Trial Statistical Analysis Plan

c02159131-03

BI Trial No.:	1280.4
Title:	A Phase Ib/II Randomized Study of BI 836845 in Combination with Exemestane and Everolimus Versus Exemestane and Everolimus Alone in Women with Locally Advanced or Metastatic Breast Cancer Including Protocol Amendment 03 [c02243064-12]
Investigational Product(s):	Xentuzumab, BI 836845
Responsible trial statistician(s):	[redacted] Phone: +[redacted]
Date of statistical analysis plan:	25 APR 2018 REVISED
Version:	Revised

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2 LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALKP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
ATC	Anatomical, Therapeutic, Chemical (classification system)
ANOVA	Analysis of Variance
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BI	Boehringer Ingelheim
BIcMQ	BI customised MedDRA Queries
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BLQ	Below lower Limit of Quantification
BMI	Body Mass Index
BRPM	Blinded Report Planning Meeting
BSA	Body Surface Area
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
C1V1	Cycle 1 Visit 1
CI	Confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
CR	Complete Response
CRF	Case Report Form
CSD	Company Standard Displays
CT	Concomitant Therapy

Term	Definition / description
[redacted]	[redacted]
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DC	Disease Control
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DMS	Data Management and Statistics
[redacted]	[redacted]
ECG	Electrocardiogram
ECGS	ECG set
eCRF	Electronic Case Report Form
E_{max}	Maximum measurement of pharmacodynamic parameter
ENR	Enrolled Set
EOT	End of Treatment
EOTV	End of Treatment Visit
[redacted]	[redacted]
FDA	Food and Drug Administration
[redacted]	[redacted]
FU	Follow-up
HR	Hazard Ratio
ICH	International Conference on Harmonisation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IPV	Important Protocol Violation
IRT	Interactive Response Technology

Term	Definition / description
ITT	Intent-to-Treat
LLT	Lowest Level Term
LLOQ	Lower Limit of Quantification
LSMeans	Least-Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Max	Maximum
MQRM	Medical Quality Review Meeting
MMRM	Mixed-effects model for repeated measures
MRI	Magnetic Resonance Imaging
[redacted]	[redacted]
MTD	Maximum Tolerated Dose
MS	MTD Set
NE	Not Evaluable
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PPS	Per Protocol Set
PR	Partial Response
PR interval	ECG interval from the onset of the P wave to the beginning of the QRS complex
PT	Preferred Term
PV	Protocol violation
Q1	25^{th} percentile
Q3	75^{th} percentile
QRS	Combination of the Q, R and S waves
QT	ECG interval from the beginning of the QRS complex to the end of the T wave

Term	Definition / description
QTc	Generic term for QTcF and QTcB intervals
QTcB	QT interval, corrected by Bazett's formula
QTcF	QT interval, corrected by Fridericia's formula
RD	Reference Document
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual Effect Period
RP2D	Recommended Phase II Dose
RPM	Report Planning Meeting
RS	Randomised Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SIR	Synoptic Interim Report
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SOP	Standard Operating Procedure
[redacted]	[redacted]
TCM	Trial Clinical Monitor
[redacted]	[redacted]
[redacted]	[redacted]
TMCP	Translational Medicine and Clinical Pharmacology
TSAP	Trial Statistical Analysis Plan
TTP	Time to Progression
TS	Treated Set
UDAEC	User-Defined Adverse Event Category
ULN	Upper Limit of Normal
URPM	Unblinded Report Planning Meeting
V	Visit
WHO-DD	World Health Organisation - Drug Dictionary

3 INTRODUCTION

As per International Conference of Harmonisation (ICH) E9 (8), 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 Trial Statistical Analysis Plan (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 Ingelheim's (BI) internal reference (1).

The trial consists of two parts, the first part is the dose escalation phase (Phase Ib) and the second part is the randomised phase (Phase II).

The TSAP describes the analysis for both parts of the trial. After the Phase Ib part, safety analyses were performed and documented in a Synoptic Interim Report (SIR) (see Section 9.1) (c03569433-01).

In general, study or trial medication refers to the combination of xentuzumab with exemestane and everolimus, as well as the combination of exemestane and everolimus or the monotherapy of any of the aforementioned medications.

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

Some efficacy endpoints were added in the protocol as further endpoints for the phase Ib part.

[redacted]

4.2 CHANGES

After the decision of the sponsor to stop recruitment on October 28th, 2016 and to stop treatment with xentuzumab, a protocol amendment has been written to cover all applicable changes in the analysis. This TSAP covers the analyses as planned in this protocol amendment (amendment 3, dated 15 DEC 2016)

[redacted]

A final Clinical Trial Report (CTR) will be written before all patients have discontinued trial medication to serve as documentation for future trials. The CTR will be revised after the last patient has completed participation in the trial.

4.3 CLARIFICATIONS

The following points warrant further clarification:

- If not stated otherwise, date of randomisation will be replaced by first treatment administration of any study medication in the outputs (i.e. including the run-in period) for the Phase Ib part of this trial.
- 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. These terms may be used for any combination of everolimus, exemestane or xentuzumab, or any of these medications alone. Clarification is given when necessary.
- [redacted]

5 ENDPOINTS

5.1 PRIMARY ENDPOINTS

Best overall response to trial medication will be determined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (see Appendix 10.4 of the CTP) recorded from first administration of trial medication (Phase Ib part) or from randomisation (Phase II part) until the earliest of disease progression, death or last adequate tumour assessment before new anti-cancer therapy. Details about derivation of best overall response are given in Section 5.4.7.

All timepoints utilised for Progression Free Survival (PFS) assessment, should be used for the evaluation of all RECIST 1.1 based endpoints.

5.1.1 Phase Ib

The primary endpoints are 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 28 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 28 days will be used.

Patients that have a DLT event before Cycle 1 Visit 1 (C1V1) may have to be replaced. This DLT will not be taken into consideration for the MTD determination. Other reasons for replacing patients are described in CTP Section 3.3.5.

The MTD and the safety profile (including DLTs occurring after first treatment course), will be the basis to define the Recommended Phase II Dose (RP2D) to be used for the phase II part of this trial and further trials in the development of xentuzumab in combination with exemestane and everolimus.

5.1.2 Phase II

The primary endpoint for the Phase II part of the study is PFS based on investigator assessment.

PFS is defined as the time from randomisation until radiological tumour progression according to RECIST guideline (version 1.1) (R09-0262) or death from any cause, whichever occurs earlier.

Tumour assessments are planned to be performed at screening and then every 8 weeks after randomisation until week 48 and every 12 weeks thereafter. After amendment 3 of the CTP (see also Section 4.2), the imaging schedule has been made more flexible. However, it was decided to keep the initial planned schedule for the definition of time windows for censoring rules (see also Section 6.7.2).

For each follow-up imaging timepoint an overall tumour response will be determined according to RECIST 1.1. The overall tumour response for each imaging timepoint will be selected from the following categories: Complete Response (CR); Partial Response (PR); Stable Disease (SD); Progressive Disease (PD); Non-CR/Non-PD; Not Evaluable (NE).

For details on the imaging process and RECIST 1.1 evaluation, see Sections 5.1.2 and 10.4 of the CTP.

Derivation of endpoint PFS

Derivations below are described in days. However, the endpoints below will be presented in months in the outputs produced for the CTR.

For patients with 'event' as an outcome for PFS: (according to RECIST version 1.1)

- PFS [days] = date of outcome - date of randomisation + 1.

For patients with 'censored' as an outcome for PFS: (according to RECIST version 1.1)

- PFS (censored) [days] = date of outcome - date of randomisation + 1.

The censoring rules for PFS (i.e. outcome and date of outcome) are given in Table 5.1.2: 1. Clinical disease progression will not be considered for determination of a PFS event, unless the outcome of the progression is death.

If patients would have their radiological examinations over a number of days, i.e. target lesions assessed on day x, non-target lesions assessed on day y and new lesion (if applicable) on day z, the following rules will be applied:

- If the overall response is PD, the earliest date of multiple assessments will be taken.
- If the overall response is SD, Non-CR/Non-PD, PR, CR or NE, the latest of multiple assessment dates will be taken, i.e. in the case of SD, Non-CR/Non-PD, PR, CR, the latest of multiple dates will be used to censor the patients.

Imaging assessments for which NE is assigned as the overall response at an imaging time-point are considered to be missed assessments. Please note that NE does not indicate lack of progression.

Table 5.1.2: 1 Derivation rules for PFS

Situation	**Outcome (event or censored)**	**Date of outcome**
No baseline radiological assessment		
Patient with death on or before the second planned radiological assessment	Event	Date of death

Table 5.1.2: 1 Derivation rules for PFS (cont.)

Situation	**Outcome (event or censored)**	**Date of outcome**
Patient without death or patient with death after second performed radiological assessment	Censored	Date of randomisation (or first treatment administration, in non-randomised trials)
Without post-baseline radiological assessments		
Vital status is unknown or patient is known to be alive	Censored	Date of randomisation (or first treatment administration, in non-randomised trials)
Death prior or on the second planned radiological assessment	Event	Date of death
Death beyond the second planned radiological assessment	Censored	Date of randomisation (or first treatment administration, in non-randomised trials)
With baseline and post-baseline radiological assessments BUT no other anti-cancer therapy		
Alive and not progressed, no more than one consecutively missed radiological assessments	Censored	Date of last radiological assessment
Alive and not progressed, two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, zero or one missed radiological assessment prior to progression	Event	Date of radiological assessment of progression

Table 5.1.2: 1 Derivation rules for PFS (cont.)

Situation	**Outcome (event or censored)**	**Date of outcome**
Progressed, but two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessment
Death but no progression, zero or one missed radiological assessment prior to death	Event	Date of death
Death without progression, but two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent-anti cancer therapy started prior to a death	Censored	Date of randomisation (or first treatment administration, in non-randomised trials)

In order to identify that consecutive imaging timepoints are missing for a given patient, a nominal time point [8, 16, 24, 32, 40, 48 weeks, and every 12 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.

Last evaluable imaging

An evaluable radiological image for the censoring of PFS is an image for which an overall response assessment of SD, Non-CR/Non-PD, PR or CR has been assigned. This is used for censoring of patients without progression at end of trial, or censoring prior to missed assessments, or censoring prior to subsequent anti-cancer therapy.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Other secondary endpoints

5.2.2.1 Phase Ib

There are no secondary endpoints.

5.2.2.2 Phase II

Time to progression (TTP)

TTP is defined as the time from randomisation until tumour progression according to RECIST 1.1.

For patients with 'event' as an outcome for TTP:

- TTP [days] = date of outcome - date of randomisation +1.

For patients with 'censored' as an outcome for TTP:

- TTP (censored) [days] = date of outcome - date of randomisation +1.

Patients without a progression event at the time of the primary analysis will be censored at the time of the last evaluable radiological image. An evaluable radiological image for censoring of time to progression is an image for which an overall response assessment of SD, Non-CR/Non-PD, PR or CR has been assigned. This is used for censoring of patients without progression at end of trial, or censoring prior to missed assessments, or censoring prior to subsequent anti-cancer therapy.

More detailed censoring rules are indicated in Table 5.2.2.2: 1.

Table 5.2.2.2: 1 Derivation rules for Time to Progression

Situation	**Outcome (event or censored)**	**Date of outcome**
No baseline radiological assessment	Censored	Date of randomisation (or first treatment administration, in non-randomised trials)
Without post-baseline radiological assessments	Censored	Date of randomisation (or first treatment administration, in non-randomised trials)
With post-baseline radiological assessments BUT no subsequent anti-cancer therapy		
Alive and no tumour progression, no more than one consecutively missed radiological assessments	Censored	Date of last radiological assessment

Table 5.2.2.2: 1 Derivation rules for Time to Progression (cont.)

Situation	**Outcome (event or censored)**	**Date of outcome**
Alive and not progressed, two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Tumour progression, zero or one missed image prior to progression	Event	Date of radiological assessment of progression
Progression, two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessments
Death but no progression	Censored	Date of last radiological assessment prior to death
With post-baseline radiological assessments AND subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression	Censored	Date of last radiological assessment before subsequent anti-cancer therapy

Objective response (OR)

OR is defined as best overall response of CR or PR, where best overall response is determined according to RECIST 1.1 from randomisation until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

Time to OR

Time to objective response is defined as the time from randomisation until first documented CR or PR.

Time to objective response will only be calculated for patients with an objective response:

- Time to OR [days] = date of first documented CR or PR - date of randomisation +1.

Duration of OR

Duration of objective response is defined as the time from first documented CR or PR until the earliest of disease progression or death among patients with objective response.

Duration of objective response will only be calculated for patients with an objective response. For patients with disease progression or death:

- Duration of OR [days] = date of outcome – date of first assessment indicating OR + 1.

For patients without disease progression or death:

- Duration of OR (censored) [days] = date of outcome – date of first assessment indicating objective response + 1

The censoring rules for duration of OR are given in Table 5.2.2.2: 2.

Table 5.2.2.2: 2 Derivation rules for Duration of Objective Response

Situation	**Outcome (event or censored)**	**Date of outcome**
No other anti-cancer therapy		
Alive and not progressed, no more than one consecutively missed radiological assessments	Censored	Date of last radiological assessment
Alive and not progressed, two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, zero or one missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, but two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessments
Death but no progression, zero or one missed radiological assessment prior to death	Event	Date of death
Death without progression, but two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death, no more than one consecutively missed radiological assessments prior to start of subsequent anti-cancer therapy	Censored	Date of last radiological assessment before initiation of subsequent anti-cancer therapy

Only radiological assessments after first assessment indicating objective response will be taken into consideration.

Disease control (DC)

DC is defined as best overall response of CR or PR, or SD ≥24 weeks, or Non-CR/Non-PD for ≥24 weeks where best overall response is defined according to RECIST version 1.1 from date of randomisation until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy (see Section 5.4.7).

Duration of DC

Duration of DC is defined as the time from randomisation until the earliest of disease progression or death, among patients with DC.

Duration of DC will only be calculated for patients with a DC. For patients with disease progression or death:

- Duration of DC [days] = date of outcome – date of randomisation + 1.

For patients without disease progression or death:

- Duration of DC (censored) [days] = date of outcome – date of randomisation + 1.

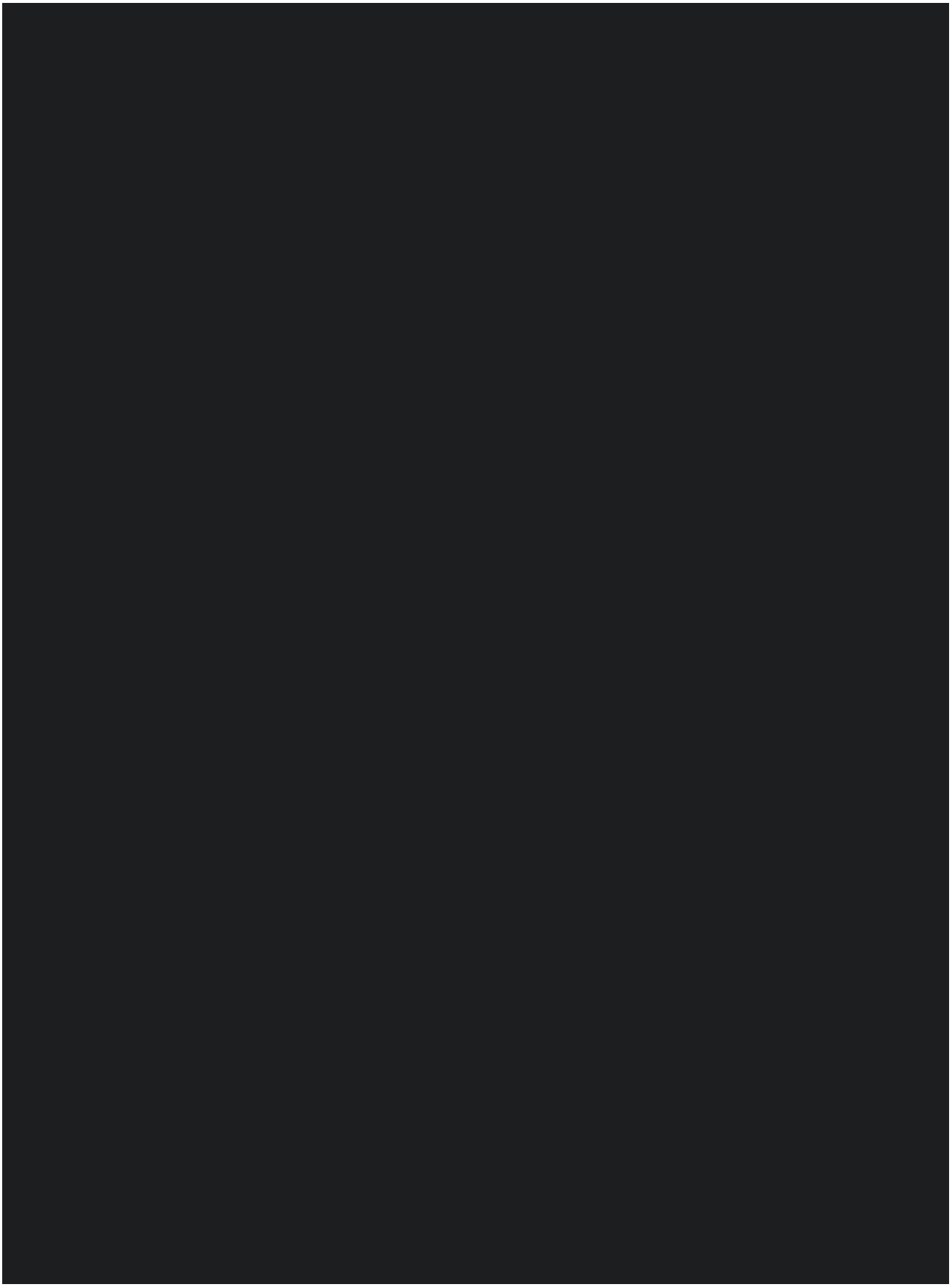
The censoring rules for duration of DC are given in Table 5.2.2.2: 3.

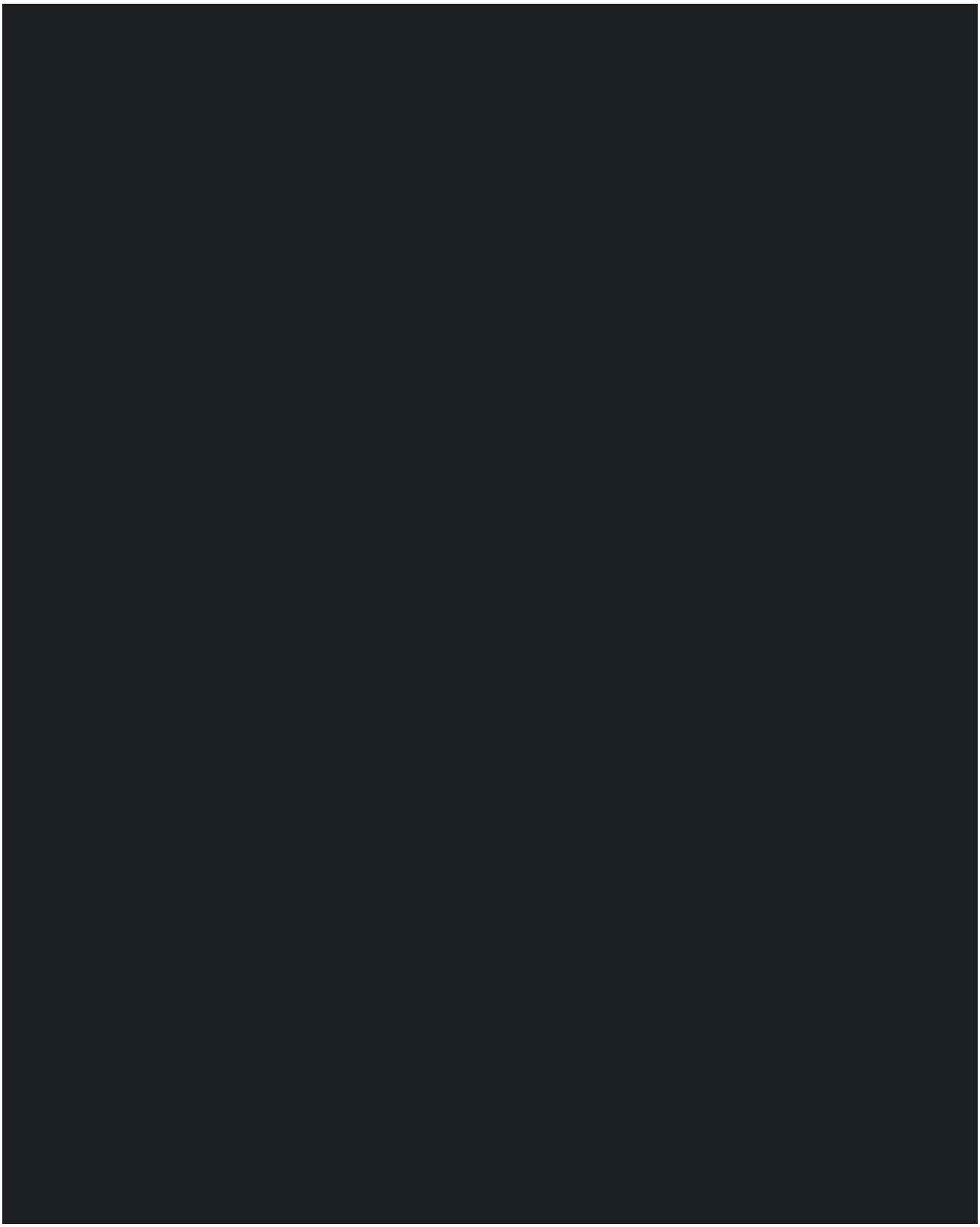
Table 5.2.2.2: 3 Derivation rules for Duration of Disease Control

Situation	**Outcome (event or censored)**	**Date of outcome**
With baseline and post-baseline radiological assessments BUT no other anti-cancer therapy		
Alive and not progressed, no more than one consecutively missed radiological assessments	Censored	Date of last radiological assessment
Alive and not progressed, two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, zero or one missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, but two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessments
Death but no progression, zero or one missed radiological assessment prior to death	Event	Date of death

Table 5.2.2.2: 3 Derivation rules for Duration of Disease Control (cont.)

Situation	**Outcome (event or censored)**	**Date of outcome**
Death without progression, but two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent anti-cancer therapy started prior to a death	Censored	Date of randomisation (or first treatment administration, in non-randomised trials)





5.4.2 Treatment exposure

Total treatment duration [days]:

Date of last administration of any trial medication – date of first administration of any trial medication + 1.

As the date of first administration corresponds to the first intake of xentuzumab or everolimus or exemestane, total treatment duration includes the run-in period in the phase Ib part. Total treatment duration therefore also includes time when treatment was temporarily discontinued and subsequently reintroduced.

Duration of specific medication exposure [days]:

Date of last administration of specific medication – date of first administration of specific medication + 1.

Duration of specific medication exposure will be calculated separately for xentuzumab, exemestane and everolimus.

Number of courses initiated [N]:

Course initiated means that the patient received at least one administration of trial medication in the initiated course.

Total number of xentuzumab infusions [N]:

Sum of xentuzumab infusions calculated across all courses.

It will be calculated for each patient who received at least one infusion of xentuzumab.

Number of patients with at least one dose reduction

Number of patients with at least one dose reduction will be counted.

The number of patients with at least one dose reduction will first be calculated for any medication and then separately for each specific medication for which dose reduction is allowed. This means that it will be calculated separately for xentuzumab and everolimus.

Time to first dose reduction of specific medication [days]:

Date of first administration of the first reduced dose of specific medication – date of first administration of specific medication + 1.

Time to first dose reduction will be calculated only for patients who had a dose reduction.

This will also be calculated separately for patients with a dose reduction of xentuzumab or everolimus.

Total dose of specific trial medication [mg]:

Total dose of trial medication will be calculated separately for xentuzumab, exemestane and everolimus.

For xentuzumab, this is the sum of the administered doses calculated across all courses and this takes into account the dose reductions.

For exemestane and everolimus, this is calculated as the total duration of treatment with this medication in days multiplied by the actual dose taken (using the actual dose recorded on the Case Report Form (CRF)) for the days the medication was taken. This takes into account the dose reductions of everolimus.

This calculation is only an approximation of the total dose taken, since the way the data are collected does not allow a more precise calculation.

Dose intensity of specific trial medication during all treatment duration (%):

Dose intensity of trial medication will be calculated separately for xentuzumab, exemestane and everolimus:

100*(Total dose of specific trial medication actually received by a patient / Planned total dose of specific trial medication during the entire duration of treatment).

The planned total dose is calculated as the total dose of the medication a patient should have received from the date of first administration of the medication to the date of last administration.

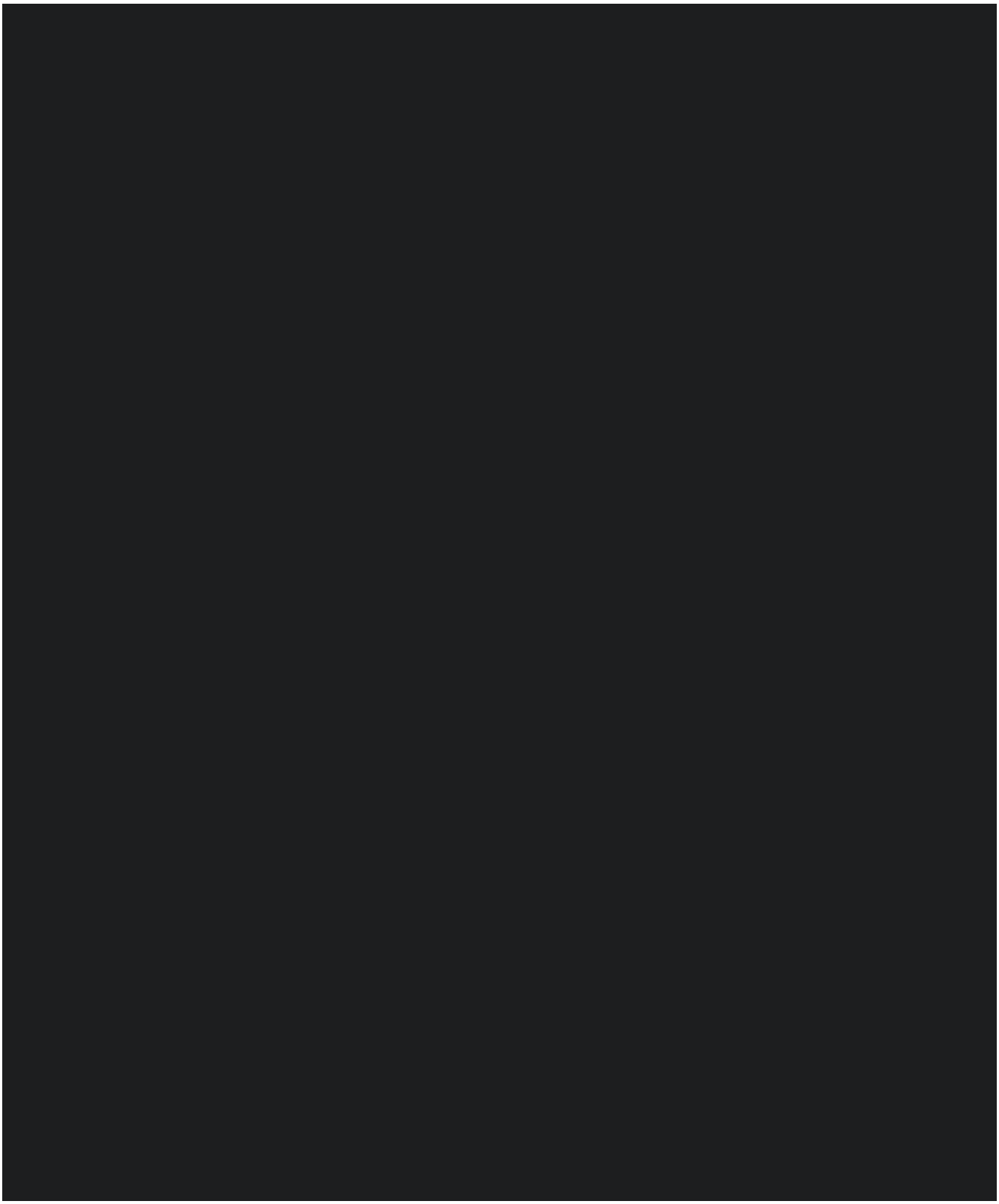
The planned total dose of xentuzumab for each patient is calculated using the following formula: planned dose per infusion (e.g. 1000 mg) multiplied by number of visits with administration of xentuzumab.

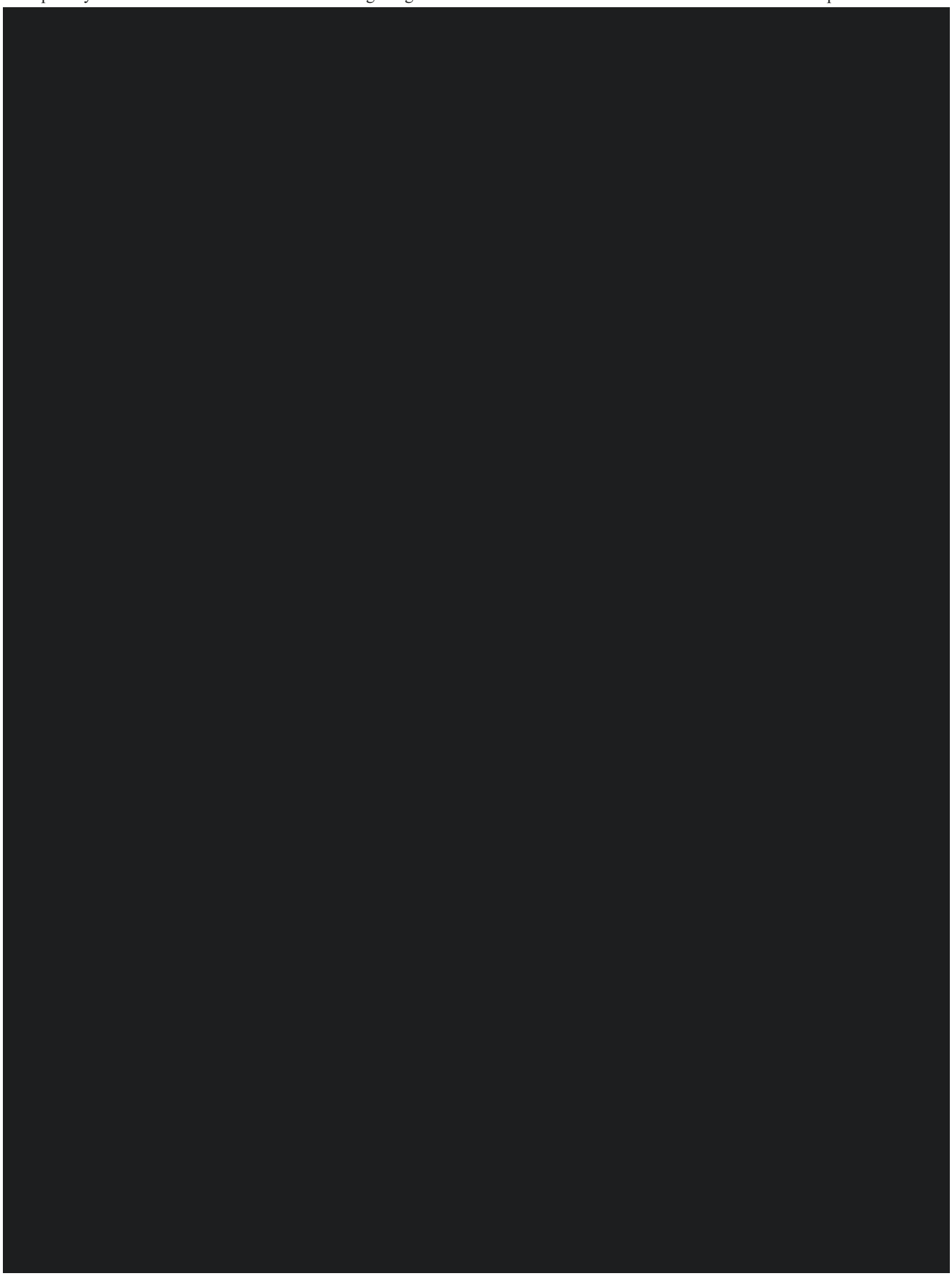
For exemestane and everolimus, the planned total dose for each patient is calculated using the following formula: total duration of treatment with this medication in days multiplied by the planned daily dose (e.g. 10 mg, using the dose the patient was assigned (Phase Ib part) or randomised to (Phase II part)).

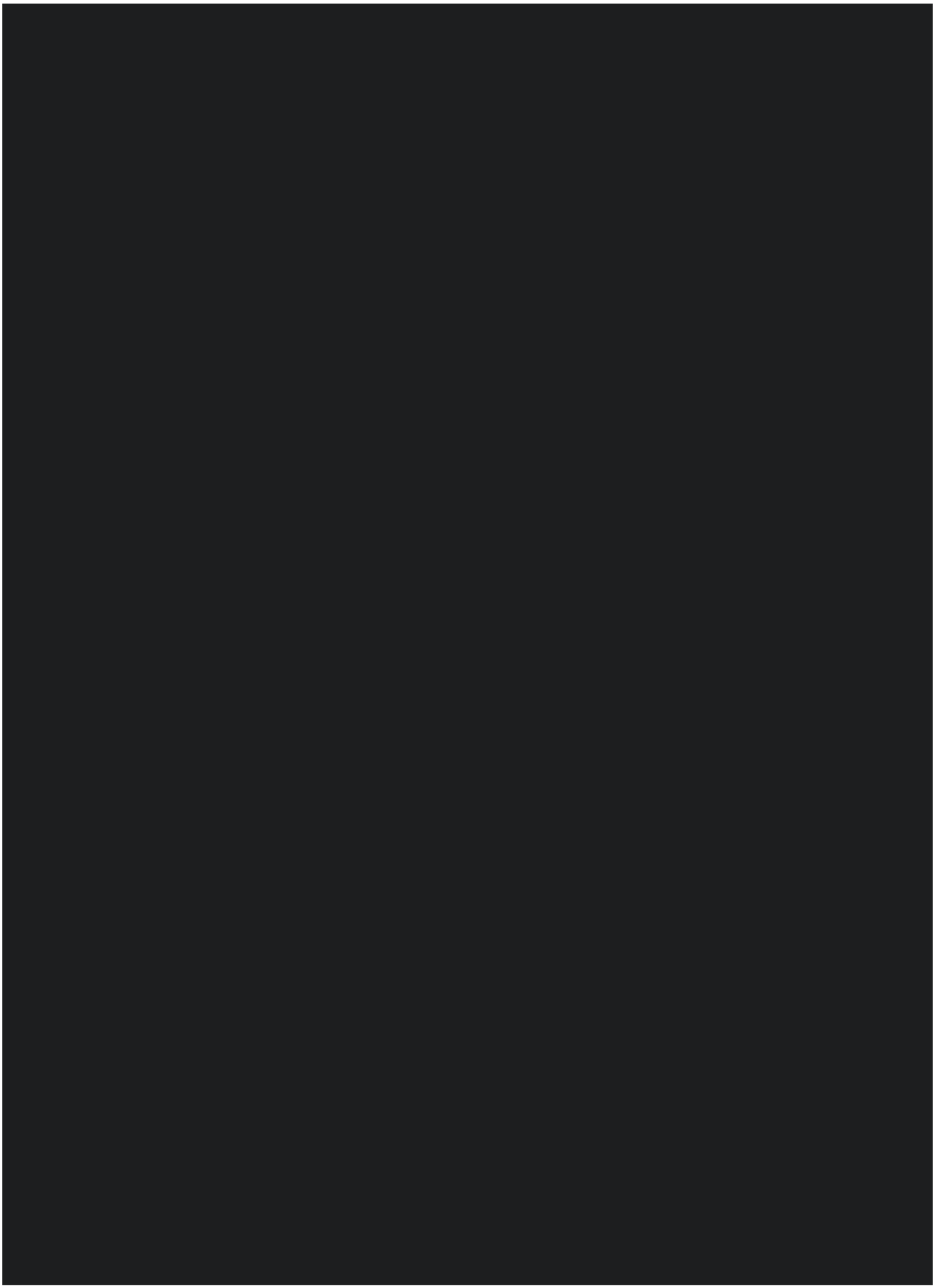
This is done assuming that the initial dose was taken throughout, and dose reduction as specified in the protocol will not be considered in the calculation. This means that if a patient

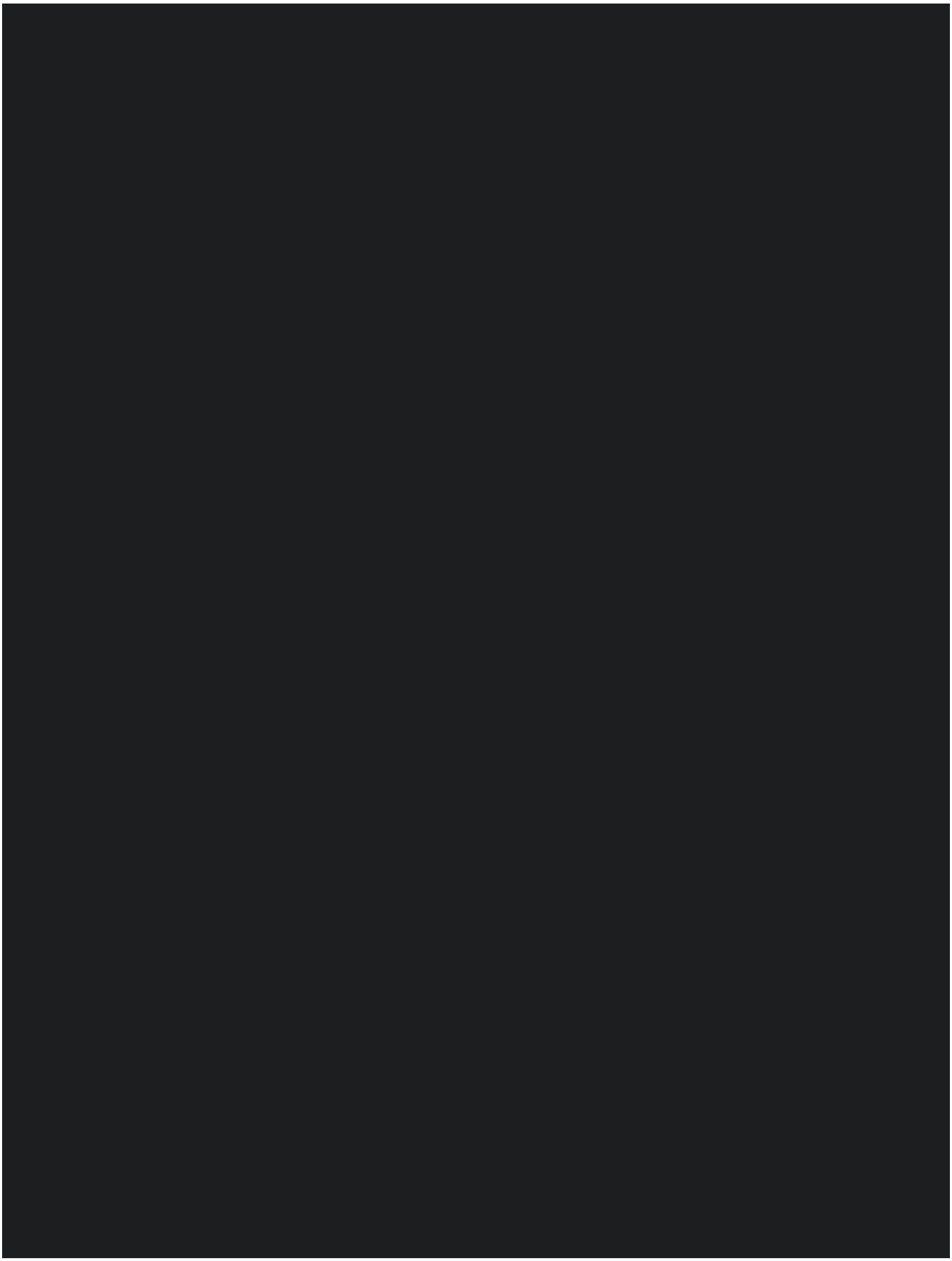
had protocol-defined dose reduction due to an AE, the reduced dose will not be used in the calculation of the denominator.

For everolimus and exemestane, this calculation is only an approximation of the dose intensity, since the way the data are collected does not allow a more precise calculation.









5.4.6 Electrocardiogram (ECG) assessments and variables

Please refer to Section 9.2.1 for derivation of ECG variables. The generic term QTc for heart rate corrected QT intervals comprises the fixed corrections QTcF (Fridericia's correction) and QTcB (Bazett's correction) intervals. The term 'on-treatment' refers to all scheduled ECG recordings following the first administration of study medication until end of the residual effect period (see also Section 6.1).

Continuous endpoints

- Changes in QTcF interval between baseline and on-treatment
- Absolute QTcF intervals at baseline and on-treatment

The above endpoints will also be computed for the variables QTcB, uncorrected QT interval, heart rate, PR interval and QRS complex. Furthermore, the percentage change will be calculated for PR interval and QRS complex.

Categorical endpoints

- QTcF intervals ≤ 450 msec, > 450 to ≤ 480 msec, > 480 to ≤ 500 msec or > 500 msec at baseline and maximum on-treatment value
- QT intervals ≤ 500 msec, > 500 msec at baseline and maximum on-treatment value
- Maximum change from baseline to on-treatment value in QTcF interval ≤ 30 msec, 30 msec < QTcF interval ≤ 60 msec, > 60 msec
- Maximum change from baseline to on-treatment value in QT interval ≤ 60 msec, > 60 msec
- Increase of the PR interval from baseline ≥ 25%, when the corresponding PR interval is > 200 msec
- Increase of QRS complex from baseline ≥ 25%, when the corresponding QRS complex is > 110 msec

The categorical endpoints based on the QTcF interval will be derived for the QTcB interval correspondingly.

Notable findings are defined as

- QTcF change from baseline to on-treatment value > 60 msec at any time on-treatment
- new onset of QT/QTcF > 500 msec, where "new onset" denotes the occurrence of a finding on-treatment which was not present at baseline

Morphological (qualitative ECG) assessments will include

- qualitative ECG findings, like new onset of rhythm, conduction, ST segment, T and U wave findings, evidence of myocardial infarction, etc., where "new onset" denotes the occurrence of an on-treatment finding, while at baseline this finding was not observed.

6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Phase Ib: Patients will be analysed according to the cohort initially assigned. All planned analysis 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 Database Lock (DBL) meeting (but prior to DBL).

Phase II: For safety analyses, treated patients will be analysed according to the treatment they actually received. For efficacy analyses, the Intent-To-Treat (ITT) approach will be used, i.e. patients will be analysed according to the treatment group they were randomised to.

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 “8-07-other-sdtm-trial-arms-trial-elements”, which can be found in Data Management and Statistics (DMS) folder, Section 8, within Boehringer Ingelheim Regulatory Documents for Submission (BIRDS).

6.2 IMPORTANT PROTOCOL VIOLATIONS

No per protocol set (PPS) analysis will be performed for this study, hence, no patient will be excluded from the analyses (except those with missing informed consent or not adhering to age limit). However patients with potentially important protocol violations (IPVs) will be documented. The following list of potentially IPVs in Table 6.2: 1 will be used; note that this is a working list and may not be finalised until the final Blinded Report Planning Meeting (BRPM) or DBL meeting (but prior to DBL for the primary analysis). Potentially IPVs will be handled according to BI standards (6).

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 violations

Category/ Code		**Description**	**Requirements**	**Excluded from**
A [1]		**Entrance criteria not met**		
	A1	Diagnosis of trial disease questionable	Inclusion criteria* IN 1 or IN 2 not met.	None

Table 6.2 : 1 Important protocol violations (cont.)

Category/ Code		Description	Requirements	Excluded from
	A2	Prohibited baseline condition, diagnosis or treatment	At least one of inclusion criteria* IN 4- 9 or IN 12 is not met or At least one of exclusion criteria* is met.	None
	A3	Laboratory result indicating inadequate organ function at screening	Inclusion criteria* IN 10 or IN 11 not met	None
	A4	Adequate archival tumour tissue not available	Inclusion criterion* IN 3 not met.	None
B [1]		**Legal Criteria**		
	B1	Informed consent not available / not done	Informed consent date missing or inclusion criterion* IN 13 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	Calculate age given the date of birth and date of informed consent. Patients must be ≥ 18 years old.	All
C		**Trial medication and randomisation**		
	C1 **[2]**	Time window violation for procedures performed at screening	Screening imaging earlier than 28 days to first drug intake; Safety labs, ECG performed earlier than 28 days to, or later than first drug intake; Timeframe > 4 days between randomisation and first drug intake	None

Table 6.2 : 1 Important protocol violations (cont.)

Category/ Code		Description	Requirements	Excluded from
	C2 **[2]**	Trial medication not given according to protocol	Dose reduction scheme not followed (see CTP section 4.1.4.3); Administration of trial medication(s) not compliant. Indicated by medical review (i.e. where Administration of xentuzumab according to the protocol = 'No' and associated comments, or compliance data from Exemestane/Everolimus with associated comments) Please note: This excludes the investigational treatment given outside the boundaries specified in the CTP (covered in Category C3)	None
	C3 **[1]**	Infusion time for the investigational treatment outside of CTP specific boundaries	Infusion duration of xentuzumab given <50 minutes or >200 minutes (Infusion time should be from 60 to 180 minutes, but the thresholds above are accepted). The exact duration of the infusion should be calculated taking interruptions into account. In case of missing administration times, the violation will not be considered important if administration according to protocol = 'Yes'	None
	C4 **[2]**	Patient assignment not followed	Patients do not receive the initial treatment they were randomised / allocated to	None
	C4.1	Randomisation not followed	This applies only for phase II part of the trial	None

Table 6.2 : 1 Important protocol violations (cont.)

Category/ Code		Description	Requirements	Excluded from
	C4.2	Treatment allocation not followed	This applies only for phase Ib part of the trial. Treatment taken at C1V1 is not the treatment assigned at screening.	None
D [2]		**Concomitant medication**		
	D1	Prohibited treatment during trial conduct phase	Treatment taken during the treatment period as described in Section 4.2.2.1 of the CTP. For phase Ib part only, during run-in and course 1: CYP3A4 strong inhibitors, CYP3A4 moderate inhibitors, CYP3A4 strong inducers, CYP3A4 moderate inducers, inhibitors of P-glycoprotein	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 TSAP Section 6.7.2).	None
F [2]		**Trial Specific protocol violations**		
	F1	Other protocol violations affecting patient rights or safety	Manual Protocol Violations (PVs) will be collectively captured.	None

[1] IPV will be derived automatically
[2] IPV will be identified via individual review at MQRM/Report Planning Meeting (RPM)/DBL.

* During the amendments of CTP the inclusion and exclusion criteria were adapted. Therefore, the inclusion/exclusion criteria valid at subject's enrolment have to be considered.

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 any study medication during the treatment cycles (from day 1).

In the Phase Ib part, the TS includes the run-in period and will be used for all planned safety and efficacy analyses, unless otherwise specified (some analyses will be performed on the MTD set, details are provided in technical TSAP). In the Phase II part, the TS will be used for all planned safety analyses.

- MTD Set (MS)

The MTD set defines the set of patients in the Phase Ib part of the trial that are fully evaluable for determination of the MTD in the first treatment course. The MTD set will be used for some safety analyses in the Phase Ib part, this is specified in the technical TSAP. Patients in the Phase Ib part that are treated at the MTD after the MTD determination are not included in the MTD set (the list of patients included in the MTD Set is provided in a separate document that is archived in BIRDS).

Patients in the TS who were replaced within the MTD evaluation period in the Phase Ib part of the trial will be excluded from the determination of the MTD. Replacement of patients in the Phase Ib part 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.

- Randomised Set (RS)

This patient set includes all randomised patients in the Phase II part of the trial, regardless of whether or not they have received treatment. Patients are assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised. The randomised set will be used for the efficacy analyses of patients in the second part of the study.

[redacted]

- ECG Set (ECGS)

This patient set includes all patients in the treated set who do not have an artificial cardiac pacemaker and have at least one on-treatment value (based on data collected until the safety cut-off date of 9th December 2016 (end of xentuzumab administration on 28th October 2016 + 42 days (length of REP)) for at least one ECG variable.

- ECG-PK Set

This patient set includes all patients in the ECG set from the Phase II part who are

- in the comparator group ('everolimus+exemestane') or
- in the 'xentuzumab + everolimus+exemestane' group and have at least one time-matching pair of valid xentuzumab plasma concentration and QTcF change from baseline (see Section 7.8.4).

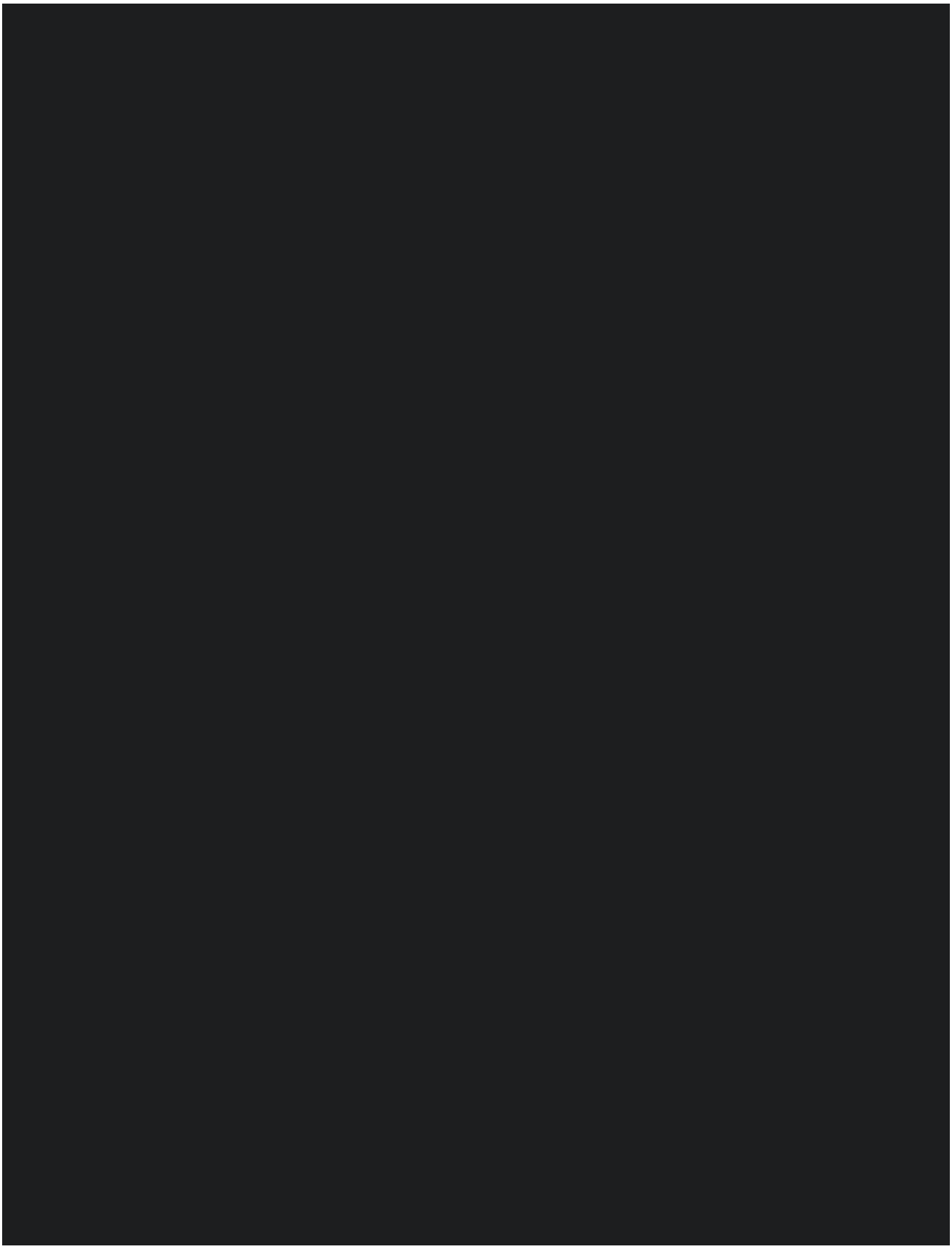
The decision whether a concentration is considered valid will be made no later than at the final BRPM before DBL.

Please refer to Section 7.8.4 for the definition of the maximum acceptable time deviation between PK blood sampling and ECG recording at different time points during the trial.

The analyses of ECG data will be based on the ECG set except those concerning the relationship between plasma concentrations and ECG variables which will be based on the ECG-PK set. Listings for patients with artificial pacemakers will be based on the TS.

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 previous 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 BRPM before database lock at the latest.

The rules in the Table 6.6: 1 below have been agreed by the trial and project teams, and will be used in this trial, if applicable.

Table 6.6: 1 Rules for imputations of missing or incomplete dates

Date	Imputation rule
Date of birth	In case only the year is given: 31st of December
Date of death	Date last known to be alive. If only year and month are given: this will be imputed with 1st of the month for the analysis of OS
Date of first histological diagnosis	1st of month if day is missing 1st of January if month also missing
Date of first appearance or recurrence of metastasis	1st of month if day is missing 1st of January if month also missing
Date of start of concomitant medication	No imputation required
Date of end of concomitant medication	No imputation required
Date of start of subsequent anti-cancer therapy (imputation required only for censoring of PFS)	If the day (respectively day and month) of the start date of subsequent anti-cancer therapy is missing, then the first of the month (respectively 1st January) will be imputed unless this date leads to a date before the stop date of study medications. In this case, the study medications stop date + 1 day will be imputed. Additionally, all imputed start dates of subsequent anti-cancer therapy should be before death date if available.
Date of stop of subsequent anti-cancer therapy	No imputation required
Date of end of treatment (only for patients still ongoing at time of snapshot/DBL)	Date of snapshot/DBL

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 C1V1 (before the very first administration of study medication) data from preceding visits will be used.

[redacted]

6.6.4 Randomisation and stratification (IRT versus CRF) (only for phase II)

In general, data as reported in the eCRF will be used for analyses. If data are missing in the eCRF (e.g. stratification factors) they will be imputed with the data from Interactive Response Technology (IRT).

6.6.5 ECG

If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced (1 or 2) number of recordings.

If single cardiac cycles (also denoted as beats or waveforms) are missing, the arithmetic means per single ECG will be computed with the reduced (1 or 2) number of cardiac cycles.

If baseline is missing, a QTcF/QT interval > 500 msec at any time on treatment will be a notable finding. In case of a missing qualitative ECG finding at baseline, a finding observed on-treatment will be categorized as 'new onset'.

Exposure-response analyses

Missing xentuzumab plasma concentration data, identified in the ADPC dataset by below lower limit of quantification (BLQ), will be replaced by zero if measured at baseline and by ½ lower limit of quantification (LLOQ) if measured on-treatment.

If the actual sampling time of the blood sample or of the ECG recording is not available, the pair of plasma concentration and time-matched ECG endpoint will be excluded from the analyses at the corresponding planned time point. Furthermore, all plasma concentrations flagged with 'exclusion' by the PKEXC variable ADPC dataset will be excluded from the exposure-response analyses.

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. The run-in period in the Phase Ib part is considered as time with study medication. If this criterion is not fulfilled then no baseline will be derived, except in the following case: if a patient is entered (phase Ib part) or randomised (phase II part), but not treated, the last value we have for the patient is considered baseline.

Laboratory values:

Baseline is defined as the latest time-point before the very first administration of any study medication.

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.

ECG

Baseline values will be derived from the triplicate at the time-point closest to but prior to the first administration of study medication.

6.7.2 Time windows for every RECIST assessment

In order to identify whether consecutive imaging timepoints are missing for a given patient, a nominal time point [8, 16, 24, 32, 40, 48 weeks and every 12 weeks thereafter] will be assigned to each and every image. This is achieved by creating windows for every RECIST 1.1 assessment. The windows are defined in Table 6.7.2: 1 below. Day 1 corresponds to date of randomisation for the Phase II part (for the Phase Ib part it corresponds to the date of first drug intake of xentuzumab).

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]**
8	57	1 to =< 85
16	113	86 to =< 141
24	169	142 to =< 197
32	225	198 to =< 253
40	281	254 to =<309
48	337	310 to =<379

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

Nominal time-point [weeks from start of therapy]	**Due date of scans [days]**	**Window [days]**
60	421	380 to =<463
72	505	463 to =<547
every 12 weeks interval	etc (1)	etc (1)

(1) Due date of scans = (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, she will be said to have 'missed an assessment' for that timepoint. 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 (7).

Unless otherwise specified, outputs will be displayed separately for each part of the trial.

Descriptive statistics for continuous variables will generally contain N (number of patients in that patient set with non-missing values), Mean, Standard Deviation, Minimum (Min), 25th percentile (Q1), Median, 75th percentile (Q3), Maximum (Max). In general, means, standard deviations, medians, Q1 and Q3 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.

For time-to-event analysis tables, the set of statistics is: number of patients [N (%)], Number of patients with event [N (%)], Number of patients censored [N (%)], <Time to event> [months] followed by Q1 (25th percentile), Median, Q3 (75th percentile). If not specified otherwise, the duration as well as time to event will be displayed in months.

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, if there are missing data for the corresponding variable. Percentages will also generally be based on all patients in the respective patient set whether they have non-missing values or not.

The primary analysis will include all treated (Phase Ib) or randomised patients (Phase II), following the ITT approach (as specified in Section 6.3).

The analyses for the primary endpoint of PFS as well as best overall response, OR, time to OR, duration of OR, DC, duration of DC, time to progression, tumor shrinkage, tumor size as well as the [redacted] will be based on data obtained until November 25th 2016. A sensitivity analysis for the primary endpoints PFS will be performed using all data. Analyses of other RECIST based endpoints will also only utilise data obtained from assessments scheduled until November 25th 2016. For overall survival all available data will be used.

Analyses of AEs for the phase II will be split in two parts. The first part considers all AEs with onset date on or before the cut-off date 9th of December 2016 (28th of October 2016 + length of REP (42 days)) and AEs with onset date after 9th of December 2016. Details are given in Section 7.8.1.

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.

In general, a "Total" column will be displayed in section 15.1 (Trial subjects) of the CTR. In Sections 15.2 and 15.3 of the CTR, a "Total" column will be displayed in Phase Ib outputs, but not in Phase II outputs.

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 = days × 12 ÷ 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/CSD (Company Standard Displays) catalogue will be populated. Additionally, patients with discontinuations by initial treatment and the reasons will be listed and tabulated, overall and for each treatment separately. The same output will also contain an overview of discontinued and non-discontinued, as well as completed and non-completed patients. In Appendix 16.1.9.2, a disposition table by country will be produced.

Disposition of patients will also be displayed by visceral involvement.

7.1.2 Important protocol violations

A table and a listing of patients with important protocol violations based on Table 6.2: 1 will be created in Section 15.1.3 and Appendices 16.2.3 and 16.1.13.1 (if needed) respectively, of the 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.

For the subgroup of the first tier visceral involvement demographic characteristics as well as oncological history will be provided as well.

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 analysed separately by treatment received. The number of missed doses of any medication as recorded on the eCRF will be listed by patient.

7.4 PRIMARY ENDPOINTS

7.4.1 Phase Ib

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 5.1.1). An overall summary of the DLTs (see CTP Section 5.2.6 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. A plot with an overview of the phase Ib escalation part (showing the patients and their doses, replaced patients as well as patients with DLTs) will be displayed.

At the end of the dose escalation phase, a safety analysis will be performed to determine the RP2D. The results will be documented for internal use and communication with the participating investigators. (see also in Section 9.1)

7.4.2 Phase II

The primary analysis will be conducted for all patients of the randomised set in the Phase II part of this trial; following the changes described in Section 4.2, only response assessments until the cut-off date of 25th November 2016 will be used (as described in protocol). For the derivation of the censoring rules, the status of the patient (e.g. treatment ongoing / discontinued / new anti-cancer therapy) will be taken as of the cut-off date. This means if a patient was ongoing at the cut-off date, its PFS with cut-off will be censored at last assessment before the cut-off, with reason treatment ongoing.

PFS by investigator's assessment is the primary endpoint and will be assessed based on the Kaplan-Meier method for each treatment arm separately. Point estimates together with confidence intervals (CIs) (based on Greenwood's method) will be provided for median PFS.

An estimation of the effect on PFS of xentuzumab plus exemestane plus everolimus compared to the effect on PFS of exemestane and everolimus will be given by the hazard ratio (HR) and its 95% CI using a stratified Cox proportional hazards model (using visceral involvement as stratification factor). The validity of the underlying assumptions of this model will be checked. HRs < 1 will favour treatment with xentuzumab plus exemestane plus everolimus; p-value from the two-sided log-rank test will be also displayed but it should be emphasised here that this is only to be understood in an exploratory way. The Breslow method for handling ties will be used. The censoring rules for PFS are as stated in Section 5.1.2.

7.4.2.1 Subgroup analyses for PFS

Subgroup analyses will be conducted for the primary endpoint of the Phase II part (PFS) as follows:

For each of the subgroups specified in Section 6.4 HRs will be produced in order to investigate the subgroups. HRs will be obtained from the models fitted for each level of the baseline covariate. All Cox models will be adjusted (but not stratified, due to the low number of patients) with the stratification factor visceral involvement. However, in the case when investigating the stratification factor, the model will not be adjusted.

To provide a statistical framework for interpretation of the consistency of the treatment effect interaction p-values will be created using a model adjusted for treatment, stratification factor, subgroup and treatment by subgroup interaction. However, in the case when investigating the stratification factor, the model will not be adjusted additionally for this factor. For the evaluation of the interaction between treatment effect and the baseline variables, all subgroups showing an interaction p-value ≤ 0.1 will be considered as potential subgroup and might be investigated in more detail.

Forest plots will be produced for the graphical interpretation of subgroup analyses.

Standardized effect size plot

Furthermore, standardized effect size plots (as described below) will be applied to the two tiers (defined in Section 6.4). These may also be provided separately, if deemed useful.

Generally, the higher the number of subgroup analyses performed, the higher the probability of a positive finding by chance (pure randomness) alone. Therefore, a standardized effect size evaluation will be performed in addition in order to consider the number of subgroups, the correlation between the subgroups, the observed effect size within the subgroup and the sample size of the subgroups.

Standardized effect size plots will be produced to identify on a permutation basis the minimum and maximum difference from the null hypothesis (no treatment effect overall) across all subgroups. This illustrates how extreme the results are expected to be by chance given the number, the size, and the correlation structure of subgroups.

For each subgroup the observed standardized effects will be calculated and compared to permutation-based confidence bands (5 and 95% percentiles) taking into account the multiplicity issues based on permuted datasets (10.000 times). For each permuted dataset the standardized effects for each subgroup will be calculated and thereof the maximum of the absolute values of the standardized effects are received. Repeating this 10.000 times, we will

use the 90th percentile $B$of the maximum absolute effects which provides us with a 90%-confidence band $[-B; B]$. Any subgroups showing an adjusted p-value outside this 90%CI are identified. In a stepwise procedure, those subgroups are then excluded and the standardized effect method is applied to the remaining subgroups in order to again identify the minimum and maximum difference from the null hypothesis (no treatment effect overall). The procedure ends in case no selected subgroup for the maximum or minimum is identified.

If deemed appropriate, subgroups with missing values may be excluded from the calculation of the standardized effect size plot.

7.4.2.2 Sensitivity analyses for PFS

Using all available data

As a sensitivity analysis, the PFS analysis (without subgroup analysis) will be repeated, using all available radiological response assessment data (including those measured after the cut-off date from the primary analysis). As for the primary analysis, the randomised set will be used.

Stratification factor based on IRT

The PFS analysis will be repeated, using data from IRT stratification (for the factor visceral involvement) instead of using data collected in the CRF. As for the primary analysis, only response assessments until the cut-off date of 25th November 2016 will be used.

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

7.5.2.1 Phase Ib

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

7.5.2.2 Phase II

Secondary endpoints will be analysed descriptively for all patients in the randomised set in the second part of this trial. As for the primary analysis, only response assessments until the cut-off date of 25th November 2016 will be used for the analysis of all response-based endpoints.

Time-to-progression

TTP will be assessed based on the Kaplan-Meier method for each treatment arm separately. Point estimates together with CIs (based on Greenwood's method) will be provided for median time to event.

Objective response

The binary endpoint OR will be analysed in an exploratory manner.

Moreover, logistic regression will be used to test for a difference between the two arms for objective response rate. The model will be adjusted for the stratification factor visceral involvement by fitting this as an explanatory variable. The exploratory p-value will be generated from the likelihood ratio test statistic. An odds ratio and corresponding 95% CI will be generated using the likelihood ratio CI in order to obtain a direct correspondence between the p-value and the odds ratio CI. Odds ratios >1 favour xentuzumab + everolimus + exemestane.

Disease control

DC will be analysed similarly to OR, see above.

Time to OR

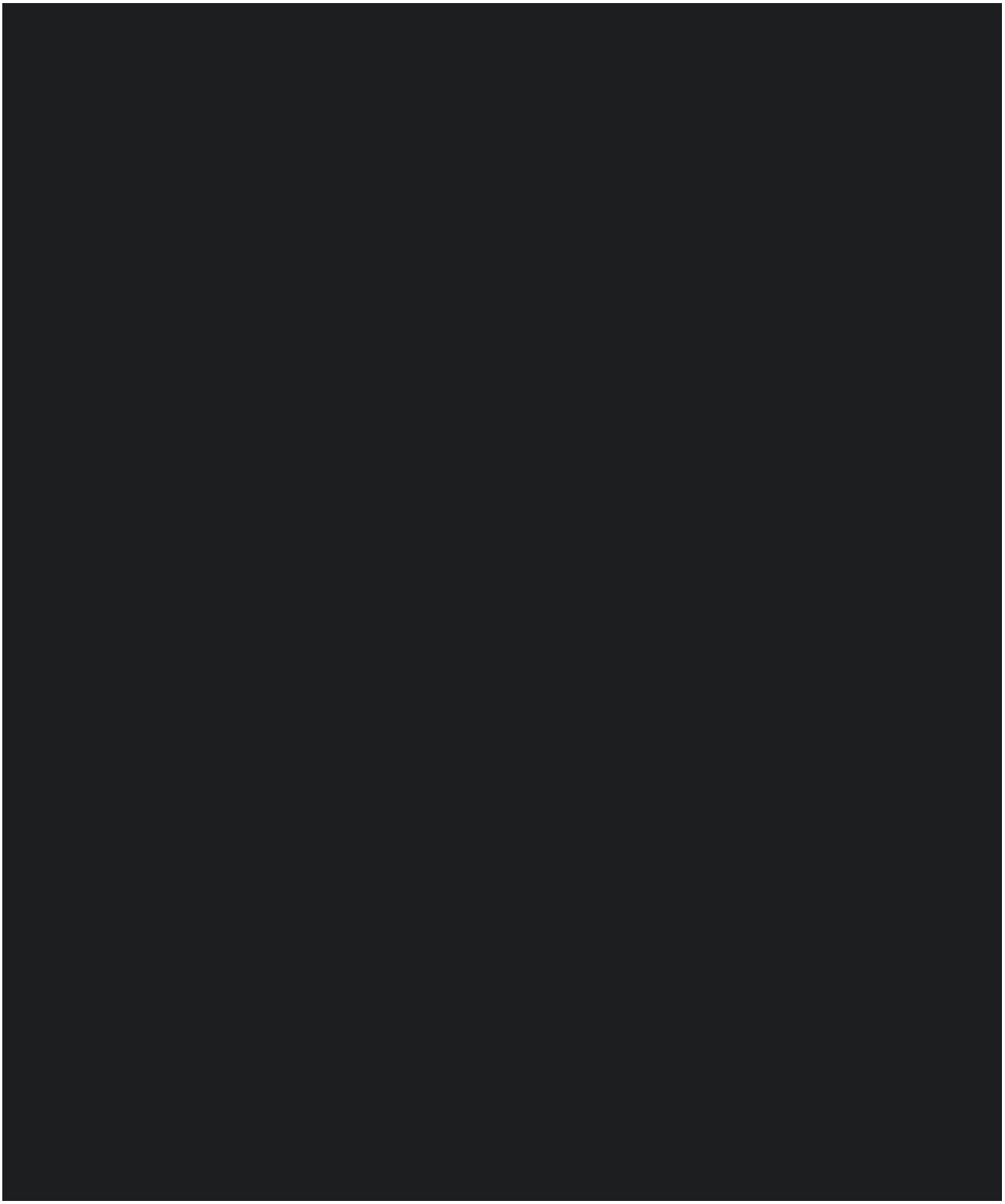
Descriptive statistics will be calculated for time to OR. This will only be computed for patients who have an OR.

Duration of OR

Duration of OR will be assessed based on the Kaplan-Meier method for each treatment arm separately. Point estimates together with CIs (based on Greenwood's method) will be provided for median time to event and quartiles. This will only be computed for patients who have an OR.

Duration of DC

Duration of DC will be analysed similarly to Duration of OR, see above.



7.7 EXTENT OF EXPOSURE

The variables defined in Section 5.4.2 will be summarised descriptively for each dose cohort (Phase Ib) or treatment group (Phase II).

For the phase II part, this variables will also be provided by visceral involvement.

7.8 SAFETY ANALYSES

All safety analyses will be performed on the TS (unless otherwise specified; for example, the MTD Set will be used for some safety outputs). Patients in the Phase Ib part of the trial who were replaced within or before 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 (4).

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 (R10-4848)).

The analyses of AEs will be based on the concept of treatment-emergent AEs. For the phase Ib, that means that all AEs 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 REP will be assigned to 'post-treatment'; these AEs will be displayed in separate tables and listings. First drug intake includes the run-in period for Phase Ib part.

For the phase II part it has to be taken into consideration that the sponsor decided to stop treatment with xentuzumab on 28th of October 2016, but continued treatment with everolimus and exemestane. Therefore, the analysis of on-treatment AEs will be split in two parts:

1) AEs with onset date on or before 9th of December 2016

   This includes the following patients:

   - Patients of both arms who completed the REP on or before 9th of December 2016, i.e. AEs until the end of REP will be considered.
   - Patients who stopped xentuzumab on 28th of October 2016 due to sponsor's decision, i.e. AEs with onset date on or before the 9th of December 2016 will be considered.
   - Patients receiving everolimus and exemestane only, i.e. AEs with onset date on or before 9th of December 2016 will be considered.

2) AEs with onset after 9th of December 2016

   This includes the following patients:

   - Patients who stopped xentuzumab on 28th of October 2016 due to sponsor's decision, i.e. AEs with onset date after 9th of December 2016 will be considered.
   - Patients receiving everolimus and exemestane only, i.e. AEs with onset date after 9th of December 2016 will be considered.

Both parts will be analyzed by treatment and a total column will be given.

For the Phase II part all AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after the REP will be assigned as 'post-treatment'.

AEs will be displayed by the initial dose of study medication administered on the first day of treatment (or planned to be administered, for the run-in period of the Phase Ib part).

An overall summary of AEs will be presented. The frequency of patients with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with drug-related AEs, AEs leading to dose reduction, AEs leading to discontinuation, serious adverse events (SAE), serious drug-related AEs, AEs leading to death, other significant AEs, adverse events of special interest (AESI), and AEs fulfilling the DLT definition (for phase Ib part only). For the Phase II part an overall summary of AEs as well as a table for AEs and SAEs by treatment will be provided for the subgroups of visceral involvement.

Sorting order:

In tables presenting SOC and PT, 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 "Missing 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. In the appendix (Section 16.1.9.2), the categorisation "All grades", "Grade 1/2", "Grade 3/4/5", will be used.

Listings of AEs

AEs will be reported with start and end day as calculated from the first day of treatment with study medication. This includes the run-in period for the Phase Ib part.

Incidence and severity of AEs

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

Other significant AEs

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 dose reduction of everolimus

- AEs leading to permanent discontinuation of xentuzumab
- AEs leading to permanent discontinuation of everolimus
- AEs leading to permanent discontinuation of exemestane

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 grade 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 AESIs

Protocol-specified AESIs are specified in the CTP Section 5.2.2.1. Their incidence will also be reported. DLTs are considered as AESIs only in the Phase Ib part.

Adverse events by user defined AE categories (UDAEC)

UDAEC as defined on project level by the pharmacovigilance working group will be derived and the latest version will be used for the analysis. The categories will be taken as defined in the most recent signed version of the safety Statistical Analysis Plan (SAP) at the time of the DBL. These categories can be found in Table 7.8.1: 1. This document is entitled "8-02-sap-safety-core", which can be found in the Project Data Management and Statistics folder, section 8 (project level), within BIRDS.

Table 7.8.1: 1 Adverse events by user defined AE categories

Term	**Group**[#]
Hepatic impairment	Drug related hepatic disorders – comprehensive search (SMQ)
Hyperglycaemia narrow	Hyperglycaemia/new onset diabetes mellitus (SMQ) – narrow
Infusion related reaction	IRR (BIcMQ) Hypersensitivity (SMQ) – narrow
Non-infectious pneumonitis	Interstitial lung disease (SMQ) – narrow
Renal insufficiency	Acute renal failure (SMQ) – broad
Weight loss	Weight loss (BIcMQ) – broad
Neutropenia	Haematopoietic leukopenia (SMQ) – narrow
Stomatitis	Stomatitis (BIcMQ) – broad
Asthenia	Asthenic conditions (BIcMQ) – narrow
Anemia	Haematopoietic erythropenia (SMQ) – broad
Thrombocytopenia	Haematopoietic thrombocytopenia (SMQ) – narrow

[#] This column indicates whether the Term(s) provided in the first column are MedDRA preferred terms (***PT***), Standardised MedDRA Queries (***SMQ***) or BI customised MedDRA Queries (***BIcMQ***).

The incidence of AE by UDAEC will be analysed.

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 (5). For both the phase Ib and the phase II part the on-treatment period as considered for the analysis of adverse events of the phase Ib part will be applied for laboratory values except for that the baseline laboratory value will be included in the 'on-treatment' 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 (R10-4848). The following outputs will be presented:

- Worst CTCAE grade experienced during the on-treatment phase.
- 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 reference 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" (5), Reference Document 9.

7.8.2.2 Laboratory values of special interest

Hepatic enzyme elevations (potential Hy’s law cases):

These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of Alanine Aminotransferase (ALT) and/or Aspartate Transaminase (AST) > 3 Upper Limit of Normal (ULN) with total bilirubin ≥ 2ULN and Alkaline Phosphatase (ALKP) < 2 ULN. The events can occur in any order, but must occur within 14 days of the previous event, i.e. the second event must occur within 14 days of the first event, and the third event must occur within 14 days of the second event, etc.

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 Drug-Induced Liver Injury (DILI) cases, are created in accordance with the Food and Drug Administration (FDA) DILI guidance (P09-12413).

7.8.3 Vital signs

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

7.8.4 ECG

Newly emergent abnormalities will be recorded and analysed as AEs if judged clinically relevant by the investigator.

The ECG analyses will be performed using the ECG Set, except those concerning the relationship between plasma concentrations and ECG endpoints which will be based on the ECG-PK set. All analyses will be based on the centrally evaluated ECG data collected until the safety cut-off date of 9th December 2016. Centrally evaluated ECGs recorded after this date, will only be presented in listings.

Descriptive analyses (separate analysis of Phase Ib and Phase II parts)

Absolute values and change from baseline in QTcF interval, QT interval, heart rate, PR interval, and QRS complex will be summarized descriptively by initial treatment, cycle, day and planned time.

Frequency tables will be provided for all categorical endpoints including notable findings and qualitative ECG assessments. Frequencies of the increases in QTcF and QT intervals above thresholds such as 450 msec, 480 msec, and 500 msec between baseline and on-treatment values will be displayed in two-way shift tables by initial treatment.

Notable findings (occurring until the safety cut-off date) of patients in the TS who are excluded from the ECG Set will be listed in separate listings which will be presented in Section 15 of the CTR.

The QTcB interval as well as the percentage changes for PR interval and QRS complex will only be displayed in Listings (Appendix 16.2.8)

Additional statistical analyses will be performed for the Phase II part as described below:

Repeated measures analyses

The endpoint ‘change in QTcF interval between baseline and on-treatment’ will be analysed by a linear mixed-effects model for repeated measures (MMRM). This model will include the fixed, categorical effects of ‘treatment’ and ‘timepoint’, the ‘treatment-by- timepoint’ interaction, as well as the continuous, fixed covariate ‘baseline’ and the ‘baseline-by-timepoint’ interaction. An unstructured covariance structure will be used to model the within-patient measurements. The SAS® procedure MIXED will be used, involving the restricted maximum likelihood estimation method, and the Kenward-Roger method will be applied to adjust standard errors and estimate denominator degrees of freedom. The model is detailed in Section 9.2.2.

Timepoints will only be included as long as evaluable data in ‘change in QTcF between baseline and on-treatment’ from at least 30 patients are still available in any of the treatment groups. The choice of 30 patients is relatively arbitrary and is conceived as a compromise, i.e. balancing out between precision of the estimates and receiving preliminary information over time on the other hand. The analyses of heart rate, QT, PR and QRS endpoints will be aligned to the respective QTcF analyses.

For the pairwise comparisons of ’xentuzumab + everolimus+exemestane’ versus ’everolimus+exemestane ’, the treatment differences at each timepoint will be estimated by the difference in the corresponding Least-Squares Means (LSMeans). Two-sided 90% CIs

based on the t-distribution will also be computed. Having estimated the treatment difference at each timepoint by the analysis described above, the timepoint at which the difference is largest will be identified.

This analysis will also be performed using the corresponding endpoints based on the QT interval, heart rate, PR interval and QRS complex, respectively.

The repeated-measures analysis will also be applied to the absolute on-treatment QTcF interval, heart rate, QT interval, PR interval and QRS complex values, respectively. Least squares means of 'treatment-by-timepoint' and two-sided 95% CIs based on the t-distribution will be computed.

Sensitivity analysis

In the model described above, a covariance structure of type 'unstructured' will be used to model the within-patient measurements. This model does not consider the particular underlying time structure, being consecutive pairs of within-day measurements (pre- and post-dose measurements approximately 1 hour apart) separated by one (or more) week(s). To account for this particular time structure, a modified covariance structure will be used in the sensitivity analysis: A two-by-two unstructured covariance matrix will be used to model the within-patient measurements on each day (pre- and post-dose measurements). A second two-by-two unstructured covariance matrix will be used to model the within-patient measurements between days; this matrix will be the same for all combinations of days. Hence, in this analysis the number of necessary covariance parameter estimates will not depend on the number of included timepoints. The sensitivity analysis will be restricted to the endpoints based on the QTcF interval. The model is detailed in Section 9.2.2.

Exposure-response analyses

The exposure-response analyses will be based on the ECG-PK set. Patients of the Phase Ib part will not be included as they were pre-treated with 'everolimus+exemestane'. Data of patients receiving everolimus+exemestane alone will be included with xentuzumab plasma concentrations set to zero (see also R17-0553).

Pairs of xentuzumab plasma concentrations and QTcF changes from baseline that are not time-matched (i.e. a time deviation between PK blood sampling and ECG recording that is not acceptable) will be excluded from the analyses.

The maximum acceptable time deviations between PK blood sampling and ECG recording at different time points during the trial are presented in Table 7.8.4: 1 below. Pairs of plasma concentrations and QTc changes from baseline with time deviations exceeding those specified in the table will be excluded from exposure-response analyses. When the sampling time of the blood sample, the time of ECG recording or the time of infusion are not available, the pair will also be excluded.

Table 7.8.4: 1 Maximum acceptable time deviations between PK blood sampling and ECG recording during the trial, Phase II part

Timepoint	Pre-dose timepoints	Post-dose timepoints
	Both measurements taken before "start of infusion"	Both measurements taken not earlier than 15 min before "end of infusion"
Cycle 1, Day 1	n.a. (Baseline ECG)	Deviation ≤4 h
Cycle 1, Day 8, 15 Cycles 2 and 3, Day 1	Deviation ≤6 h	Deviation ≤4 h
Cycles >3, Day 1	Deviation ≤6 h	n.a.
EoT, FU	(no infusion) Deviation ≤8 h	

For further details see also Section 6.6.5.

The relationship between xentuzumab plasma concentrations and QTcF change from baseline will be explored using a random coefficient model including a categorical variable 'treatment' with the two levels 'xentuzumab+ everolimus+exemestane and 'everolimus+exemestane' to estimate the adjusted mean difference between 'xentuzumab + everolimus+exemestane ' and 'everolimus+exemestane' in QTcF change from baseline and its two-sided 90% CI at clinically relevant plasma concentrations, which are the geometric means of the $C1D1_{1:15h}$, $C2D1_{1:15h}$ and $C3D1_{1:15h}$ values of the RP2D. The model is detailed in Section 9.2.3. For visualization, plasma concentration against QTcF changes from baseline will be plotted, as well as the (fixed effect) regression line, its 90% CI and the geometric means of $C1D1_{1:15h}$, $C2D1_{1:15h}$ and $C3D1_{1:15h}$.

The assumption of a linear relationship will be checked by visual inspection of diagnostic plots (presented in Section 16.1.9.2 of the CTR). If linearity is not given, the concentrations may be log-transformed prior to the analysis.

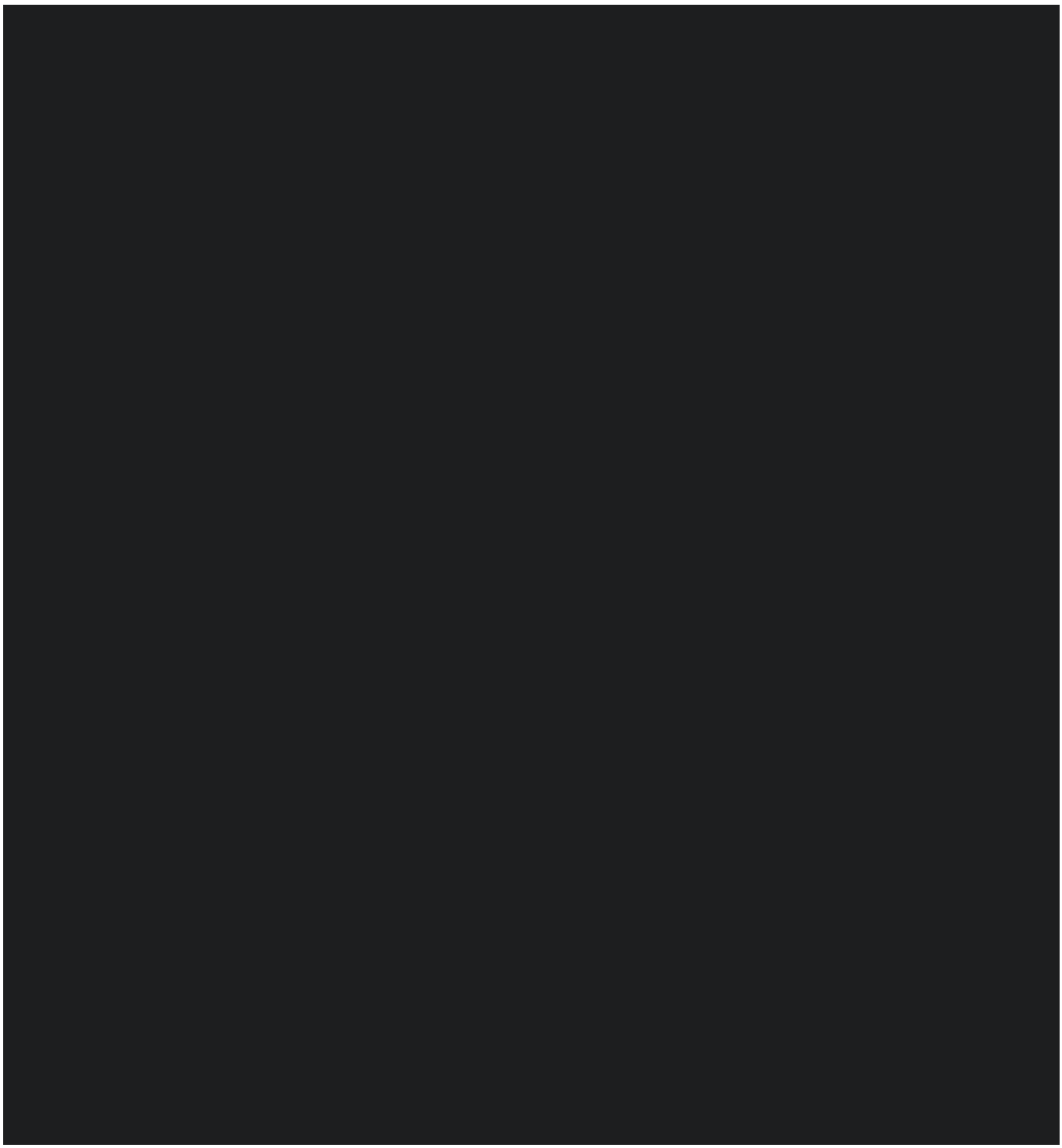
To inspect (graphically) whether the peaks of the time-profiles for xentuzumab plasma concentrations and QTcF interval changes from baseline coincide, figures of the individual time profiles of xentuzumab plasma concentrations and QTcF interval changes from baseline will be generated for each patient (presented in Appendix 16.1.9.2 of the CTR), as well as for the means (presented in Section 15 of the CTR). Mean time profiles from the patients treated with 'everolimus+exemestane' alone will be displayed as well.

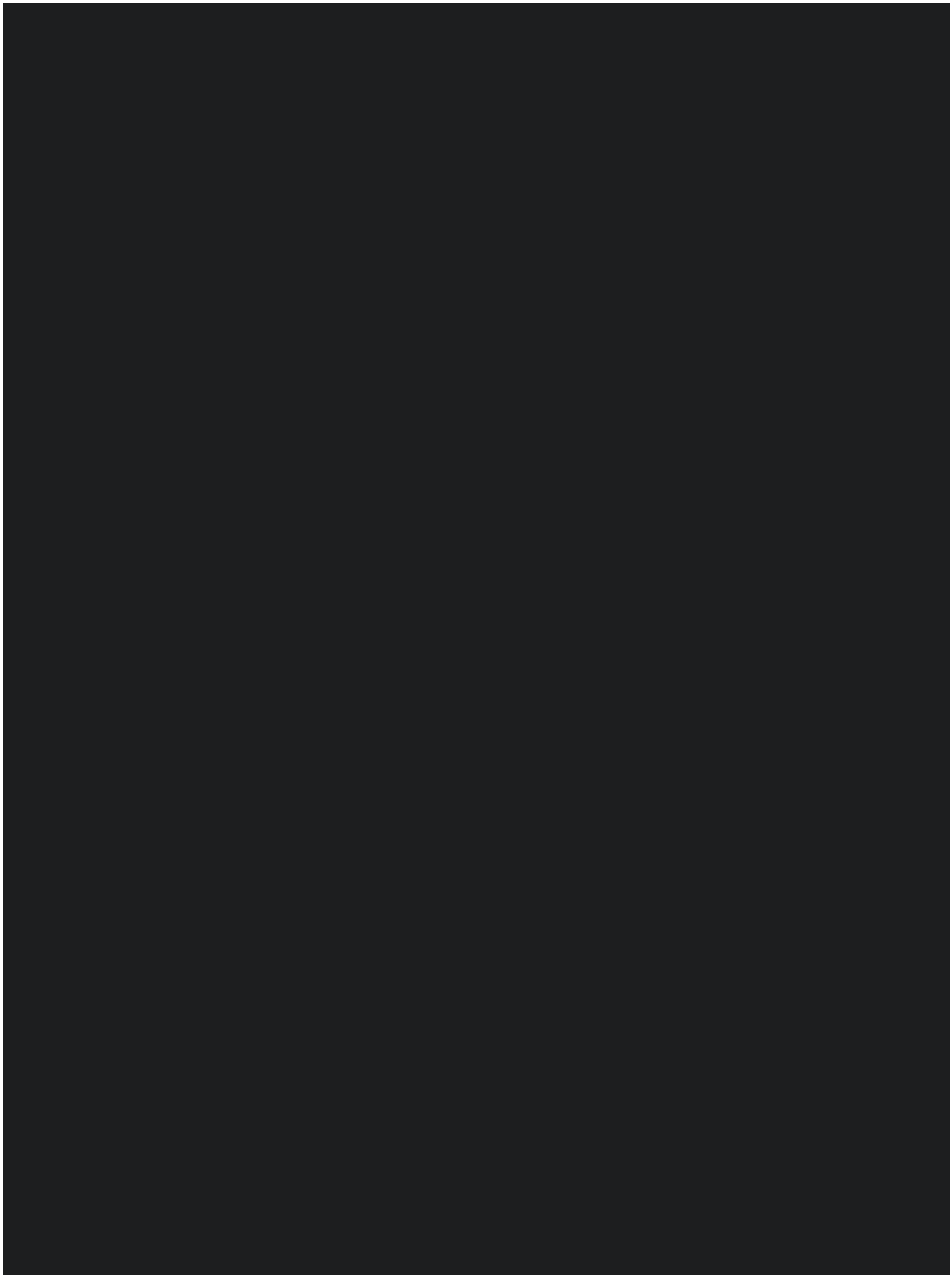
These analyses will also be performed using the corresponding endpoints based on the QT interval and heart rate.

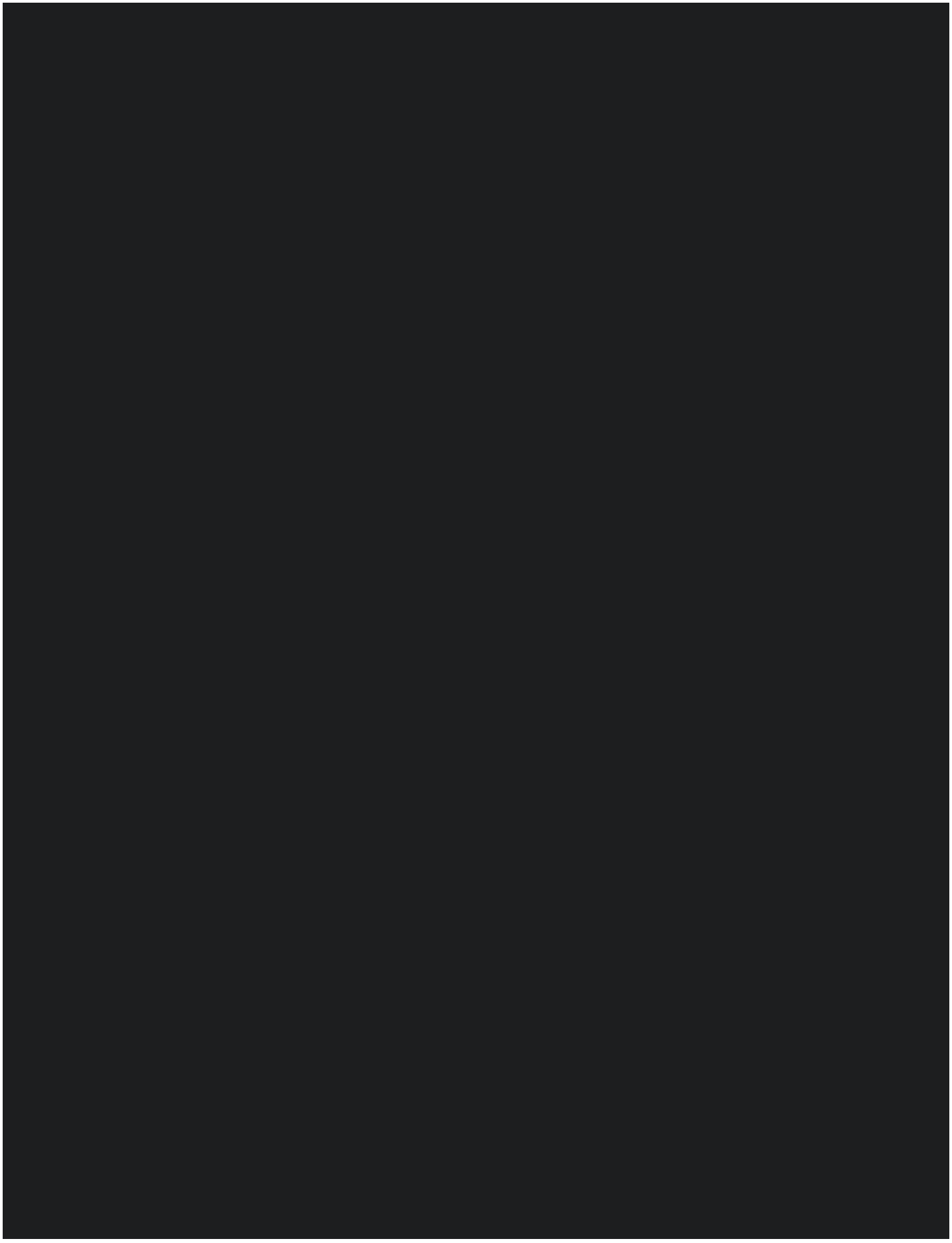
Furthermore, a first sensitivity analysis will be performed using the random coefficient model described above including the categorical effect 'day', and a second sensitivity analysis will be done including the categorical effect 'time' with the two levels pre- and post-dose, instead. A further analysis will consider the influence of baseline and will include the centered baseline as a covariate additionally to the factors used in the first sensitivity analysis. These analyses will only be applied to the QTcF changes from baseline.

Appropriateness of QT interval correction methods for heart rate

To evaluate the appropriateness of the methods, slopes of the relationship of QT, QTcF, and QTcB interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying a random coefficient model (see Section 9.2.4) separately for the treatments ‘xentuzumab+ everolimus+exemestane’ and ‘everolimus+exemestane’. These analyses will be based on the three single on-treatment ECG recordings per time point. A table of the resulting (fixed effect) slopes will be displayed together with two-sided 95% CIs in Appendix 16.1.9.2 of the CTR.







7.9.6 Immune response (ADA)

Following the changes described in Section 4.2, immunogenicity will be analysed as follows:

The number and percentage of ADA-positive, ADA-negative and ADA-negative-inconclusive patients may be presented. Further analyses related to immunogenicity might be performed if feasible and considered reasonable, e.g. potential impact on PK or PD parameters.

8 REFERENCES

1 *001-MCS-40-415_RD-02:* "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-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.

5 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

6 *001-MCS-50-413*: "Handling of Protocol Violations in Clinical Trials and Projects", current version; IDEA for CON.

7 *001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.

8 *CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.

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[redacted]

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9 ADDITIONAL SECTIONS

9.1 SAFETY ANALYSIS

After 12 evaluable patients treated at the designated MTD dose completed at least the first course of treatment during the phase Ib part, a safety analysis was performed. For this purpose a database snapshot was performed. The safety analysis summarised results regarding safety and was used for recommendation of the dose of trial medication to be taken forward as recommended phase II dose. The selection of the RP2D considered overall safety observed during available treatment cycles for all treated patients, including the ones that were replaced for the determination of the MTD. These analyses were documented in a SIR for the Phase Ib part (c03569433-01).

Disposition of patients, demographic characteristics and oncological history, previous therapies (listing), concomitant therapies (listing), exposure (total duration of treatment, patients with dose reduction), adverse events and laboratory parameters (listing of laboratory values, table of frequency of patients with transitions of CTCAE grades at baseline and worst grade on treatment) were shown in the safety analysis.

A version of the TSAP was signed before the snapshot of the safety analysis was performed.

9.2 ECG EVALUATION

This section only applies to the centrally evaluated digital ECG recordings.

9.2.1 Derivation of ECG variables

Three replicate digital ECG recordings will be collected at each time point (see also Section 9.2.5). Each of the three recorded single ECGs will then be evaluated for cardiac intervals, which comprise the RR interval, PR interval, QT interval, and QRS complex. Measurements of these intervals will be made on the three (possibly consecutive) cardiac cycles (also denoted as beats or waveforms) from the lead chosen (usually lead II). The measurements of the cardiac cycles will be stored in the database, i.e., 9 values per time point. All cardiac intervals will be given in milliseconds (msec). The three cardiac cycles will be averaged prior to the calculation of heart rate and heart-rate-corrected QT intervals (QTc).

Heart rate will be derived from the RR interval as

Heart Rate [beats/min] = 60 000 / RR [msec]

Two Heart Rate-correction methods of the QT interval will be applied:

- QTcF is the length of the QT interval corrected for heart rate by Fridericia's formula:

$$QTcF\left[m\sec\right]=\left(\frac{1000}{RR}\right)^{1/3}*QT\left[m\sec\right]$$

- QTcB is the length of the QT interval corrected for heart rate by Bazett's formula:

$$QTcB\left[m\sec\right]=\left(\frac{1000}{RR}\right)^{1/2}*QT\left[m\sec\right]$$

Further aggregation of the three replicate QT/QTc intervals and heart rates at each scheduled time point will be performed using arithmetic means. These values will be used for the derivation of the ECG endpoints as they are specified in Section 5.4.6.

9.2.2 Description of the model used for the repeated measures analyses

The model (M1) is described by the following equation

$$Y_{ijk} - B_i = \mu + \tau_j + \zeta_k + (\tau\zeta)_{jk} + (\gamma + \gamma_k)B_i + e_{ik},$$

$$(e_{i1}, \dots, e_{iK}) \sim N_K(0, \Psi)$$

where

	i=1,...,I indicates the patient, *k=1,...K* the on-treatment timepoint and *j=1,2* the treatment group,
Y_{ijk}	is the QTcF interval measured on patient *i* receiving treatment *j* at timepoint *k*,
B_i	is the baseline measurement of patient *i*,
μ	is the overall intercept,
τ_j	is the fixed, categorical effect of treatment *j,*
ζ_k	is the fixed, categorical effect of timepoint *k*,
$(\tau\zeta)_{jk}$	is the interaction effect between treatment *j* and timepoint *k,*
γ	is the fixed coefficient for baseline,
γ_k	is the fixed coefficient for baseline at timepoint *k*,
e_{ik}	is the random error associated with patient *i* at timepoint *k,*
Ψ	is a *K-by-K* covariance matrix of the type 'unstructured'.

The following SAS code (1) will be used to fit the model:

```
PROC MIXED DATA=xxxx ORDER=data CL METHOD=REML;
   CLASS patient treat timepoint;
   MODEL ECGep= treat timepoint treat*timepoint base base*timepoint
/DDFM=KR;
   REPEATED timepoint / SUBJECT=patient TYPE=UN R RCORR;
   LSMEANS treat*timepoint/ diffs CL ALPHA=0.10;
RUN; QUIT;
```

The variable names (e.g. 'patient', 'treat' etc.) given in the SAS code above have to be replaced by the respective variable names used in the analysis data set. ECGep corresponds to the 'QTcF change from baseline'.

The variable 'timepoint' will be concatenated of 'day' and 'time'. The variable 'day' denotes the consecutive days with ECG recordings (i.e., C1D1, C1D8, C1D15, C2D1, C3D1 etc.) and the variable 'time' will have 2 values (0, 1) indicating whether the ECG was recorded before ('0') or after ('1') drug administration. In terms of SAS code, the interaction 'day*time' corresponds to the effect 'timepoint'.

Therefore, the following SAS code using 'day' and 'time' as separate class variables will be equivalent to the SAS code (1) above:

```
PROC MIXED DATA=xxxx ORDER=data CL METHOD=REML;
   CLASS patient treat day time;
   MODEL ECGep= treat day*time treat*day*time base base*day*time /DDFM=KR;
   REPEATED day*time / SUBJECT=patient TYPE=UN R RCORR;
   LSMEANS treat*day*time/ diffs CL ALPHA=0.10;
RUN; QUIT;
```

In case of convergence problems, apply step 1)-6):

1) Set SINGULAR=1E-10 as option in the model statement
2) Set MAXITER=100 and/or MAXFUNC=200
3) Use option SCORING=4 in the final run to request a Fisher scoring algorithm to be used for the first 4 iterations
4) Include the additional statement in the PROC MIXED call:
   PERFORMANCE NOTHREAD;
5) Perform an initial run including the statement
   ODS OUTPUT COVPARMS=covstart;

   followed by a final run using

   PARMS / PARMSDATA=covstart;

   In the special case with the note "Convergence criteria met but final hessian is not positive definite" try instead/in addition

   PARMS / OLS;

   to request ordinary least squares starting values.
6) One may also use estimates from a simpler model (e.g. using TOEPH) as starting values for the run with TYPE=UN

In case that an unstructured covariance matrix still does not converge, even after application of the above steps, the Toeplitz structure with heterogeneous variances (TOEPH) will be applied.

The statistical model applied as sensitivity analysis will be identical to the model (M1) described above, with the exception of the covariance structure used to model the within-patient measurements.

The following model (M2) will be used (note that the index *k* is now replaced by the two indices *d* and *t*):

$$Y_{ijdt} - B_i = \mu + \tau_j + \zeta_{dt} + (\tau\zeta)_{jdt} + (\gamma + \gamma_{dt})B_i + s_{it} + e_{idt},$$

$$(s_{i0}, s_{i1}) \sim N_2(0, \Sigma), (e_{id0}, e_{id1}) \sim N_2(0, \Psi)$$

where

	i=1,…,I indicates the patient, d=1,…D the day of ECG recording, t=0, 1 the time of ECG recording (0= before and 1= after drug administration), and j=1, 2 the treatment group,
s_{it}	is the random effect associated with patient i at time t; assumed to be independent across patients,
e_{idt}	is the random error associated with patient i on day d and time t; assumed to be independent across day and patient. The e_{idt} are assumed to be independent of the s_{it},
Σ, Ψ	are 2-by-2 covariance matrices of the type 'unstructured'.

The following SAS code will be used to fit this model:

```
PROC MIXED DATA=xxxx ORDER=data CL METHOD=REML;
   CLASS patient treat day time;
   MODEL ECGep= treat day*time treat*day*time base base*day*time /DDFM=KR;
   RANDOM time / SUBJECT=patient TYPE=UN R RCORR;
   REPEATED time / SUBJECT=patient*day TYPE=UN R RCORR;
   LSMEANS treat*day*time/ diffs CL ALPHA=0.10;
RUN; QUIT;
```

9.2.3 Description of the random coefficient model used for the exposure-response analyses

The relationship between xentuzumab plasma concentrations and ECG endpoints will be explored using a random coefficient model which includes a categorical effect 'treatment'(with the two levels 'xentuzumab+ everolimus+exemestane' and 'everolimus+exemestane'), 'day' or 'time', respectively, as fixed categorical effects (only used in the sensitivity analyses), as well as a random intercept and slope for each patient (R17-0553, Model ΔQTc3):

$$Y_{ijk} = \tau_j + \zeta_k + a_i + b_i X_{ijk} + \beta X_{ijk} + e_{ijk},$$

$$(a_i, b_i) \sim N_2(\mathbf{0}, \Sigma), \quad e_{ijk} \sim iid\ N(0, \sigma^2),$$

where

	$i = 1,2,\ldots, I$ indicates the patient (I = total number of patients across all treatment groups, k = $1,2,\ldots, K_i$ the time point and $j=1,2$ the treatment,
Y_{ijk}	is the QTcF change from baseline in patient i receiving treatment j at time point k,
X_{ijk}	is the plasma concentration in patient i receiving treatment j at time point k
τ_j	is the effect of treatment j on intercept,
ζ_k	is the effect of day (or time, respectively) k on intercept (will only be used in the sensitivity analyses),
a_i	is the random effect on intercept associated with patient i,
β	is the overall slope for the relationship between Y_{ik} and X_{ik}
b_i	is the random effect on slope associated with patient i,
e_{ijk}	is the random error associated with patient i receiving treatment j at time point k, and
Σ	is a 2-by-2 unstructured covariance matrix.

The random error is assumed to be independent of random intercept and slope effects.

The following SAS code will be used to fit the model:

```
PROC MIXED DATA=xxxx METHOD=REML;
CLASS patient treat day[1];
MODEL ECGep = conc treat day[1]/ NOINT CL ALPHA=0.1 ALPHAP=0.1
DDFM=KENWARDROGER;
RANDOM INT conc / TYPE=UN SUBJECT=patient;
ESTIMATE "Pred. value at conc. xx.xx" conc xx.xx treat 1 -1/ CL ALPHA=0.1;
ESTIMATE "Slope estimate" conc 1 / CL ALPHA=0.1;
RUN
QUIT;
1: class variable 'day'(or 'time',respectively) will only be included in the sensitivity
analyses.
```

Note that the variable names (e.g. 'patient', 'conc' etc.) given in the SAS code above have to be replaced by the respective variable names used in the analysis data set. ECGep corresponds to 'QTcF change from baseline'.

The TYPE=UN option causes the two specified random coefficients to have a bivariate normal distribution. In case of convergence problems one may also use TYPE=FA0(2), which requests a G matrix estimate that is constrained to be nonnegative definite. If the note 'estimated G matrix is not positive definite' appears in the SAS log file, the random slope might be removed from the RANDOM statement.

9.2.4 Random coefficient model used to evaluate the appropriateness QT interval correction methods for heart rate

To evaluate the appropriateness of the QT correction methods, the (fixed effect) slopes will be estimated by treatment by applying the following model (R10-2920) separately to patients

with the treatments 'xentuzumab+ everolimus+exemestane' and 'everolimus+exemestane', respectively:

$$Y_{ijk} = \mu_0 + s_{0i} + (\delta_1 + s_{1i})X_{ijk} + e_{ijk},$$

$$(s_{oi}, s_{1i}) \sim N_2(\mathbf{0}, \Sigma), e_{ijk} \sim iid\ N(0, \sigma^2),$$

where i=1,...,I indicates the patient, k=1,…,K the number of the measurement and *j=1,2* the treatment,

Y_{ijk}	is the log-transformed QT interval of measurement *k* in patient *i* receiving treatment *j*,
μ_0	is the overall intercept,
s_{0i}	is the random effect on intercept associated with patient *i*,
δ_1	is the common slope associated with the relationship between the log-transformed QT and RR intervals,
s_{1i}	is the random effect on slope associated with patient *i*,
X_{ijk}	is the log-transformed RR interval of measurement *k* in patient *i* receiving treatment *j*,
e_{ijk}	is the random error associated with the measurement *k* in patient *i* receiving treatment *j*, and
Σ	is a 2-by-2 unstructured covariance matrix.

The random effects s_{0i} and s_{1i} are assumed to be independent of the random errors e_{ik}.The analysis will be based on single ECG recordings that will be log-transformed using the natural logarithm.

The following SAS code will be used to fit the model

```
PROC MIXED DATA=xxxx CL METHOD=REML;
CLASS patient;
MODEL logQT[or logQTc] = logRR / DDFM= KENWARDROGER ALPHA=0.05 CL;
RANDOM INT logRR / TYPE=UN SUBJECT=patient;
ESTIMATE 'Slope' logRR 1 / ALPHA=0.05 CL;
/* individual slope estimates:*/
ESTIMATE 'Slope f. patient 1' logRR 1 | logRR 1 /SUBJECT 1   ALPHA=0.05 CL;
ESTIMATE 'Slope f. patient 2' logRR 1 | logRR 1 /SUBJECT 0 1 ALPHA=0.05 CL;
/* etc. */
RUN;
```

Note that the variable names given in the SAS code above have to be replaced by the respective variable names used in the analysis data set.

The TYPE=UN option causes the two specified random coefficients to have a bivariate normal distribution. In case of convergence problems one may also use TYPE=FA0(2), which requests a G matrix estimate that is constrained to be nonnegative definite. If the note 'estimated G matrix is not positive definite' appears in the SAS log file, the random slope might be removed from the RANDOM statement.

9.2.5 Technical details on handling of ECG recordings

In this section, administration of comparator treatment means administration of everolimus+exemestane.

Due to safety reasons the CTP allowed for additional unscheduled ECG monitoring. Therefore, the following process will be applied to select the scheduled three single ECG recordings to be included in the analyses.

Within patient, visit and planned time, all single ECG recordings (scheduled or unscheduled) will be ordered by ECG date and time.

Screening: The last three single ECG recordings available will be selected.

Baseline time point:

ECG date and time will be compared with xentuzumab infusion **start** date and time (or date and time of comparator treatment administration for patients of Phase II not receiving xentuzumab, respectively).

If less than or equal to three single ECG recordings are available prior to start of first infusion or time of first drug administration, all of these values will be selected.

If more than three single ECG recordings are available prior to start of infusion or time of drug administration, only the three single ECG recordings closest to (but prior to) infusion start time or time of drug administration will be selected.

On-treatment time points:

Only ECGs recorded after start of first xentuzumab infusion (or first administration of comparator treatment for patients of Phase II not receiving xentuzumab, respectively) will be taken into account.

The following selection will be performed at each time point (PTM) within a visit:

If less than or equal to three single ECG recordings are available, all single ECG recordings will be selected.

If more than three single ECG recordings are available, the three single ECG recordings being closest to the planned time point will be selected. As the duration of an infusion may deviate from the planned duration of one hour, the selection of ECG recordings will be based on the **actual end of infusion** time. For patients not receiving an infusion, the planned time point is one hour after administration of the comparator treatment.

End of treatment (EOTV, FU): The first three single ECG recordings will be selected.

All measurements which were not selected will be excluded from the statistical analyses. All excluded single ECG recordings will be listed in a separate listing in Appendix 16.2.8 and the reason for exclusion will be given.

10 HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**11-JUN-15**	[redacted]	None	This is the final TSAP without any modification
Revised	**03-MAY-17**		All	The whole TSAP has been adapted including the following: The analysis of the phase II part has been added (it was not fully available in the first version). The analysis of other assessments such as [redacted] immunogenicity, [redacted] or ECG analysis has been added (it was not fully available in the first version). Protocol amendments have been implemented, as well as updates in company standards and updates/clarifications in project standards
Revised	**25-APR-2018**		All	The TSAP has been revised with regard to the following sections: Both PK analyses have been re-[redacted] ECG analyses have been extended. Analysis of AEs in the phase II were split.