessment in one window, the assessment with the latest outcome will be used for the analysis unless a PD has been recorded earlier then PD will be used.

7 PLANNED ANALYSES

The labelling and display format of statistical parameters will follow BI standards (10).

Descriptive statistics for continuous variables will generally contain N (number of patients in that patient set), Mean, Standard Deviation, Minimum (Min), P25 (25th percentile), Median, P75 (75th percentile), Maximum (Max). In general, means, SDs, medians, P25 and P75 will be presented to one more decimal place than the raw data. Minima and maxima will be presented to the same number of decimal places as the raw data.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group total. Percentages will be rounded to one decimal place.

In general a category "missing" will be displayed. Percentages will also generally be based on all patients in the respective patient set whether they have non-missing values or not.

Sort order for general categorical variables: If categories correspond to the collected categories on the eCRF and the table shells do not explicitly specify the ordering, the "default ordering" defined by the eCRF is to be used in such cases. If categories are derived the ordering as specified in the table shell document should be used; in general ordinal data (e.g. categorised continuous data) are to be displayed in ascending order.

The denominator of the main categories is defined by the number of patients in the used patient set. The main categories define the denominators of the subcategories. Subcategories should be indented and "[N (%)]" to be displayed only for the main category.

If a table includes only categorical data, "[N (%)]" is to be displayed in the column header.

Abbreviations (e.g., Wors.) or acronyms (e.g., PD) should not be displayed in tables and patients data listings without any explanation. They will be either spelled out in the table or explained in footnotes (whatever is more reasonable from the programming point of view).

If applicable, conversion from days to weeks, months and years will be as follows:

- Weeks = days ÷ 7
- Months = 12 × days ÷ 365.25
- Years = days ÷ 365.25

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

7.1.1 Disposition of patients

For patient disposition the standard descriptive table from the EOT catalogue will be populated.

7.1.2 Important protocol deviations

A table and a listing of patients with important protocol deviations based on Table 6.2: 1 will be created in Section 15.1.3 and Appendices 16.2.3 and 16.1.13.1.3 respectively, of the clinical trial report (CTR).

7.1.3 Demographic and other baseline characteristics

Standard descriptive analysis and summary tables for all patients treated by initial treatment will be created for demographic data, oncological history and baseline conditions.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Concomitant diseases will be coded similarly as adverse events based on the most current Medical Dictionary for Regulatory Activities (MedDRA) version. Concomitant therapies will be coded according to World Health Organisation - Drug Dictionary (WHO-DD). Concomitant therapies (CT) will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorise CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level-three category will be counted more than once; footnotes will clarify this possible double counting in tables.

Concomitant medications will be presented according to whether they are concomitant with the reception of study medication, or whether they were given prior to study medication. In case start and stop dates of the medications are completely missing, they are assigned as given prior to study medication.

7.3 TREATMENT COMPLIANCE

Compliance was not analysised separately, but assessed in terms of exposure (including dose intensity, refer to Section 7.7 for further details on exposure analysis).

7.4 PRIMARY ENDPOINTS

The primary endpoints are the MTD and the occurrence of DLT. The MTD is determined from the occurrences of DLTs during the MTD evaluation period (this period is defined in Section 5.1). An overall summary of the DLTs (see CTP Section 4.1.3.2 for definitions of DLT) which occurred during the MTD evaluation period and the on-treatment period will be provided for each dose cohort.

Patients that were treated but replaced for the MTD evaluation (see CTP Section 3.3.5) will be excluded from the MTD determination. Replacement of patients will be determined on a case by case basis; exclusion of these patients from the MTD evaluation will be confirmed by the trial team at the report planning meeting prior to database lock.

A listing of patients with DLTs by initial treatment will be performed.

In case the MTD will not be reached until 1400 mg, it will be deemed as a sufficient tolerability in Japanese patients with advanced solid tumours at 1400 mg.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Other secondary endpoints

This section is not applicable as no secondary endpoint has been specified in the protocol.

7.7 EXTENT OF EXPOSURE

The variables defined in Section 5.4.2 will be summarised descriptively for each dose cohort.

7.8 SAFETY ANALYSES

All safety analyses will be performed on the TS. Patients who were replaced within the first treatment cycle will be excluded from the determination of the MTD.

7.8.1 Adverse events

The analyses of AEs will be descriptive in nature. All analyses will be based on the number of patients with AEs (not the number of AEs).

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE event provided that all of the following applies:

- All AE attributes are identical (Lowest Level Term (LLT), Common Terminology Criteria for Adverse Events (CTCAE) grade, action taken with trial medication, therapy

required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)

- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)

For further details on summarisation of AE data, please refer to (2) and (6).

Adverse events will be coded with the most recent version of MedDRA. The severity of AEs will be scaled according to CTCAE (CTCAE version 4.03 (11)).

The analyses of adverse events will be based on the concept of treatment-emergent adverse events. That means that all adverse events with an onset between first treatment administration until end of the REP will be assigned as 'on treatment'. All adverse events occurring before first drug intake will be assigned to 'screening' and all adverse events occurring after the residual effect period will be assigned to 'post-treatment'; these AEs will be displayed in listings only. Adverse events will be displayed by the initial dose of Xentuzumab administered on the first day of treatment with Xentuzumab. Adverse events will be displayed by the initial dose of study medication administered on the first day of treatment

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with drug-related adverse events, adverse events leading to dose reduction, adverse events leading to discontinuation, serious adverse events, adverse events leading to death, other significant adverse events, adverse events of special interest, and adverse events fulfilling the DLT definition

Sorting order:

In tables presenting System Organ Classes (SOCs) and Preferred Terms (PTs), SOCs will be sorted alphabetically and PTs (within SOC) by descending frequency.

Reporting of CTCAE grades in tables:

In tables showing AEs by worst CTCAE grade, AEs with missing CTCAE grade will only be displayed under the category "All grades", but no category "Mising grade" will be displayed. Therefore the categories "Grade 1" to "Grade 5" might not add up to the category "All grades"; a footnote will explain this handling.

Displaying of CTCAE grades in AE tables (Section 15) will be "All grades", "Grade 1", "Grade 2", "Grade 3", "Grade 4", and "Grade 5" separately.

Listings of adverse events

Adverse events will be reported with start and end day as calculated from the first day of treatment with study medication.

Incidence and severity of adverse events

The incidence of AEs overall (irrespective of relatedness to study medication), related AEs, and serious AEs (SAE) will be reported by severity according to CTCAE grades.

Other significant adverse events

Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction or permanent discontinuation of study medication. Their incidence will be reported by severity according to CTCAE grades.

A listing of patients who developed 'other significant' AEs will be provided and a flag for serious and non-serious will be included.

AEs leading to dose reduction or permanent discontinuation will include:

- AEs leading to dose reduction of Xentuzumab
- AEs leading to permanent discontinuation of Xentuzumab

AEs leading to death

AEs leading to death during the on-treatment period will be tabulated in a separate table. In this table no CTCAE grades will be shown. For fatal AEs without CTCAE garde 5 or missing grade, the grade will be imputed as CTCAE grade 5. Reported fatal AEs that occurred in the post-treatment period will be listed within the listing containing all post-treatment AEs.

Protocol-specified Adverse Events of Special Interest (AESI)

Protocol-specified AESIs are specified in the CTP Section 5.2.2.1. Their incidence will also be reported.

7.8.2 Laboratory data

7.8.2.1 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). The same on-treatment periods as considered for the analysis of adverse events will be applied for laboratory values except for that the baseline laboratory value will be included in the 'on-treatmen' period. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses.

Descriptive statistics, including change from baseline and frequency of patients with transitions relative to the reference range, will be provided. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE version 4.03 (11). The following outputs will be presented:

- Transitions of CTCAE grade from baseline to worst laboratory value, from worst to last laboratory value during the on-treatment phase, and from baseline to last laboratory value.

Patients with missing CTCAE grade at baseline or no baseline value but post baseline values will be displayed in the category "Missing CTCAE grade at baseline". Laboratory values without CTCAE grading will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the refrence range at baseline and the last measurement on treatment.

Analysis of potentially clinically significant abnormal laboratory values, and handling of CTCAE grade -1 and -9 laboratory parameters, are described in the SOP for "Display and analysis of laboratory data" (8).

7.8.2.2 Laboratory values of special interest

Drug-induced liver injury (DILI)

Criteria for 'potential' DILI can be found in Section 5.2.2.1 of the CTP.

Patients fulfilling these criteria will be followed up according to the procedures described in Section 10.3 of the CTP.

Patients with missing laboratory values for liver enzymes will be excluded from these analyses but will be presented separately in a listing.

Tabulations of hepatic enzyme elevations and liver laboratory values (see Section 5.2.2.1 of the CTP), including flags of true DILI cases, are created in accordance with the Food and Drug Administration (FDA) DILI guidance (12).

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

Any findings for ECG will be reported as AE. Separate ECG analyses will not be performed in this trial.

7.8.5 Others

7.8.5.1 ECOG Performance Status changes

A shift table of the worst (highest) and last ECOG performance status category recorded on treatment or during follow-up by baseline category will be produced

8 REFERENCES

1	001-MCG-160_RD-06: "Trial Statistical Analysis Plan - Template", current version; IDEA for CON.
2	001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3	001-MCS-36-472: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
4	001-MCS-36-472_RD-03: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.
5	001-MCS-36-472_RD-01: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
6	001-MCG-156: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
7	CPMP/ICH/137/95: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.
8	001-MCG-157: "Display and Analysis of Laboratory Data", current version, IDEA for CON.
9	001-MCS-40-413: “Important Protocol Deviations”, current version; IDEA for CON.
10	001-MCG-159: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
11	Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010).
12	Guidance for industry: drug-induced liver injury: premarketing clinical evaluation U.S. Departement of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), 2009.
13	Shankar G et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J 16 (4), 658 - 673 2014

10 HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**26-Jun-17**	[redacted]	None	This is the final TSAP without any modification
Revised	**10-Dec-18**	[redacted]	Section 4.2	Added the description the CTR report timing.
			[redacted]	
			Section 6.2 and 7.1.2	Terminology changed from “Protocol violation” to “Protocol deviation” followed latest SOP.
			Section 7.1.2	Appendices section from 16.1.9.2.3 to 16.1.13.1.3 changed followed latest SOP.
			Section 7.9.1 and section 7.9.2	Provided more details on the biomarker analyses.
			Section 7.9.3	Deleted the dose proportionality PK analysis based on the PK colleagues discussion.