Trial Statistical Analysis Plan

c02577053-02

BI Trial No.:	1280.8
Title:	A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination with Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone Including Protocol Amendment 6 [c02304008-09]
Investigational Product(s):	Xentuzumab, BI 836845
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	28 SEP 2017 REVISED
Version:	Revised

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2 LIST OF ABBREVIATIONS

Term	Definition / description
(e)CRF	(electronic) Case Report Form
(m)RNA	(messenger) RiboNucleic Acid
(T)SAP	(Trial) Statistical Analysis Plan
ADA	Anti-Drug Antibody
ADS	Analysis Data Set
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALKP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANOVA	Analysis Of Variance
AR-V7	Androgen Recept Variant 7
AST	Aspartate Transaminase
ATC	Anatomical, Therapeutic, Chemical (classification system)
AUC	Area Under the plasma concentration-time Curve
$AUC_{\tau,ss}$	Area under the plasma concentration-time curve over the dosing interval at steady state
AUEC	Area Under the Effect Curve
BB	Blood Biomarker Set
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
BPI-SF	Brief Pain Inventory Short Form
BRPM	Blinded Report Planning Meeting
BS	Biomarkers Set
BSA	Body Surface Area
C	Cycle
cfDNA	cell-free DNA (DeoxyriboNucleic Acid)
$C_{max,ss}$	Maximum measured plasma concentration at steady state

Term	Definition / description
$C_{pre,ss}$	Pre-dose plasma concentration at steady state
CR	Complete Response
CRPC	Castration-Resistant Prostate Cancer
CSAP	Cumulative Statistical Analysis Plan
CSD	Company Standard Displays
CT	Concomitant Therapy
CTC	Circulating Tumour Cell
CTCAE	Common Terminology Criteria for Adverse Events
CTCb	CTC biomarker set
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DC	Disease Control
DCS	Downstream Cascade Set
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DMS	Data Management and Statistics
ECG	Electrocardiogram
ECG-PK	ECG-PK analysis set
ECGS	ECG Set
E_{max}	E_{max} model (PD/PD model)
ENR	Enrolled Set
EOT	End of Treatment
EOT(V)	End of Treatment (Visit)
EWB	Emotional Well-Being (subscale score)
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FDA	Food and Drugs Administration
FFPE	Formalin Fixed Paraffin Embedded
FU	Follow-up

Term	Definition / description
FWB	Functional Well-Being (subscale score)
HR	Hazard Ratio / heart rate
ICH	International Conference on Harmonisation
IGF	Insulin Growth Factor
IGF-1	Insulin Growth Factor 1
IGF-2	Insulin Growth Factor 2
IGFBP-3	Insulin Growth Factor Binding Protein 3
IHC	Immunohistochemistry
IPV	Important Protocol Violation
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LLOQ	Lower Limit of Quantification
LLT	Lowest Level Term
LS Means	Least-Squares Means
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed-effects Model for Repeated Measures
MQRM	Medical Quality Review Meeting
MRI	Magnetic Resonance Imaging
mRNAS	mRNA set
MS	MTD Set
MSb	Mutational status biomarker set
MTD	Maximum Tolerated Dose
NCA	Noncompartmental Analysis
NCI	National Cancer Institute
ND	No Disease
NE	Not Evaluable
OS	Overall Survival
pAkt	phosphor Akt
PCS	Prostate Cancer Subscale score

Term	Definition / description
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PD	Progressive Disease / Pharmacodynamic (as applicable)
PES	Protein Expression Set
PFS	Progression Free Survival
PK	Pharmacokinetics
PKS	Pharmacokinetics Set
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
PRP	Platelet-Rich Plasma
PSA	Prostate-Specific Antigen
PT	Preferred Term
PTEN	Phosphatase and Tensin Homolog
PV	Protocol Violation
PWB	Physical Well-Being (subscale score)
Q1	25^{th} percentile
Q3	75^{th} percentile
QOL	Quality of Life
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
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 Criteria In Solid Tumours
REP	Residual Effect Period
RP2D	Recommended Phase II Dose
RPM	Report Planning Meeting
RS	Randomised Set
SAE	Serious Adverse Event

Term	Definition / description
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease / Standard Deviation
SIR	Synoptic Interim Report
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SOP	Standard Operating Procedure
SPOP	Speckle-type POZ Protein
ss	Steady state
SWB	Social/Family Well-Being (subscale score)
TCM	Trial Clinical Monitor
t_{max}	The time after dosing when C_{max} occurs
TMCP	Translational Medicine and Clinical Pharmacology
TOI	FACT-P Trial Outcome Index
TS	Treated Set
UDAEC	User Defined Adverse Events Categories
ULN	Upper Limit of Normal
URPM	Unblinded Report Planning Meeting
V	Visit
VT	Virtual Twins
WHO-DD	World Health Organisation Drug Dictionary

3 INTRODUCTION

As per International Conference on Harmonisation (ICH) E9 (5), 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 Ingelheims (BI) internal reference (1).

The trial consists of three parts, the phase Ib including the dose escalation part and the expansion cohort and phase II including the randomised part.

The TSAP describes the analysis for all parts of the trial. After the phase I escalation part, safety analyses were performed and documented in a Synoptic Interim Report (SIR) (see Section 9.1).

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

Statistical Analysis System (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

Skeletal events are analysed by investigator assessment and by central review assessment. Only the endpoint "time to first skeletal event" related to investigator assessment was planned in the protocol. The endpoint associated to central review assessment has been added in the further endpoints.

The endpoint Disease Control (DC) has been added in further endpoints.

4.2 CHANGES

There is one change in the assessment of target lesions according to Response Criteria In Solid Tumours version 1.1 (RECIST 1.1) (R09-0262) which is applied by the central review in this trial and which is described in the imaging charter. More details can be found in Section 5.2.2.3 of this TSAP.

Several criteria are used to analyse CTCs. The following one was not planned in the protocol, but will be analysed along with the other CTC criteria: "CTC status at week 12".

Prostate-Specific Antigen (PSA) endpoints (response, progression): definitions in this TSAP might be slightly different as the ones from the protocol. They have been reworked using the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) guidelines (R13-1642), previous studies and medical knowledge. They are therefore more accurate and include more details in the TSAP.

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 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 the combination of enzalutamide and xentuzumab, or any of these medications alone. Clarification is given when necessary.
- According to the current TSAP template, “Other endpoints” described in the CTP are now named “Further endpoints”.

4.4 CLARIFICATIONS TO THE PRIMARY ANALYSIS

The protocol (Section 7.3.1) mentions that the primary analysis will be conducted approximately 23 months after first patient was randomized in phase II part, in case 60 Progression Free Survival (PFS) events are not reached. According to the Table 7.6:3 from the protocol, the calculated duration was actually 22.5 months. The impact of this difference in terms of PFS events is negligible, and it has therefore been decided and agreed to perform this primary analysis 22.5 months after first patient randomized, in case 60 events are not reached.

The protocol (Section 4.1.5.1) states as well that “the BI study team will be blinded for the aggregated phase II data at the treatment level until the trial database lock”. The trial and project team clarified and agreed that it is meant until the trial database lock (DBL) of the primary analysis. Indeed, there is no additional blinded team planned for this trial and almost all patients will be off-treatment at that time. The BI study team will therefore be completely unblinded after DBL of the primary analysis.

5 ENDPOINTS

5.1 PRIMARY ENDPOINTS

Best overall response to trial medication will be determined separately according to RECIST version 1.1 (see Appendix 10.4 of the CTP) and to PCWG2 criteria, recorded from first administration of trial medication 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.

5.1.1 Phase Ib escalation

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

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 further parts of this trial as well as further trials in the development of xentuzumab in combination with enzalutamide.

5.1.2 Phase Ib expansion cohort

The primary endpoint of the phase Ib expansion cohort is the PSA response.

A PSA response in a patient is defined as a decline in PSA value >50% compared to baseline (which is confirmed by the next available value occurring at least 3 weeks later) (R13-1642). The confirmatory value should be at least 50% lower than the baseline, but may be higher than the first PSA value taken into account for response. However the confirmatory value may not be 50% higher than this first PSA. If it is >= 50% higher than the first PSA, the next available sample should be taken to determine if response has been achieved. The date of response is the date that the first 50% (or greater) decline is observed.

Patients without baseline or post-baseline assessments are considered as missing.

Patients presenting with a PSA value showing response but without any confirmatory value will be defined as "unconfirmed responders".

The percentage change from baseline in PSA will be calculated as follows:

- 100*(PSA value post-baseline - PSA value at baseline)/PSA value at baseline

A negative percentage change from baseline shows a decline in PSA.

Some particular data patterns may lead to a patient having PSA progression and PSA response at the same timepoint. Data will be carefully checked in order to detect such assessments. In case further rules are needed, these will as well be discussed at a Blinded Report Planning Meeting (BRPM) or added in a revision of the TSAP.

5.1.3 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 in bone (based on PCWG2 criteria) or soft tissue (based on modified RECIST 1.1) or death from any cause, whichever occurs earlier.

Tumour assessments will be performed at screening, week 8, week 16, week 24 and then every 12 weeks thereafter (more details in CTP Flow Chart).

For each follow-up (FU) imaging time-point an overall tumour response will be determined for soft tissue according to modified RECIST 1.1 (R09-0262 and Appendix 10.4 of the CTP) and for bone according to the prostate cancer clinical trials working group (PCWG2) criteria (R13-1642). The overall tumour response for each imaging time-point according to modified RECIST 1.1 will be selected from the following categories: Complete Response (CR); Partial Response (PR); Stable Disease (SD); No disease (ND); Progressive Disease (PD); Non-CR/Non-PD; Not Evaluable (NE). The overall tumour response for each imaging time-point (if clinically indicated) for bone lesion will be selected from the following categories: Non-progressive disease (Non-PD); Progressive disease (PD); Not Evaluable (NE).

Some patients enter the trial without any target or non-target lesion according to RECIST 1.1. Until new lesions appear and a progression is reported for this patient, the response assessment for such patients will be set to No Disease (ND) (see also Section 5.4.7).

For details on the imaging process and RECIST evaluation, see Section 5.1.2 and Section 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 Clinical Trial Report (CTR).

For patients with 'event' as an outcome for PFS: (according to modified RECIST version 1.1 or PCWG2)

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

For patients with 'censored' as an outcome for PFS: (according to modified RECIST version 1.1 or PCWG2)

- 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 5.1.3: 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, 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, Non PD, PR, CR, the latest of multiple dates will be used to censor the patients.

For PFS according to RECIST and PCWG2, the date of overall response will be determined for RECIST and PCWG2 separately. In case both RECIST and PCWG2 show PD then the date of PD will be the earliest date of these two. When either RECIST or PCWG2 show PD, then the date of outcome will be the date of PD. In case none of RECIST or PCWG2 shows PD then the latest date of RECIST and PCWG2 will be used for censoring.

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 5.1.3: 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
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

Table 5.1.3: 1 Derivation rules for PFS (cont.)

Situation	**Outcome (event or censored)**	**Date of outcome**
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
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

Table 5.1.3: 1 Derivation rules for PFS (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 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)

Data will be carefully checked in order to detect missing assessments. In case further rules are needed, these will be discussed at a BRPM and added in a revision of the TSAP.

In order to identify that consecutive imaging time-points are missing for a given patient, a nominal time point [8, 16, 24, and then every 12 weeks thereafter] will be assigned to the assessments. This is achieved by creating windows for every 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-PD, 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. If the bone and the soft tissue assessment have been done at different dates, the date of the first assessment will be the date of censoring.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Other secondary endpoints

5.2.2.1 Phase Ib escalation

There are no secondary endpoints.

5.2.2.2 Phase Ib expansion cohort

Progression-free survival (PFS) based on investigator assessment

The rules are the same as the ones described in Section 5.1.3.

Please note that the date of randomisation will be replaced by the date of the first treatment administration of any study medication.

Changes in CTC response

This is defined as a decline in CTC value from ≥5 to <5 cells per 7.5mL blood (called "specimen volume" within this section and Section 7.5.2.2 (R14-0865), for at least one post-baseline time-point.

Patients with a CTC value <5 cells per 7.5 ml blood at baseline, or with missing baseline value, are not taken into consideration for this endpoint. Patients with no post baseline value are considered as missing for this endpoint.

5.2.2.3 Phase II

Progression-free survival (PFS) based on central review

The rules are the same as the ones described in Section 5.1.3, except the rule defined below. Instead of investigator assessment, the assessment based on central review will be used.

It should be referred to the imaging charter for more details regarding the assessment of response. However, there is one important change to RECIST 1.1 in the assessment of target lesions based on central review. In case one patient has the following:

- PR at last assessment
- more than 20% increase from nadir in the sum of longest diameters of target lesions, but less than 5 mm absolute increase from nadir.

In this case the assessment of PR should be carried forward to PR. This difference will not affect the endpoint PFS of this trial.

Overall survival (OS)

OS is defined as the time from randomisation until death from any cause.

For patients with 'event' as an outcome for overall survival:

- Overall survival [days] = date of outcome – date of randomisation + 1.

For patients with 'censored' as an outcome for overall survival:

- Overall survival (censored) [days] = date of outcome – date of randomisation + 1

The censoring rules for OS (i.e. outcome and date of outcome) are given in Table 5.2.2:3: 1.

Table 5.2.2.3: 1 Derivation rules for OS

Status at time of analysis	**Outcome (event or censored)**	**Date of outcome**
Patient died and the date of death is known	event	Date of death
Patient died and date of death is unknown	event	Date of last contact when the patient is known to be alive + 1 day
Patient alive	censored	Date of last contact when the patient is known to be alive
Unknown	censored	Date of last contact when the patient is known to be alive

The date when the patient was last known to be alive will be derived using the following data sources:

- Patient status: date of patient status obtained (if patient status is alive), last date patient known to be alive (in case patient is lost to follow-up), date of refusal (in case the patient actively refused to be followed up)
- Tumour assessment and/or radiological imaging data (date of imaging target lesions, date of imaging non-target lesions, date of detection of new lesion, date of assessment of bone lesions)
- Trial medication administration pages (including dates of start and end of administration, and termination of trial medication page)
- Onset and/or end dates of Adverse Events (AEs)
- Vital signs and/or physical examination dates
- Dates of subsequent anti-cancer therapy

Imputed AE dates as well as imputed subsequent anti-cancer therapy dates will not be used for the derivation of the last contact date.

Time to PSA progression

For the definition of time to PSA progression, the following rules are used:

- If there is a decline from baseline in PSA before increasing: Time to PSA progression is defined as the time from the date of randomisation until the date where a 25% or greater increase in PSA and an absolute increase of 2 ng/mL (=ug/L, unit collected in the trial) or more from the nadir, is documented (which is confirmed by the next available value occurring at least 3 weeks later) (R13-1642). The date of the progression is the first date where the increase is observed.
- If there is no decline from baseline in PSA: Time to PSA progression is defined as the time from the date of randomisation until the date where a 25% or greater increase in PSA and an absolute increase of 2 ng/mL (=ug/L, unit collected in the trial) or more

from baseline, is documented. However, only values after 12 weeks of therapy (i.e. starting at day 84) are considered. In this case no confirmation is needed. (R13-1642)

The percentage change from nadir/baseline will be calculated as follows:

- 100*(PSA value at assessment - PSA value at nadir/baseline)/ PSA value at nadir/baseline

Derivations below are described in days. However, the endpoint will be presented in months in the statistical tables produced for the CTR.

For patients presenting with PSA progression, time to PSA progression is computed by:

- Time to PSA progression [days] = date of PSA progression - date of randomisation + 1.

For patients not presenting with PSA progression or being lost to follow-up, time to PSA progression (censored) is computed by:

- Time to PSA progression (censored) [days] = date of censoring - date of randomisation + 1.

See Table 5.2.2.3: 2 for more details about time to PSA progression rules and derivation of date of censoring.

Table 5.2.2.3: 2 Derivation rules for time to PSA progression

Situation	**Outcome (event or censored)**	**Date of PSA progression or censoring**
No baseline PSA value	censored	Date of randomisation
No post-baseline PSA value	censored	Date of randomisation
No PSA progression, irrespective of missed assessments	censored	Date of last evaluable PSA value
PSA progression, irrespective of missed assessments	event	Date of PSA progression

In the case when confirmation of progression is needed, the censoring rules are defined irrespective of the duration between the first assessment of progression and the confirmatory assessment which only needs to be the next available assessment more than 3 weeks after the first one. In this case, a patient without confirmation of progression will not be considered a progressor.

Data will be carefully checked in order to detect missing assessments. In case further rules are needed, these will be discussed at a BRPM and added in a revision of the TSAP.

Some particular data patterns may lead to a patient having PSA progression and PSA response at the same timepoint. Data will be carefully checked in order to detect such assessments. In case further rules are needed, these will as well be discussed at a BRPM and added in a revision of the TSAP.

Maximum decline in PSA

The maximum decline in PSA is defined as the change in PSA between the baseline PSA value and the minimum post-baseline PSA value. The change from baseline is defined as:

- Change from baseline in PSA (ng/mL) = PSA value post-baseline - PSA value at baseline.

Maximum decline in PSA is defined as:

- Maximum decline in PSA (ng/mL) = min(PSA value post-baseline) – PSA value at baseline.

Percentage decline will be calculated too (please refer to Section 5.1.2 for the computation). A negative change from baseline in PSA shows a decline in PSA.

Percentage change in PSA at week 12

Percentage change in PSA from baseline to week 12 of treatment is defined as:

- Percentage change in PSA (%) = 100*(PSA value at week 12 - PSA value at baseline)/PSA value at baseline

For this assessment, it is allowed to take a value:

- until one week later than week 12, in case the PSA assessment was delayed
- one day earlier due to the one day window allowed by the protocol

Values from assessments between day 84 and day 92 after first treatment administration will therefore be taken into account (according to the protocol schedule for visits at week 12).

In case there are several values within this timeframe (day 84 to 92), the closest value to Day 85 will be taken.

In case there is no value within this timeframe (day 84 to 92), but the patient discontinued all treatments earlier than day 84, then the End of Treatment (EOT) value should be used. A PSA value will be taken as EOT value if the assessment was performed between the date of discontinuation of the last study medication until 7 days (included) after this date (according to the protocol schedule for the EOT visit (EOTV)).

In case there is no value within this timeframe (day 84 to 92), and the patient did not discontinue all treatments earlier than day 84, no earlier value will be taken as replacement, the assessment will be missing.

PSA response

PSA response is defined as a decline in PSA value >50% (with confirmation at least 3 weeks later) (R13-1642). See Section 5.1.2. for more details.

Changes in CTC response

Changes in CTCs will be evaluated using the following criteria:

- CTC reduction is defined as a decline in CTC value from ≥5 to <5 cells per 7.5mL blood (called "specimen volume" within this section and Section 7.5.2.3) (R14-0865), for at least one post-baseline time-point. Patients with a CTC value <5 cells per 7.5 mL blood at baseline, or with missing baseline value, are not taken into consideration for this endpoint.
- Maximum decline in CTC counts (in number of cells) compared to baseline that occurs at any point after treatment start, defined as the difference (absolute and percentage) between the minimum post-baseline CTC value and the baseline CTC value. Patients with missing baseline value are considered missing for this criterion.
- CTC status at week 12 (≥5 or <5 cells per 7.5mL blood)

Baseline value is the value collected before a patient starts treatment with trial medication. Patients with no post-baseline value are considered as missing for the three criteria.

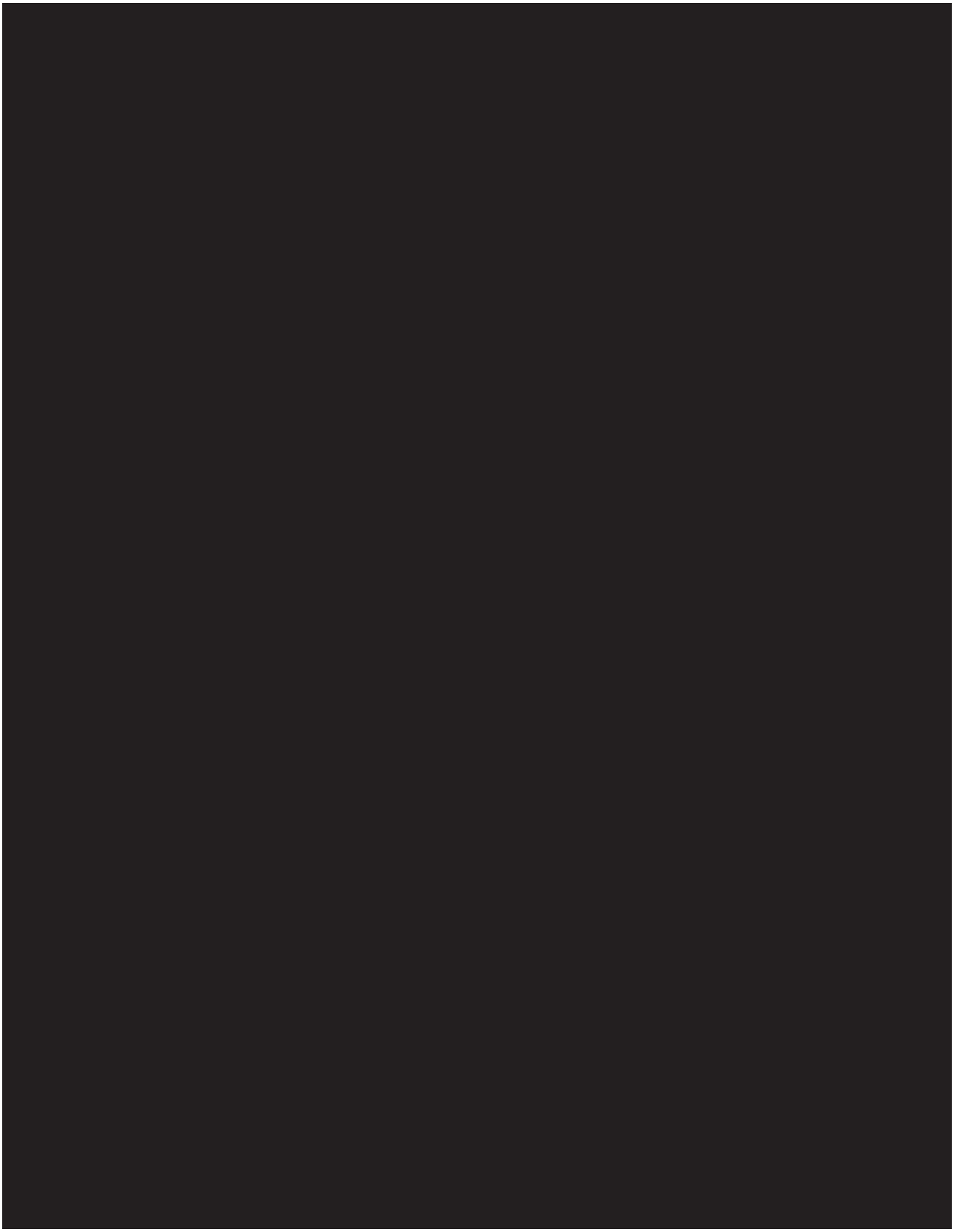
For the criterion "CTC status at week 12", the nearest assessment to C4V1 (day 85) will be used, with following window:

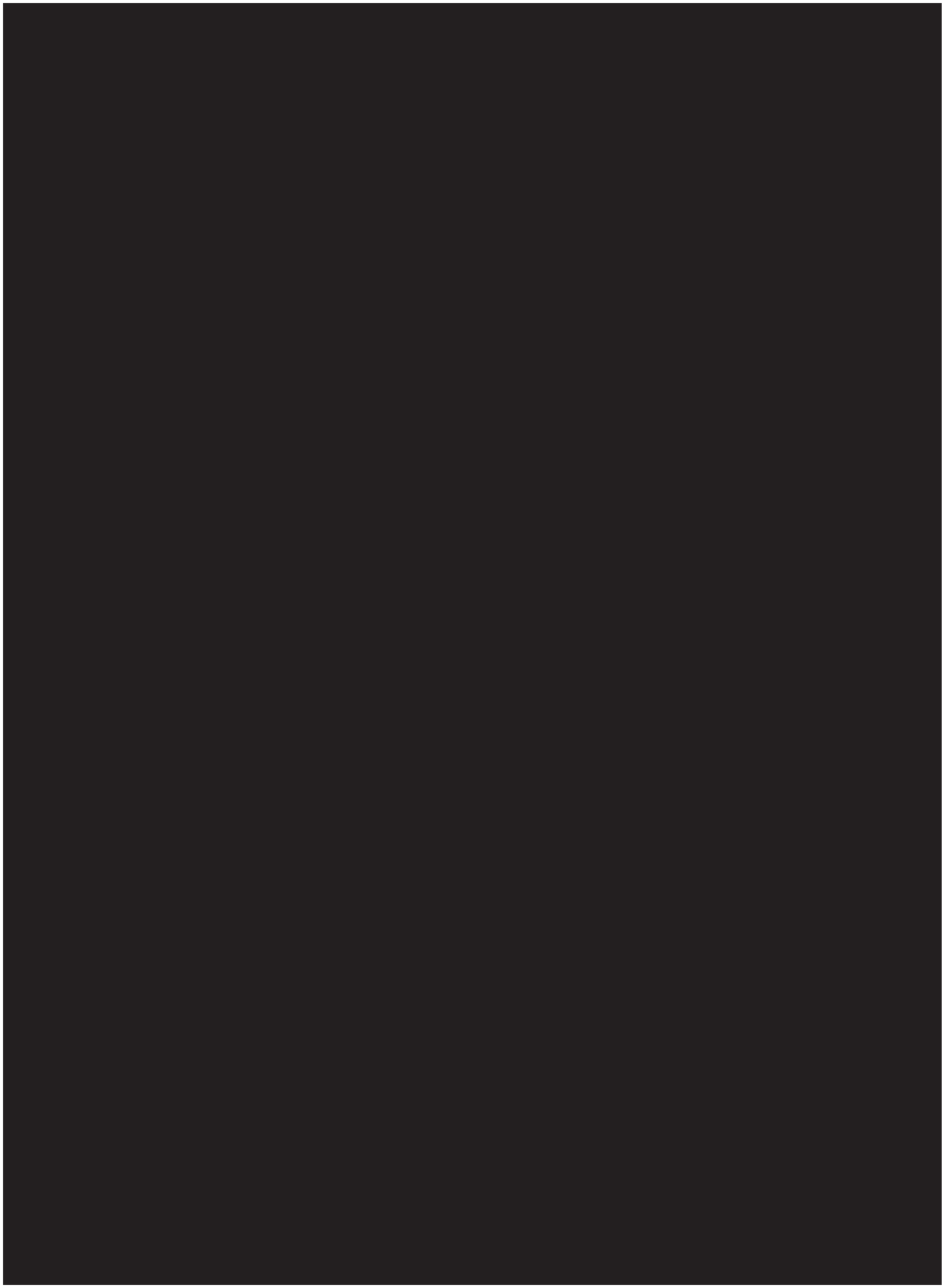
- A later value, until one week after (day 92), can be used
- An earlier value, after four weeks in trial (day 29), can be used.

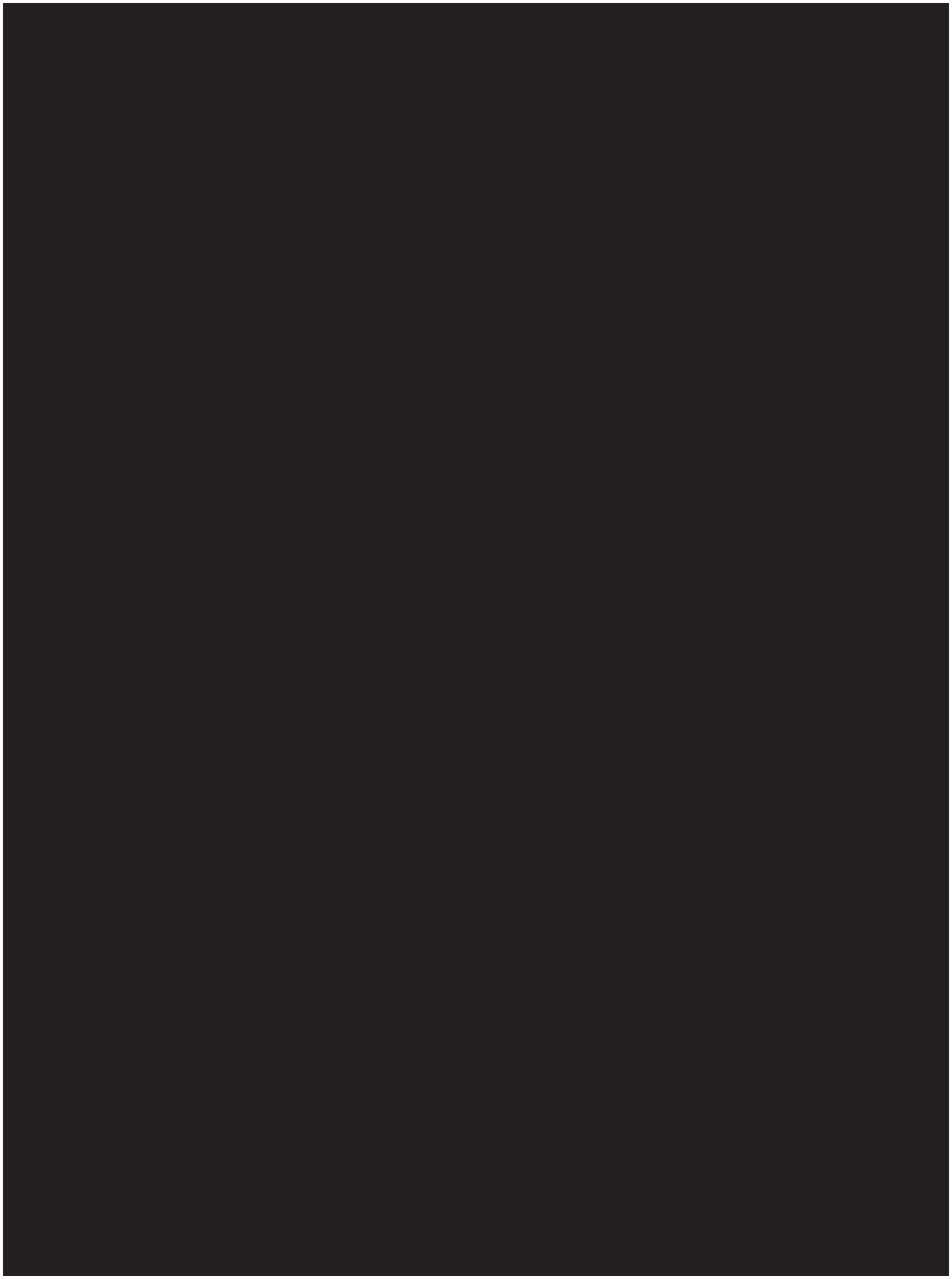
In case the patient discontinued the trial before the planned assessment, the EOT assessment will be used for this criterion in case it is the nearest to the target day.

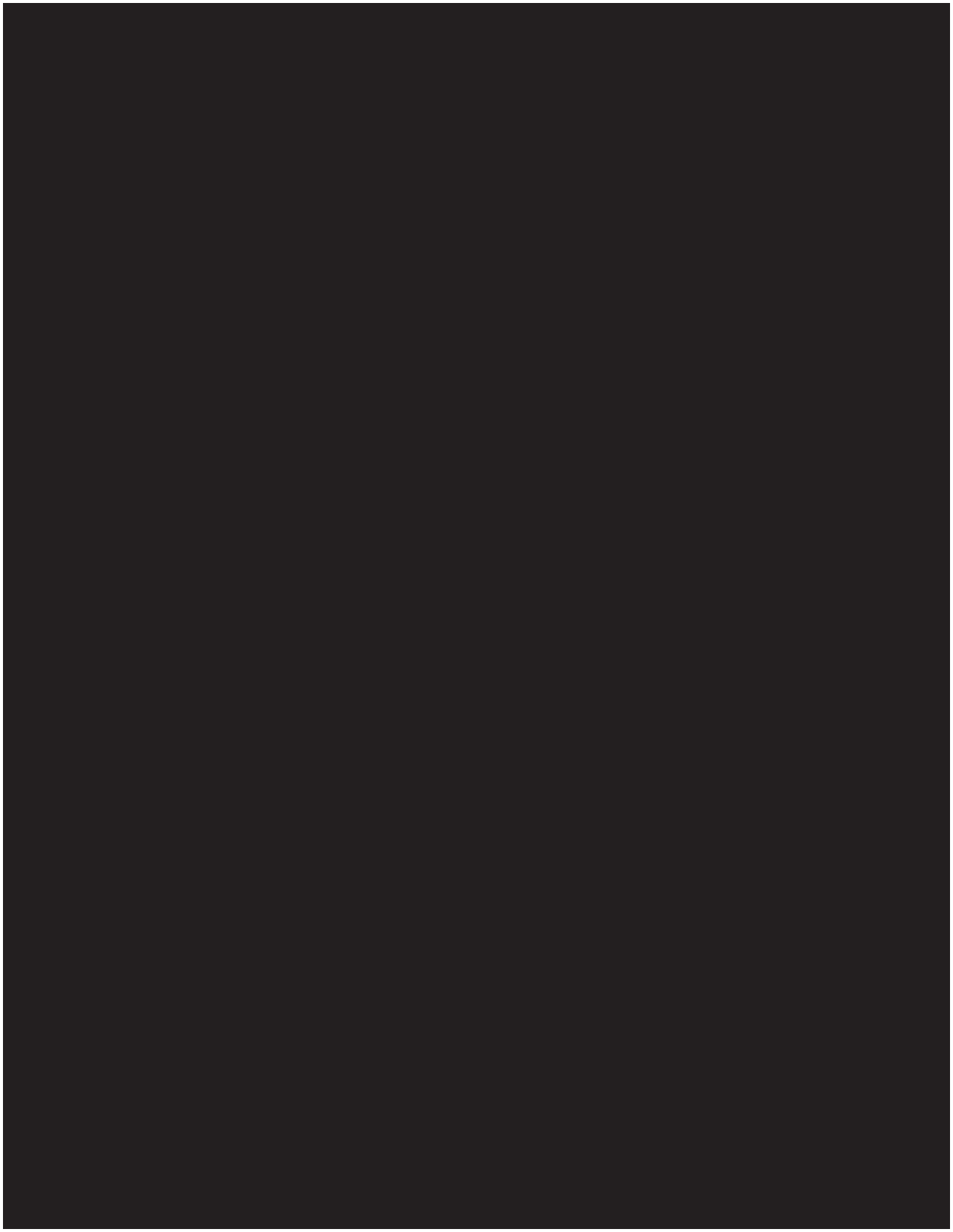
In case it is needed for descriptive tables, multiple entries for one single time point in a patient will be assessed as follows:

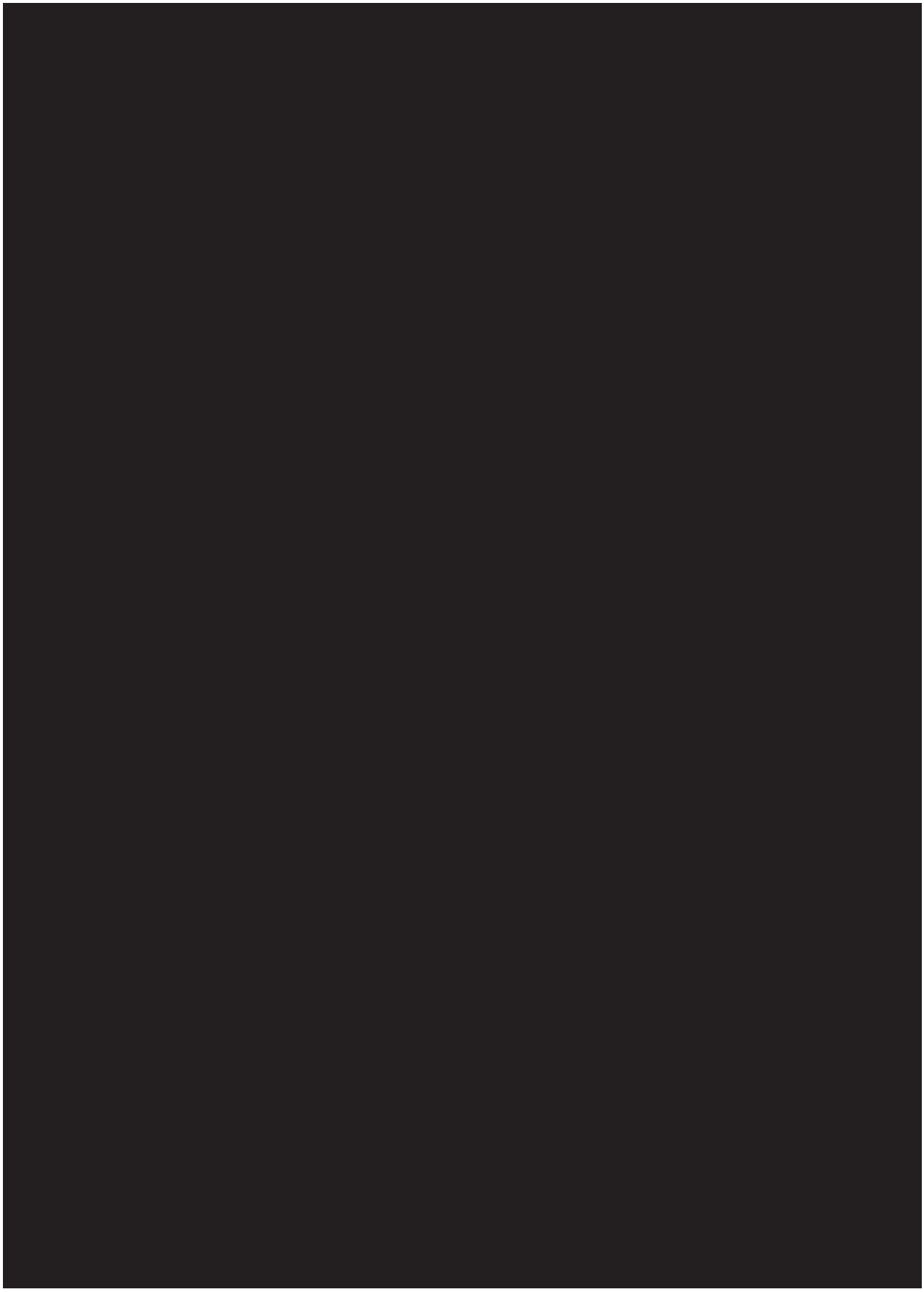
- If only one valid value (with acceptable specimen volume or imputable value) is available, this one will be used
- If several valid values are available, the value of the time point will be set as the mean of the available values

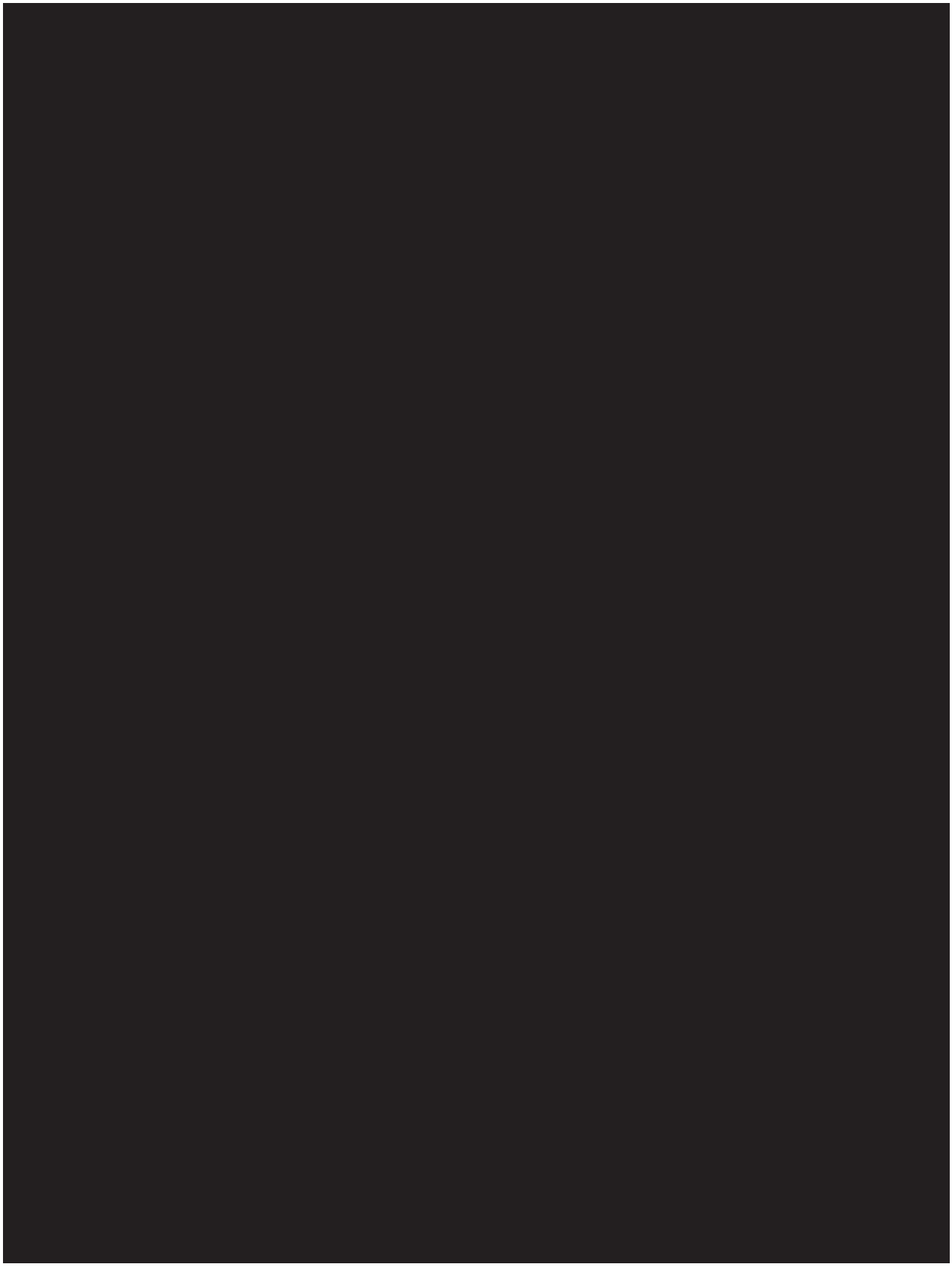


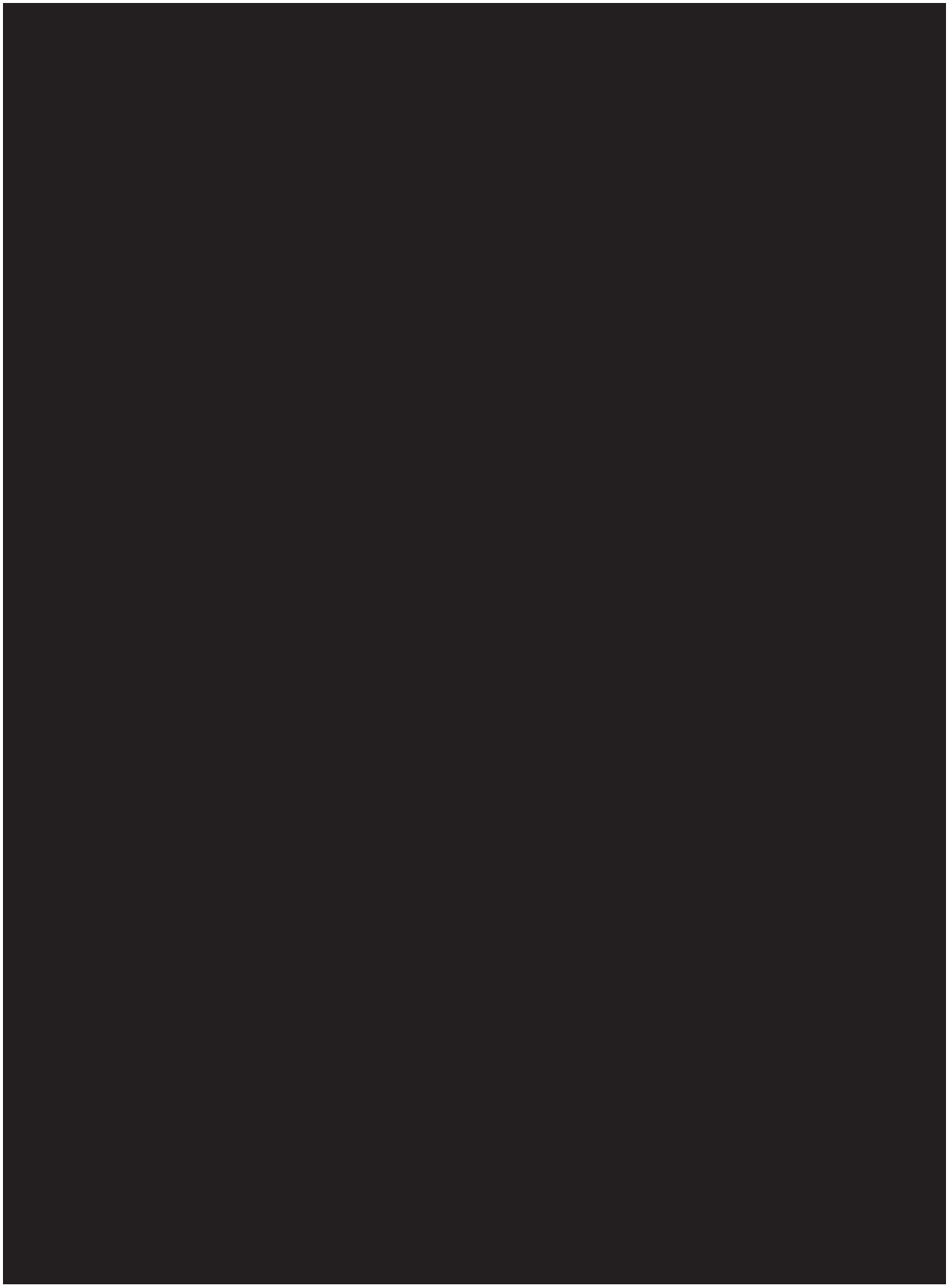


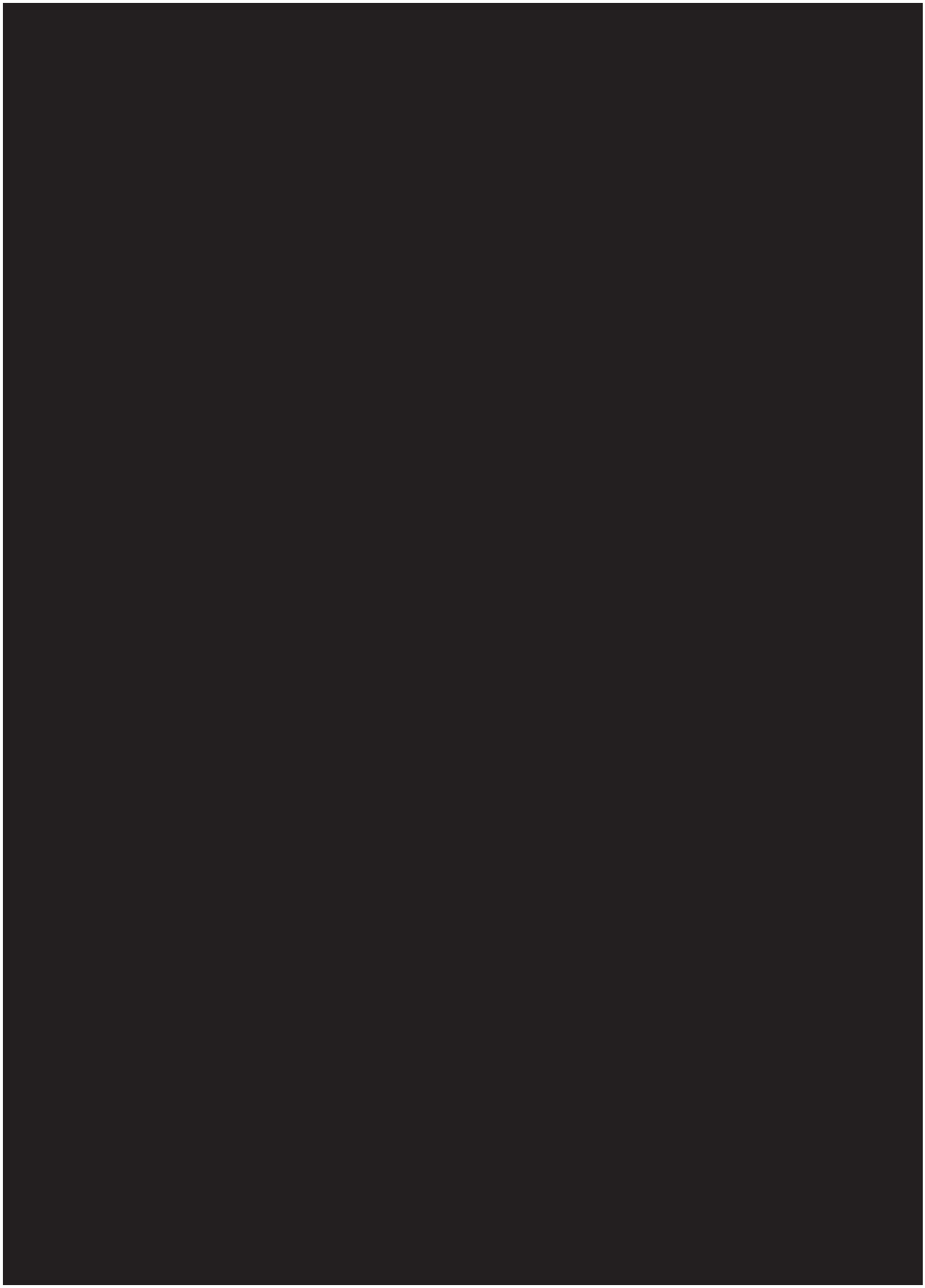


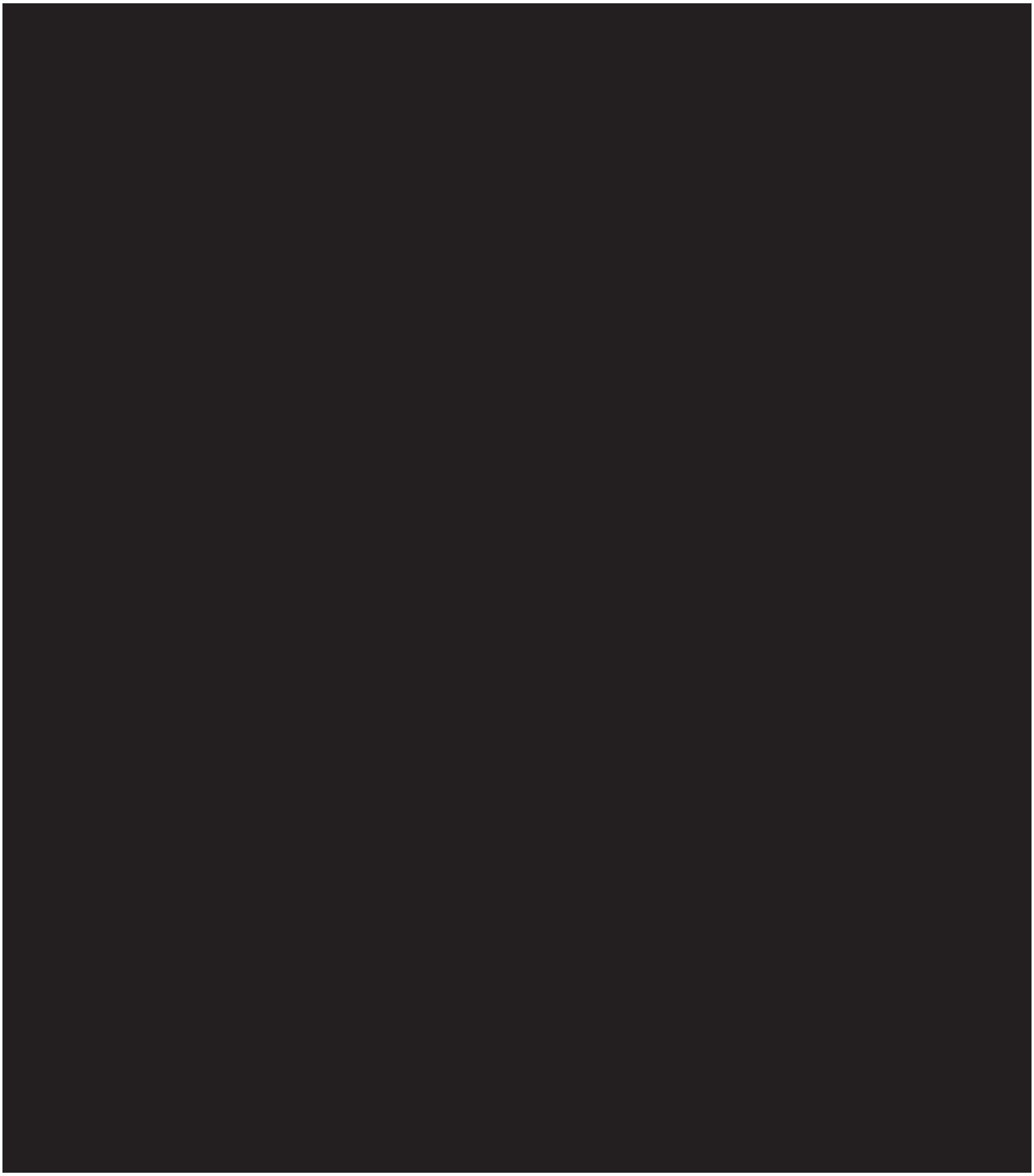












6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Phase I escalation and expansion parts: 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 DBL meeting (but prior to DBL).

Phase II part: 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 REP will be considered as on-treatment. For this trial, the length of the REP is 42 days.

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

Patients in phase I expansion part are on continuous enzalutamide treatment before the trial and during the screening period. For these patients, the on-treatment period is considered to start at the first intake of xentuzumab.

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 important protocol violations will be handled according to BI standards (7).

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* IN1, IN3, IN4 not met	None

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Requirements	Excluded from
	A2	Prohibited baseline condition, diagnosis or treatment	Inclusion criteria* IN5, IN6, IN7 or IN16, IN17, IN18 (phase Ib escalation and phase II only) or IN19, IN20 (phase Ib expansion cohort only) not met or Exclusion criteria* EX1-EX10 or EX13-EX17 or EX21 or EX18, EX22, EX23 (phase Ib escalation and phase II only) or EX19 (phase Ib expansion cohort only) met	None
	A3	Laboratory result indicating inadequate organ function at screening	Inclusion criteria* IN8 to IN15 not met or Exclusion criterion* EX12 met	None
	A4	Adequate archival tumour tissue not available	Not applicable	None
	A5	Relevant medical history available for patients undergoing tumor biopsy only	Exclusion criterion* EX20 met	None
B [1]		**Legal Criteria**		
	B1	Informed consent not available / not done	Informed consent date missing	All
	B2	Informed consent too late	Informed consent date was after Screening Visit date	None
	B3	Age limit for patient inclusion not adhered to	Inclusion criteria IN2 not met or, Calculate age given the date of birth and date of informed consent: patients must be ≥ 18 years old	All

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Requirements	Excluded from
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 or later than 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
	C2 **[2]**	Trial medication not given according to protocol	Dose reduction scheme not followed (see CTP Section 4.1.4.4); 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 Enzalutamide with associated comments) Please note: This excludes the investigational treatment given outside the boundaries specified in the CTP (covered in Category C3)	None

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Requirements	Excluded from
	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
	C4.2	Treatment allocation not followed	This applies for all non-randomized parts of the trial.	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.	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 Section 5.1.2.1 of the CTP, Section 6.7.2 of the TSAP).	None

Table 6.2: 1 Important protocol violations (cont.)

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/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 phase Ib escalation and expansion parts, the TS will be used for all planned safety and efficacy analyses, except for CTCs endpoints in phase Ib expansion part, for which the corresponding biomarker set (CTCb) will be used (see below). In 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 escalation 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 first part, this is specified in the technical TSAP.

Patients in the TS who were replaced within the MTD evaluation period in the first part of the trial will be excluded from the determination of the MTD. Replacement of patients in the first 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 (RPM) before the DBL for the safety analysis.

- Randomised set (RS)

This patient set includes all randomised patients in the phase II of the trial, regardless of whether or not they have received treatment. Patients are assigned to xentuzumab in combination with enzalutamide or enzalutamide alone. The randomised set will be used for the efficacy analyses of patients in the phase II of the study, except for CTCs endpoints, for which the corresponding biomarker set (CTCb) will be used (see below).

- Pharmacokinetic set (PKS)

This patient set includes all patients in the treated set who provide at least one PK parameter that was not excluded according to the description in Section 6.6.3 below. Thus, a patient will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment.

- Biomarker Sets

A patient set will be defined for each biomarker, if the data is available.These sets include all patients in the treated set who have at least one evaluable baseline value for a biomarker.

  - BB: Blood Biomarkers - Baseline measurements of free, dissociable and total IGF-1, free, dissociable and total IGF-2, total IGFBP-3 in serum and IGF bioactivity in heparin plasma
  - MSb: Mutational status of archival FFPE tumor samples, at baseline
  - mRNAS: Messenger RNA (mRNA) expression of IGF pathway related genes, e.g. tumor IGF-1 and IGF-2, at baseline
  - DCS: Relevant biomarkers related to IGF-1 and IGF-2 Downstream Cascade (e.g. pAkt) in tumour tissue, at baseline
  - PES: Protein Expression Set of IGF-1/2 in FFPE tumour sample, at baseline
  - CTCb: CTC baseline measurement

Biomarker sets will be used for the corresponding biomarker analyses, and the CTCb set will be used as well for the analysis of the secondary and further endpoints related to CTC assessments. In case one of the biomarker sets is identical or contains <5% difference in number of patients with the randomized set (or treated set in the phase Ib expansion part), then the randomized set (or treated set in the phase Ib expansion part) will be used and biomarker sets will not be considered at all.

- ECG Set (ECGS)

This patient set includes all patients in the treated set who do not have artificial cardiac pacemakers and have at least one on-treatment value for at least one ECG variable.

- ECG-PK Set

This patient set includes all patients in the ECG set who are

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

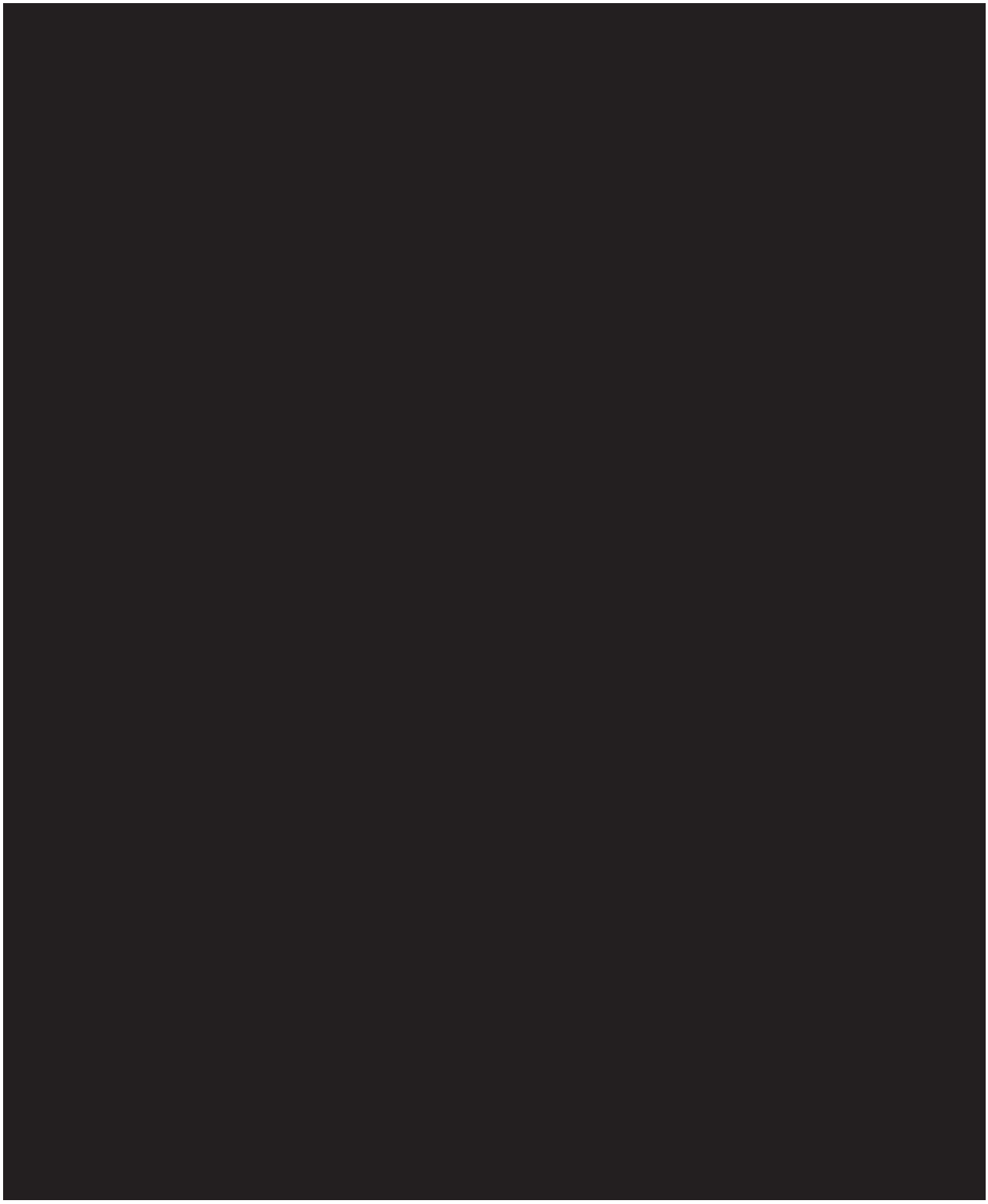
The decisions whether

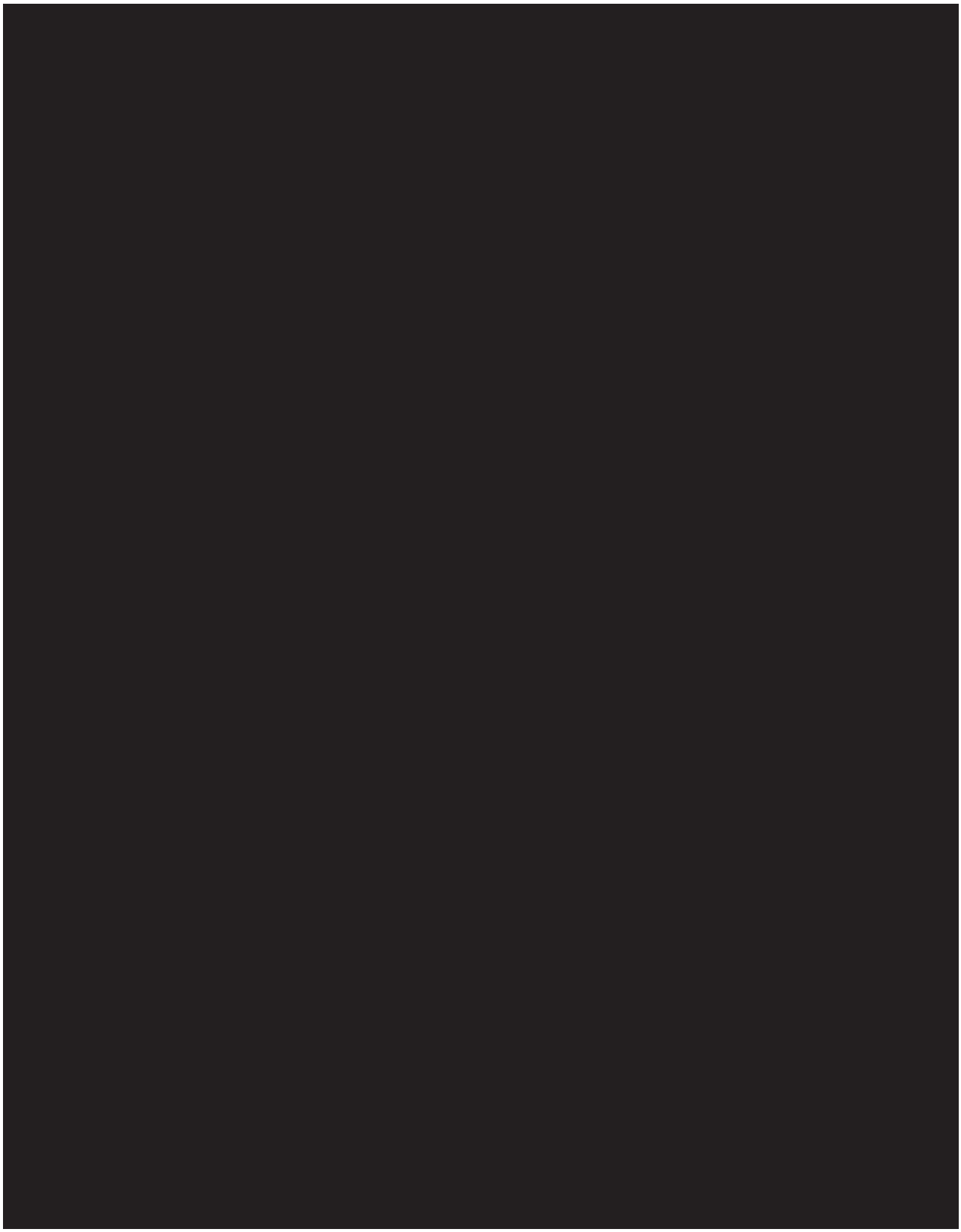
  - a concentration is considered valid or
  - a time deviation between PK blood sampling and ECG recording is acceptable

will be made no later than at the final BRPM before DBL.

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.

No per protocol population will be used for analyses.





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 DBL 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

Table 6.6:1 Rules for imputations of missing or incomplete dates (cont.)

Date	Imputation rule
Date of end of treatment (only for patients still ongoing at time of snapshot/DBL)	Date of snapshot/DBL

6.6.1 AEs

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

6.6.2 Laboratory values at baseline

For missing laboratory data at Cycle 1 Visit 1 (before the very first administration of study medication) data from preceding visits will be used.

6.6.3 PK parameters / biomarkers

Missing data and outliers of PK data are handled according to BI standards (3).

Missing biomarker data may be imputed. The rules will be described in the Unblinded Report Planning Meeting (URPM) minutes and/or in the CTR.

Plasma concentration data and parameters of a subject will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol violations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications.

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- the subject experienced emesis that occurred at or before two times median tmax of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- missing samples/concentration data at important phases of PK disposition curve.

Exclusion of PK parameters

The analysis data set (ADS) ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS are based on PK parameters with APEXC equal to "Included", regardless of the analysis flag comment APEXCO.

Exclusion of plasma concentrations

The ADS ADPC (PK concentrations per time-point) contains a column variable ACEXCO containing an analysis flag comment. Exclusion of a plasma concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to 'ALL CALC', the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point. If ACEXCO contains the addition 'TIME VIOLATION' or 'TIME DEVIATION' the value can be used for further analyses based on actual times. If ACEXCO is set to 'HALF LIFE' the value will be excluded from half-life calculation only; the value is included for all other analyses.

Further details are given in (3), RD-01 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" and RD-03 "Description of Analytical Transfer Files and PK/PD Data Files".

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

In general, the data as reported in the eCRF will be used for analyses.

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 in the PK4+ (ADPC dataset) file identified with 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 at an on-treatment time point.

When 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 of the PK4+ file (ADPC dataset) will be excluded from the exposure-response analyses.

6.6.6 FACT-P questionnaire and BPI-SF questionnaire

Handling of missing data for the FACT-P questionnaire is described in Sections 5.3 and 9.3.

Handling of missing data for the BPI-SF questionnaire is described in Section 5.3.

6.7 BASELINE, TIME WINDOWS, AND CALCULATED VISITS

6.7.1 Baseline

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

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

Unless otherwise specified, baseline is defined as the latest time-point before the very first administration of any study medication. If this criterion is not fulfilled then no baseline will be derived, except in the following case: if a patient is entered (phase Ib escalation and expansion parts) 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.

Quality of Life (QOL) questionnaires

BPI-SF questionnaire is assessed at screening and several time-points thereafter. Baseline assessment is the questionnaire assessment from screening, unless it is missing. In this case, the C1V1 assessment is considered baseline.

FACT-P questionnaire is assessed at several time-points starting at C1V1. Baseline assessment is considered as being the assessment from C1V1.

6.7.2 Time windows for every tumour assessment

In order to identify whether consecutive imaging time-points are missing for a given patient, a nominal time point [8, 16, 24, 36 weeks and every 12 weeks thereafter] will be assigned to each and every image. This is achieved by creating windows for every tumour assessment (modified RECIST 1.1 and bone). The windows are defined in Table 6.7.2: 1 below. Day 1 corresponds to date of randomisation for the phase II part (for phase Ib expansion part it corresponds to the date of first drug intake of xentuzumab). Assigning time windows for images is only needed for phase Ib expansion part and phase II part. This will therefore not be done for phase Ib escalation part.

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

Nominal time-point [weeks from start of therapy]	**Due date of imaging [days]**	**Window [days]**
8	57	1 to =< 85
16	113	86 to =< 141
24	169	142 to =< 211
36	253	212 to =< 295
48	337	296 to =< 379
60	421	380 to =<463
every 12 week interval	etc (1)	etc (1)

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

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

6.7.3 Time schedule of ECG recordings and related PK blood sampling

The scheduled time points of ECG recordings and PK blood sampling are described in the CTP, section 10.6.

7 PLANNED ANALYSES

The labelling and display format of statistical parameters will follow BI standards (8).

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

Descriptive statistics for continuous variables will generally contain number of patients in that patient set with non-missing values (N), Mean, Standard Deviation (SD), Minimum (Min), 25th percentile (Q1), Median, Q3 (75th percentile), Maximum (Max). In general, means, SDs, 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 I escalation and expansion parts) or randomised patients (phase II part), following the ITT approach (as specified in Section 6.3).

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 I part 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

In case a pooled analysis of 1280.4 and 1280.8 will be deemed appropriate, specifications of this analysis will be given in a separate CSAP before DBL.

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 Display) catalogue will be populated. Additionally, patients with discontinuations by initial treatment and the reasons will be listed and tabulated, overall and 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.

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 16.1.9.2.3 (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.

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 MedDRA version. Concomitant therapies (CT) will be coded according to World Health Organisation Drug Dictionary (WHO-DD). 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 escalation

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 5.2.3 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 RPM prior to DBL.

A listing of patients with DLTs by initial treatment will be performed. A plot with an overview of the phase I escalation part (showing the patients and their assigned doses, replaced patients and patients with DLT) will be displayed.

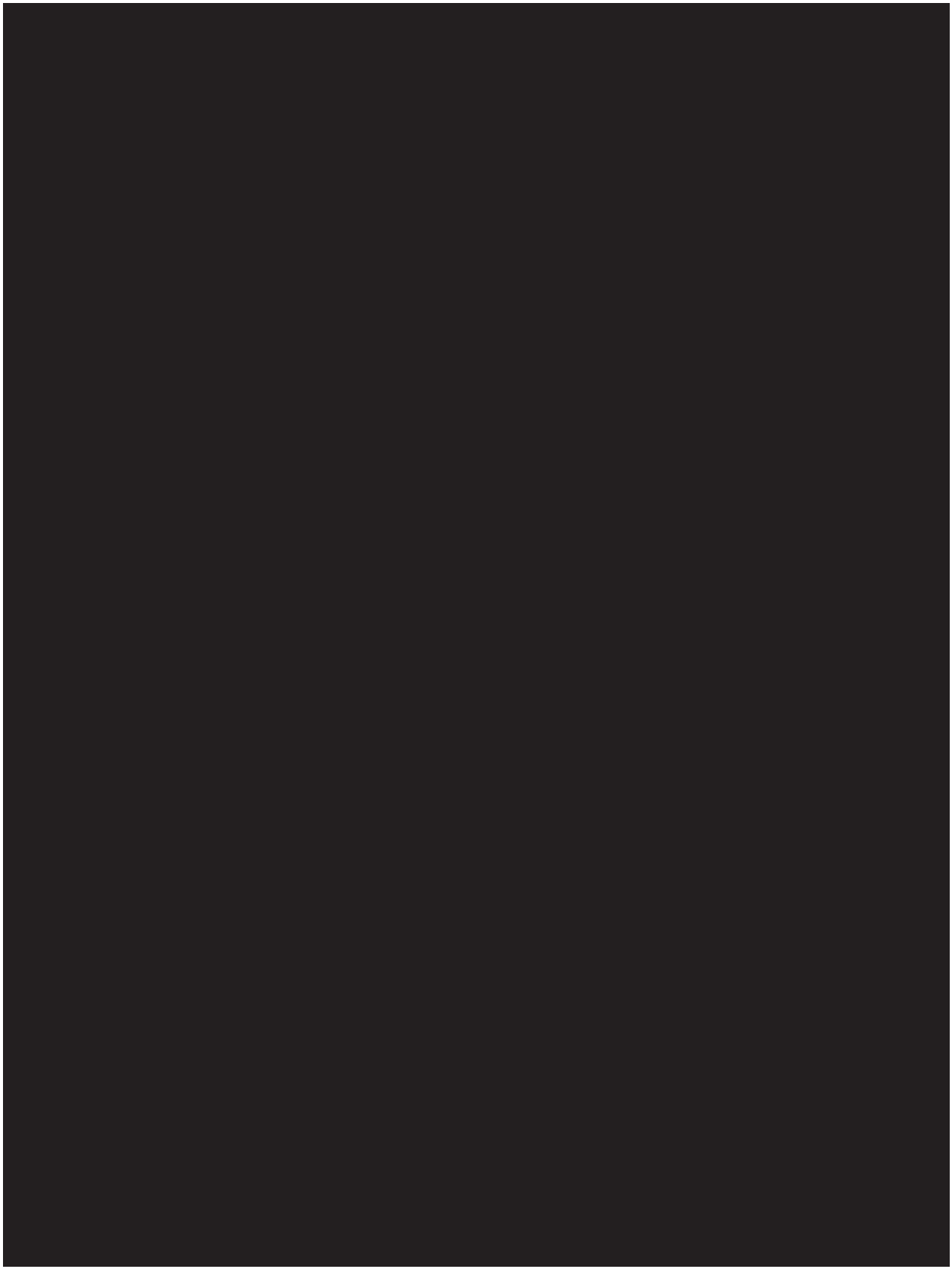
At the end of the dose escalation phase, a safety analysis will be performed to determine the RP2D. The results will be documented for internal use and communication with the participating investigators (see also Section 9.1).

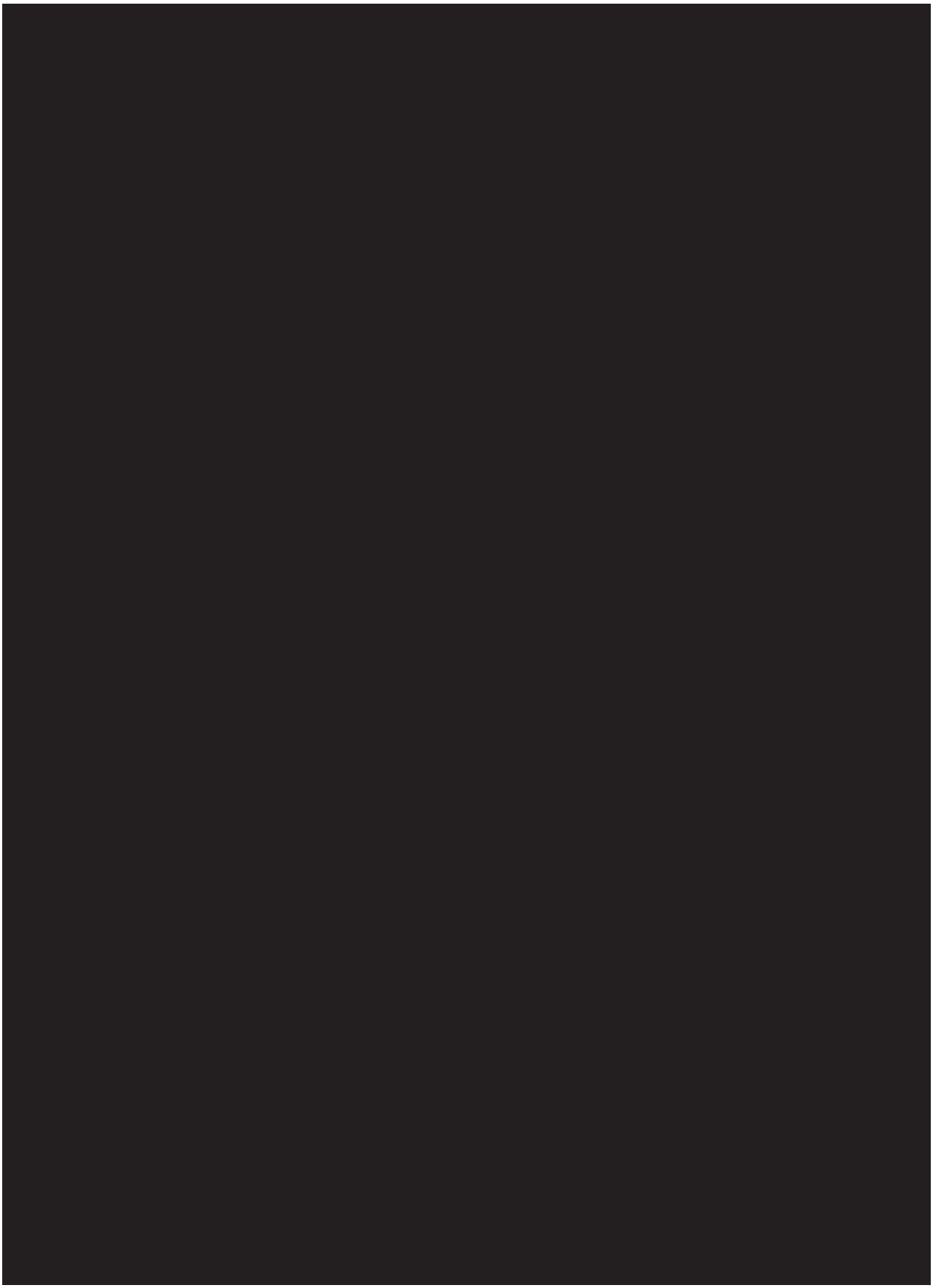
7.4.2 Phase Ib expansion cohort

Descriptive statistics for PSA response will be provided for all treated patients. Confirmed as well as unconfirmed responses will be displayed.

7.4.3 Phase II

The primary analysis for PFS based on investigator assessment will be conducted for all patients of the RS in the phase II part of this trial. 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 (based on Greenwood's method) will be provided for median PFS. An estimation of the effect on PFS of xentuzumab plus enzalutamide compared to the effect on PFS of enzalutamide will be given by the hazard ratio (HR) and its 95% confidence interval using a Cox proportional hazards model. The validity of the underlying assumptions of this model will also be checked. HR < 1 will favour treatment with xentuzumab plus enzalutamide; 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 5.1.3.





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 escalation

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

7.5.2.2 Phase Ib expansion cohort

PFS based on investigator's assessment

PFS based on investigator's assessment will be assessed based on the Kaplan-Meier method in the phase Ib expansion cohort. Point estimates together with confidence intervals (based on Greenwood's method) will be provided for median time to event and quartiles.

Changes in CTC response

The following imputation will be performed before the analysis, separately for each sample:

- If the amount of specimen volume is 7.5mL as planned, the measured cell count will be taken for the analysis
- If the amount of specimen volume is ≥5mL and <7.5, and number of cells is reported and is ≥10 then the expected number of cells for the planned

specimen volume will be imputed using linear transformation: expected cell count=7.5/(actual amount of blood in mL)*(measured cell count)

- If the specimen volume amount of blood is ≥5mL and <7.5, and number of cells is missing or is <10, then no imputation will be done and the number of cells will be set to missing for the analysis

Frequencies of patients with CTC reduction will be displayed.

The maximum decline (percentage) in CTC counts compared to baseline will be analyzed descriptively.

7.5.2.3 Phase II

PFS based on central review

PFS based on central review will be analysed using the same methods as for the primary endpoint for phase II (see Section 7.4.3), including subgroup analyses, if deemed appropriate.

OS

OS will be analysed using the same methods as for the primary endpoint for phase II (see Section 7.4.3), including subgroup analyses, if deemed appropriate.

Time to PSA progression

Time to PSA progression will be analysed using a Cox proportional hazards model in the same way as the primary endpoint for phase II (see Section 7.4.3).

Maximum decline in PSA

Descriptive statistics for maximum decline in PSA will be displayed. This endpoint will also be explored graphically by means of a waterfall plot (using the percentage decline). All PSA assessments will be displayed in a longitudinal plot.

Percentage change in PSA at week 12

Descriptive statistics for percentage change in PSA at week 12 will be provided. This endpoint will also be explored graphically by means of a waterfall plot. All percentage changes in PSA will be displayed in a longitudinal plot.

PSA response

Descriptive statistics for PSA response will be provided. Confirmed as well as unconfirmed responses will be displayed.

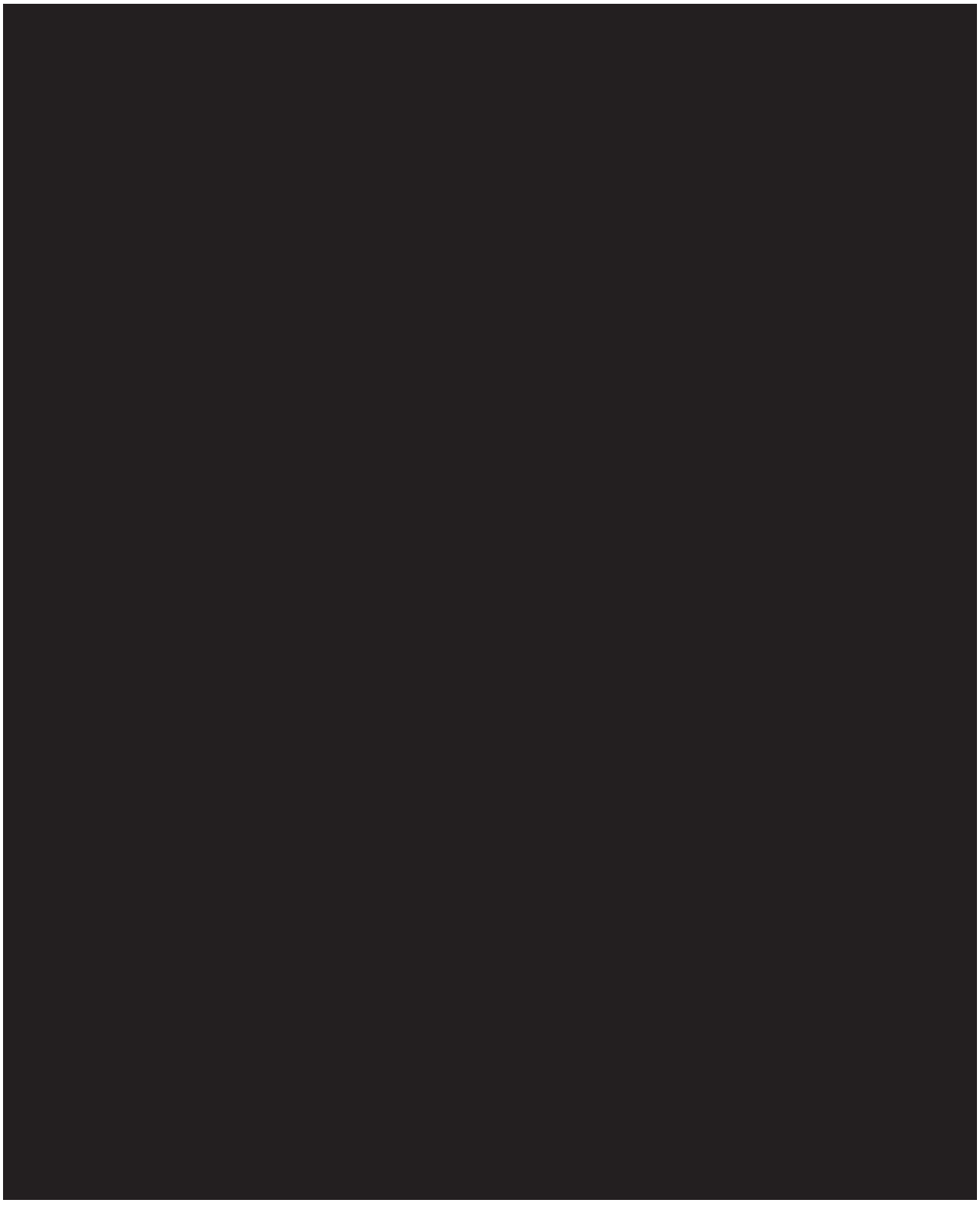
Changes in CTC response

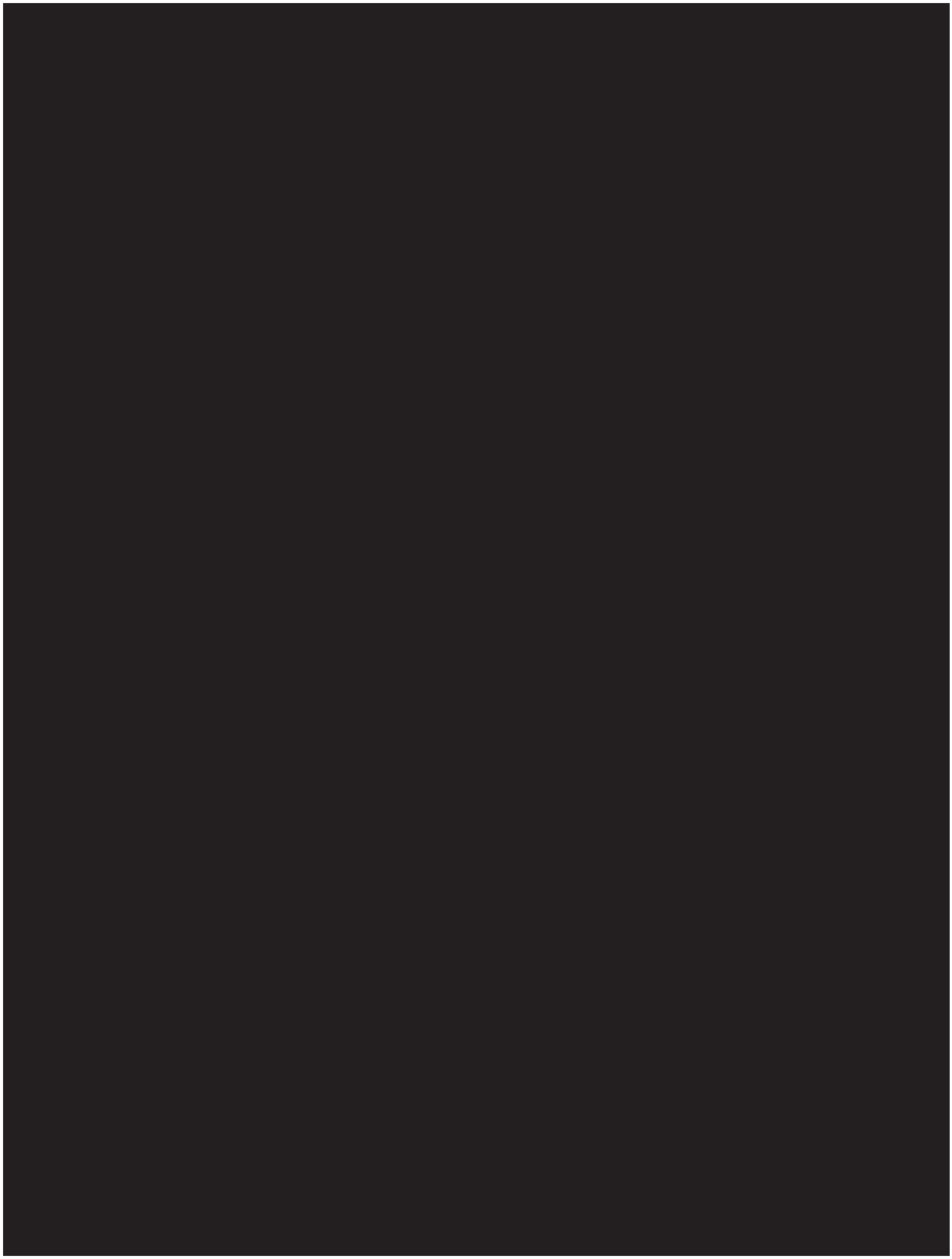
Imputations as specified in Sections 5.2.2 and 7.5.2.2 will be performed before the analysis, separately for each sample.

Frequencies of patients with CTC reduction will be displayed.

The maximum decline (percentage) in CTC counts compared to baseline will be analyzed descriptively and also explored graphically by means of a waterfall plot. All CTC assessments will be displayed in an overtime plot per patient.

Difference in proportions for week 12 status will be displayed by means of a contingency table, along with 95% confidence interval and a Fisher's exact test.





7.7 EXTENT OF EXPOSURE

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

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 first 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 (LLT, CTCAE grade, action taken with trial medication, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI)
- 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).

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

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarised by treatment, primary SOC and PT. Separate tables will be provided for patients with drug-related AEs, AEs leading to dose reduction, adverse events leading to discontinuation, SAEs, serious drug-related AEs, AEs leading to death, other significant AEs, AESI, and AEs fulfilling the DLT definition (for phase Ib escalation only).

Sorting order:

In tables presenting SOCs and PTs, SOCs will be sorted alphabetically and PTs (within SOC) by descending frequency.

Reporting of CTCAE grades in tables:

In tables showing AEs by worst CTCAE grade, AEs with missing CTCAE grade will only be displayed under the category "All grades", but no category "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

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

Incidence and severity of 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 enzalutamide
- AEs leading to permanent discontinuation of xentuzumab
- AEs leading to permanent discontinuation of enzalutamide

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 AESI

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 escalation.

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 at the time of DBL. These

categories can also be found in Table 7.8.1:1. This document is entitled "8-02-sap-safety-core", which can be found in the Project DMS folder, section 8 (project level), within BIRDS.

Table 7.8.1: 1 Adverse events by user defined AE categories

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

[#] 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 (6). The same on-treatment periods as considered for the analysis of AEs 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" (6), RD 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 DILI (Drug-Induced Liver Injury) 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

All 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.

Descriptive analyses (separate analysis of first and second parts)

Descriptive analyses of continuous and categorical endpoints will be performed. 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 of the CTR)

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.

Patients in the TS who have notable findings but are excluded from the ECG Set will be listed in separate listings which will be presented in Section 15 of the CTR.

Additional statistical analyses will be performed as described in the following.

Repeated measures analyses (Phase II part only)

The following analyses will only include the ECG interval data of both arms of the Phase II part.

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 + enzalutamide’ versus ’enzalutamide’, the treatment differences at each timepoint will be estimated by the difference in the corresponding Least-Squares Means (LS Means). Two-sided 90% confidence intervals 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% confidence intervals 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 covariances of 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 second 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 (Phase I and Phase II parts pooled)

The exposure-response analyses will be based on the ECG-PK set. The analyses will include the pooled data of the Phase I and Phase II parts. Patients in the expansion cohort of the Phase I part will be excluded as they are pre-treated with enzalutamide. Data of patients receiving enzalutamide alone (Phase II part) will be included with xentuzumab plasma concentrations set to zero (see 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, see Section 6.6.5) will be excluded from the analyses. When the collecting time of the blood sample or the ECG recording is not available, the pair will also be excluded. The decisions to exclude pairs from the analyses will be made no later than at the final BRPM before DBL (for further details see also Sections 6.3 and 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+enzalutamide’ and ‘enzalutamide’ to estimate the adjusted mean difference between ‘xentuzumab + enzalutamide’ and ‘enzalutamide’ in QTcF change from baseline and its 90% confidence interval at clinically relevant plasma concentrations, which are the geometric means of the $C1D1_{1h}$, $C2D8_{1h}$ and $C3D1_{1h}$ 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% confidence interval and the geometric means of $C1D1_{1h}$, $C2D8_{1h}$ and $C3D1_{1h}$.

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 of the group treated at RP2D/MTD (presented in Section 15 of the CTR). Mean time profiles from the patients treated with enzalutamide 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. 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 heart rate correction methods of QT interval, 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+enzalutamide' and 'enzalutamide'. These analyses will be based on the on-treatment single ECGs (i.e. three values per time point). A table of the resulting (fixed effect) slopes will be displayed together with two-sided 95% confidence intervals in Appendix 16.1.9.2 of the CTR.

7.8.5 Others

Not applicable.

7.9 STATISTICAL BIOMARKER AND PK/PD ANALYSES

The biomarkers collected in different parts of the trial will be analyzed and reported separately for each part of the trial.

As statistical biomarker analyses are purely exploratory, there will be no strict error control in a confirmatory sense.

If data is available, the following biomarkers will be evaluated and reported in the CTR:

7.9.1 Potentially prognostic biomarkers

- Baseline measurements of free, dissociable and total IGF-1, free, dissociable and total IGF-2, total IGFBP-3 in serum and IGF bioactivity in heparin plasma
- Mutational status of archival FFPE tumour samples
- mRNA expression of IGF pathway related genes, e.g. tumour IGF-1 and IGF-2
- Relevant biomarkers related to IGF-1 and IGF-2 downstream cascade (e.g. pAkt) in tumour tissue
- IGF-1/2 protein expression in FFPE tumour sample.
- CTC baseline measurement
- cfDNA baseline measurement

Statistical analyses for prognostic biomarkers

A Kaplan-Meier analysis (including median, 95% confidence interval, Q1 and Q3 statistics) plus corresponding plot will be conducted for PFS.

The categorised/binary biomarker variables for the biomarkers mentioned above will be the group determining factors. Categorisations will be data-driven and described in the URPM minutes and/or in the CTR. For mutational status the focus will be on mutations with known functional impact. For mutational status, mRNA and cfDNA the categorisations defined in the Biomarker SAP (c09122174-01) will be used as starting point for this exploratory analysis.

Cox proportional hazard analysis will additionally be conducted for biomarker-efficacy relationship. The validity of the underlying assumptions will be checked.

Corresponding sensitivity analyses, such as modelling with continuous biomarker variable may also be conducted. Further analyses may be carried out in an explorative approach and results will be discussed in the context of pharmacokinetic, efficacy, and safety data of xentuzumab in combination with enzalutamide.

7.9.2 Purely exploratory biomarkers

The following biomarkers will be listed in the CTR:

- Ki67 expression level in fresh tumour biopsies taken before and after treatment with xentuzumab
- Other exploratory biomarkers measured in fresh tumour biopsies

7.9.3 Biomarker measurements taken over time

Time series analyses will be performed on the following biomarkers:

- For relevant IGF down-stream cascade biomarkes measured in PRP, total IGF-1, total IGF-2, dissociable IGF-1, dissociable IGF-2, free IGF-1, free IGF-2, IGF bioactivity, as well as IGFBP-3 measured in peripheral blood overtime plots and descriptive statistic tables for the measured values and absolute changes from baseline will be created. Baseline values will be derived and all pre-dose values will be flagged. Correlation plots will be shown, Pearson and Spearman correlation coefficients will be calculated. If feasible, exploratory analyses including (non-)linear function fits such as population E_{max} model will be applied. Further details will be provided in the CTR.
- cfDNA concentrations from patient plasma samples assessing mutational profiling at baseline and monitoring mutational status over time of treatment. Exploratory analyses including nonlinear function fits and AUECs (Area Under the Effect Curve) will be performed if feasible (for the calculation, the linear trapezoidal method is used, as described in (3), RD_01). The measures will be compared between the treatments.
- CTC measures over time (overdispersed count data). Exploratory analyses including nonlinear function fits and AUECs will be performed in order to quantify the time for which the cell counts remain under 5 cells per 7.5ml for each patient. The measures will be compared between the treatments.

7.9.4 Potential surrogate biomarkers

If and only if PFS or OS study results are statistically significant, the CTC status at week 12 alone and in combination with lab parameters will be evaluated as potential surrogate for either PFS or OS using Prentice Criteria (R16-0801). The alpha level will be increased to 20% in order to account for the study size. The following lab parameters and their pairwise combinations will be investigated, if data allows: albumin, alkaline phosphatase, hemoglobin, lactate dehydrogenase. The time points for lab measures will be selected as close as possible

to the CTC status measure and must be on treatment. Details of the analyses are as in R16-0801 and will be described further in Cumulative Statistical Analysis Plan (CSAP).

7.9.5 Potential predictive biomarkers

The statistical analyses for potentially predictive biomarkers will be reported outside of the CTR and described in the Translational Medicine and Clinical Pharmacology (TMCP) SAP. This SAP can be found in BIRDS, on substance level, DMS folder, Section 8 and is entitled "8-02-sap-predictive-biomarkers".

7.9.6 Statistical evaluations of pharmacological endpoints

If data are sufficient and calculation of the PK parameters $AUC_{\tau,ss}$ and $C_{max,ss}$ of enzalutamide is feasible, these PK parameters at steady state (ss) in absence and presence of xentuzumab will be compared statistically.

The statistical model used for the analyses will be an ANOVA model on the logarithmic scale and will be based on the PKS. The treatment enzalutamide alone in steady state (PK parameters collected at Day -1/Day 1 in the phase Ib expansion cohort) will be regarded as reference treatment. The treatment enzalutamide + xentuzumab in steady state (PK parameters collected at cycle 2 Day -1/Day 1 in phase Ib expansion cohort) will be referred to as test treatment in this context.

The effect 'subject' will be considered as random, whereas the effect 'treatment' will be considered as fixed for the main analysis. For the sensitivity analysis the effects 'subject' and 'treatment' will be both considered as fixed. The model is described by the following equation:

$$y_{km} = \mu + \tau_k + s_m + \varepsilon_{km},$$

where

y_{km} = logarithm of response ($AUC_{\tau,ss}$ or $C_{max,ss}$) in subject m receiving treatment k,

μ = the overall mean,

τ_k = the k-th treatment effect, k = 1, 2,

s_m = the effect associated with the m-th subject, m=1,…n,

ε_{km} = the random error associated with the m-th subject receiving treatment k.

The PK parameters $AUC_{\tau,ss}$ and $C_{max,ss}$ will be log-transformed (natural logarithm) prior to fitting the ANOVA model. The difference between the expected means for the log-transformed PK parameters will be estimated by the difference in the corresponding LS Means (point estimate) and 2-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the intra-subject ratio of the geometric means for treatments test and reference.

7.9.7 Exposure- and biomarker-efficacy analyses

A Kaplan-Meier analysis (including median, 95% confidence interval, Q1 and Q3 statistics) plus corresponding plot will be conducted for PFS by exposure and selected biomarkers over time (Total and Free IGF's group).

For exposure, the categorized pre-dose concentration at steady-state (>21 days after start of treatment) $C_{pre,ss}$, closest to the efficacy assessment from noncompartmental analysis (see Section 7.6), will be the group determining factor.

For selected biomarkers over time, this analysis will be performed using pre-dose measurements at steady-state accordingly, if feasible.

Cox proportional hazard analysis will additionally be conducted for exposure-efficacy relationship. The validity of the underlying assumptions will be checked.

7.9.8 Immune response (ADA)

The presence of ADAs will be tested at the beginning of each treatment cycle (until cycle 12), at EOT and at the first FU visit. This analysis is done for patients in phase Ib and for patients in the xentuzumab arm in phase II.

The number and percentage of patients with positive and negative results will be presented.

If considered reasonable, the correlation between ADA (positive / negative) and PK and/or PD endpoints may be performed.

If considered reasonable, the correlation between ADA (positive / negative) and disease control (yes / no), and between ADA (positive / negative) and occurrence of acute/non-acute specific adverse events (yes / no) will be studied using a contingency table, along with 95% confidence interval and a Fisher's exact test.

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

6 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

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10 Jiang W, Freidlin B, Simon R. Biomarker-Adaptive Threshold Design: A Procedure for Evaluating Treatment With Possible Biomarker-Defined Subset Effect. J Natl Cancer Inst 2007, 99: 1036 – 43.

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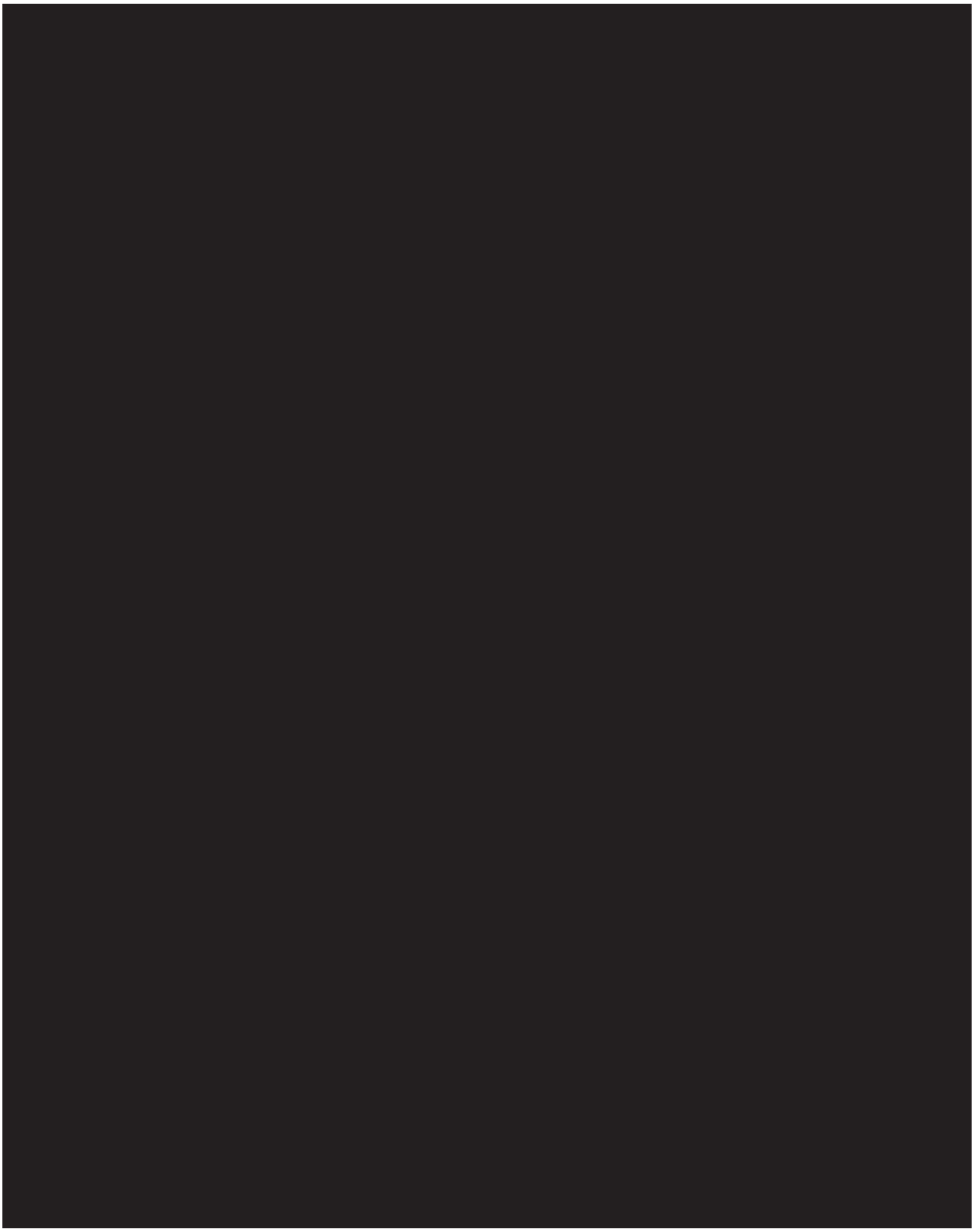

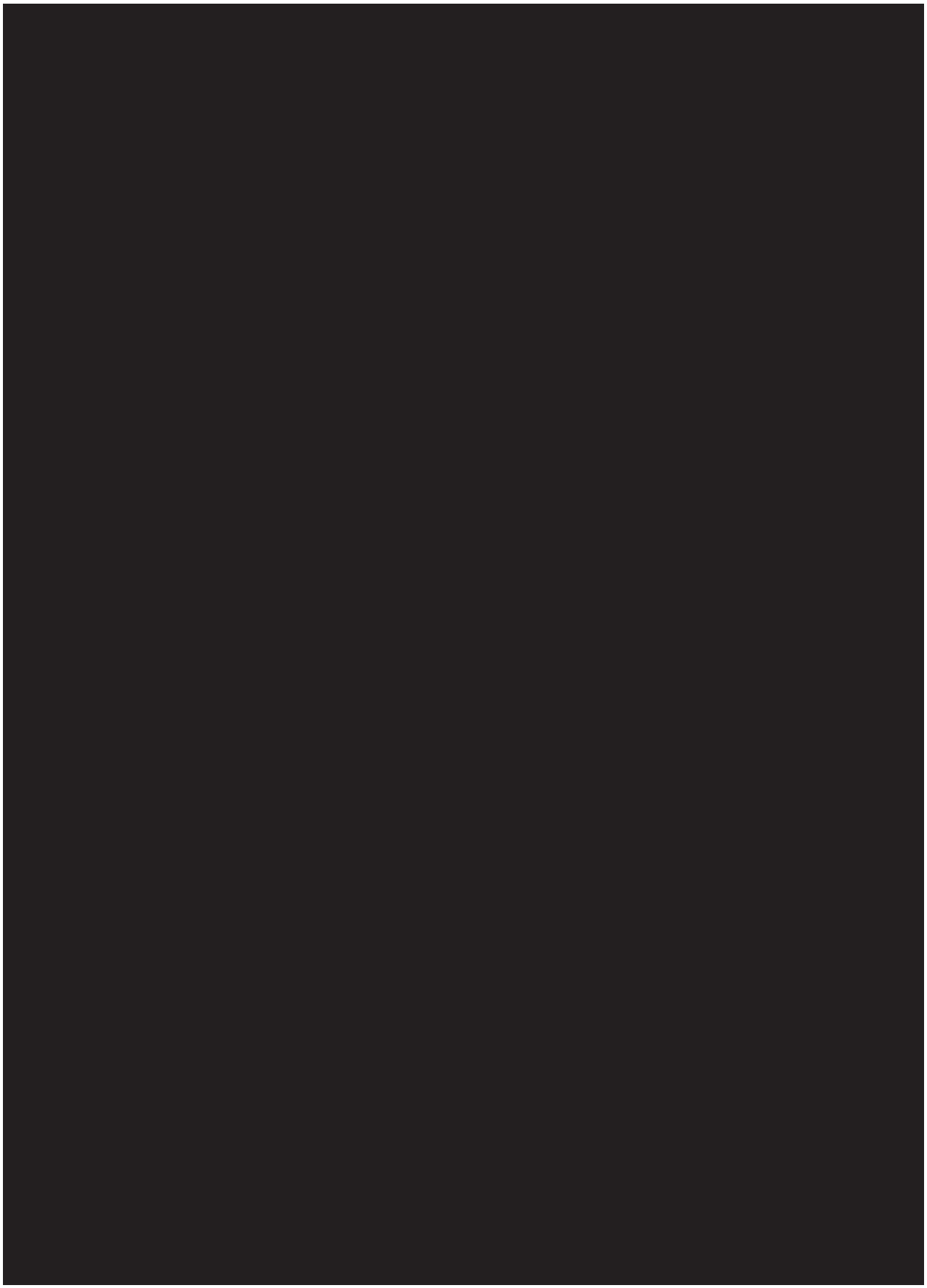

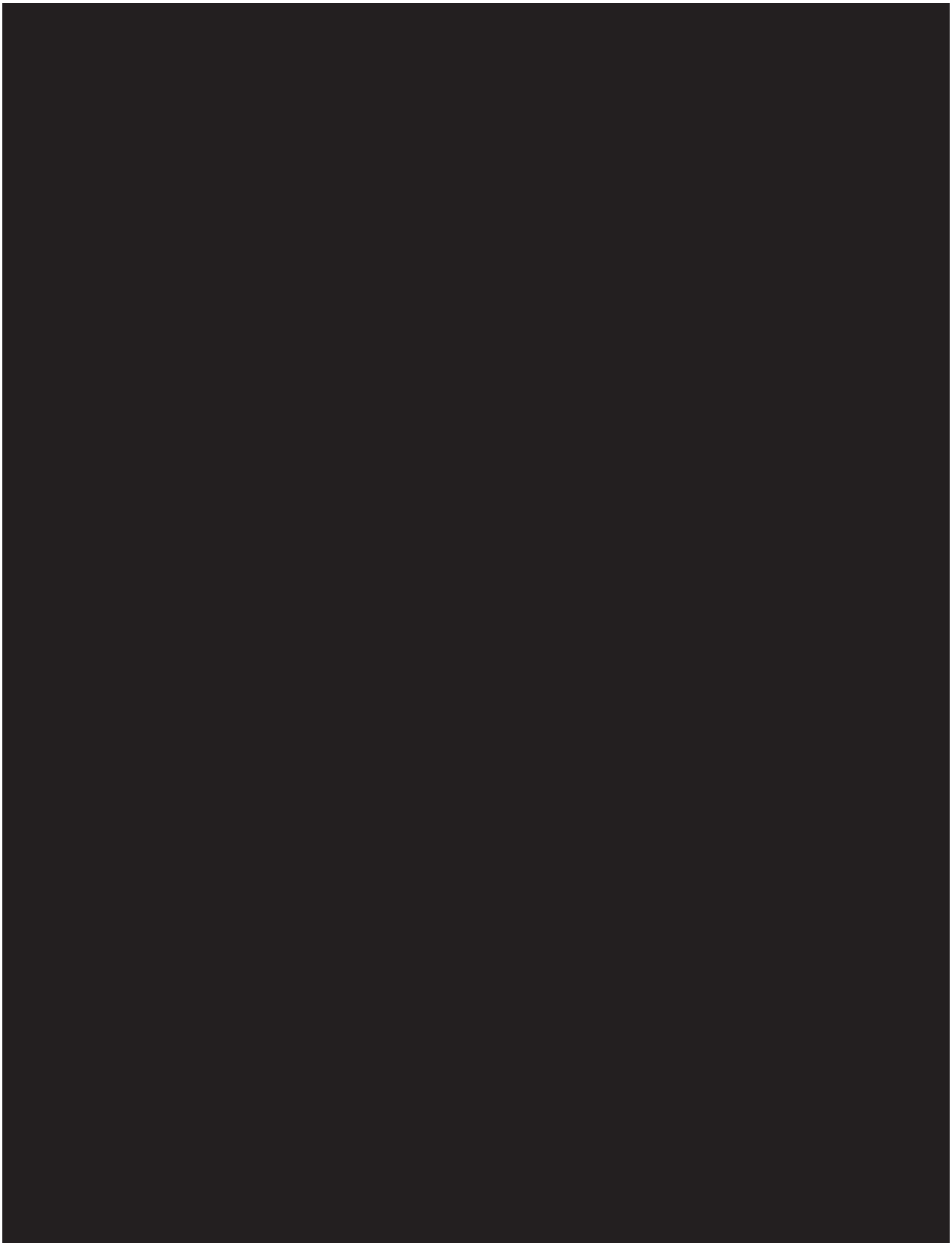

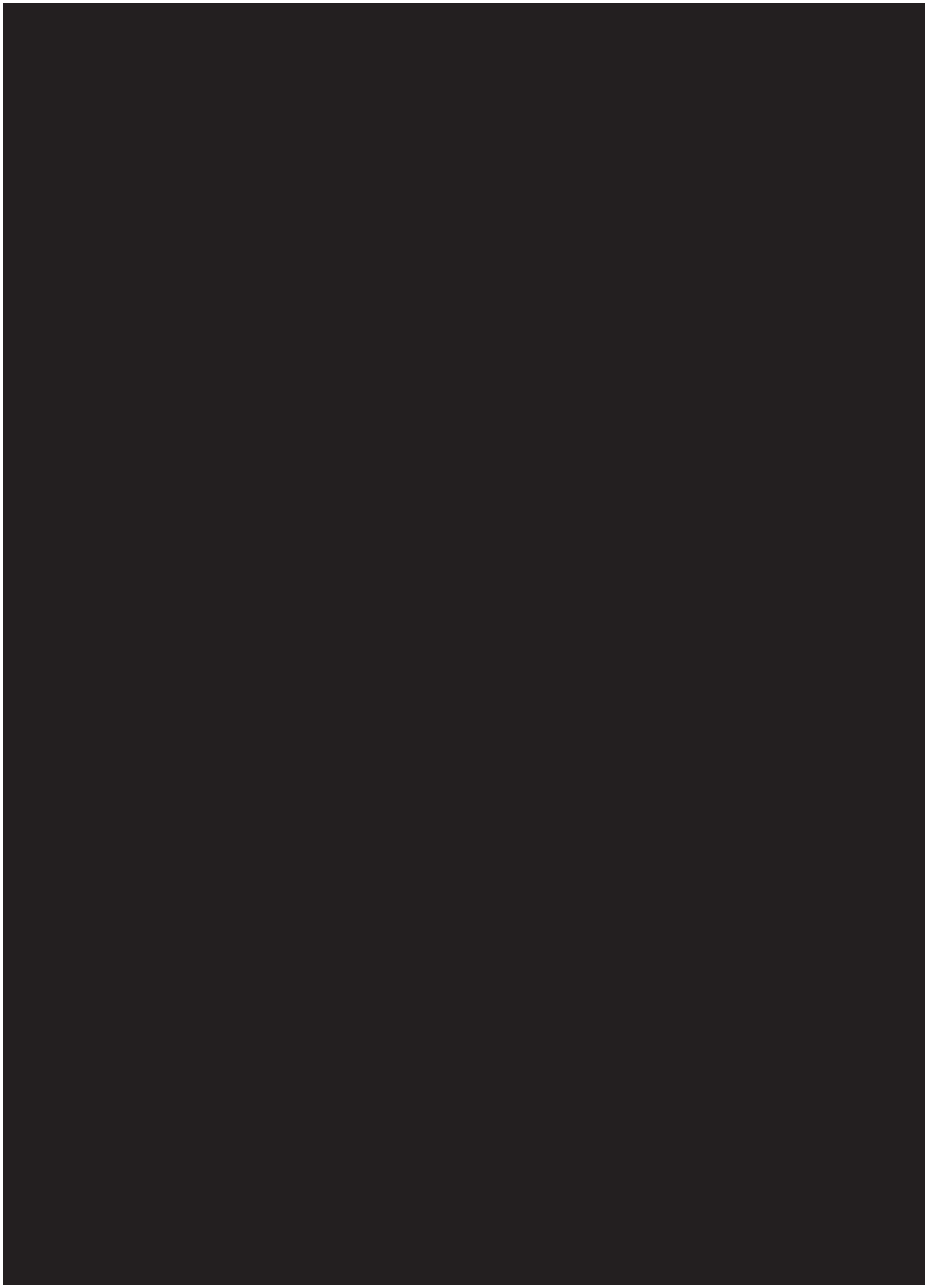

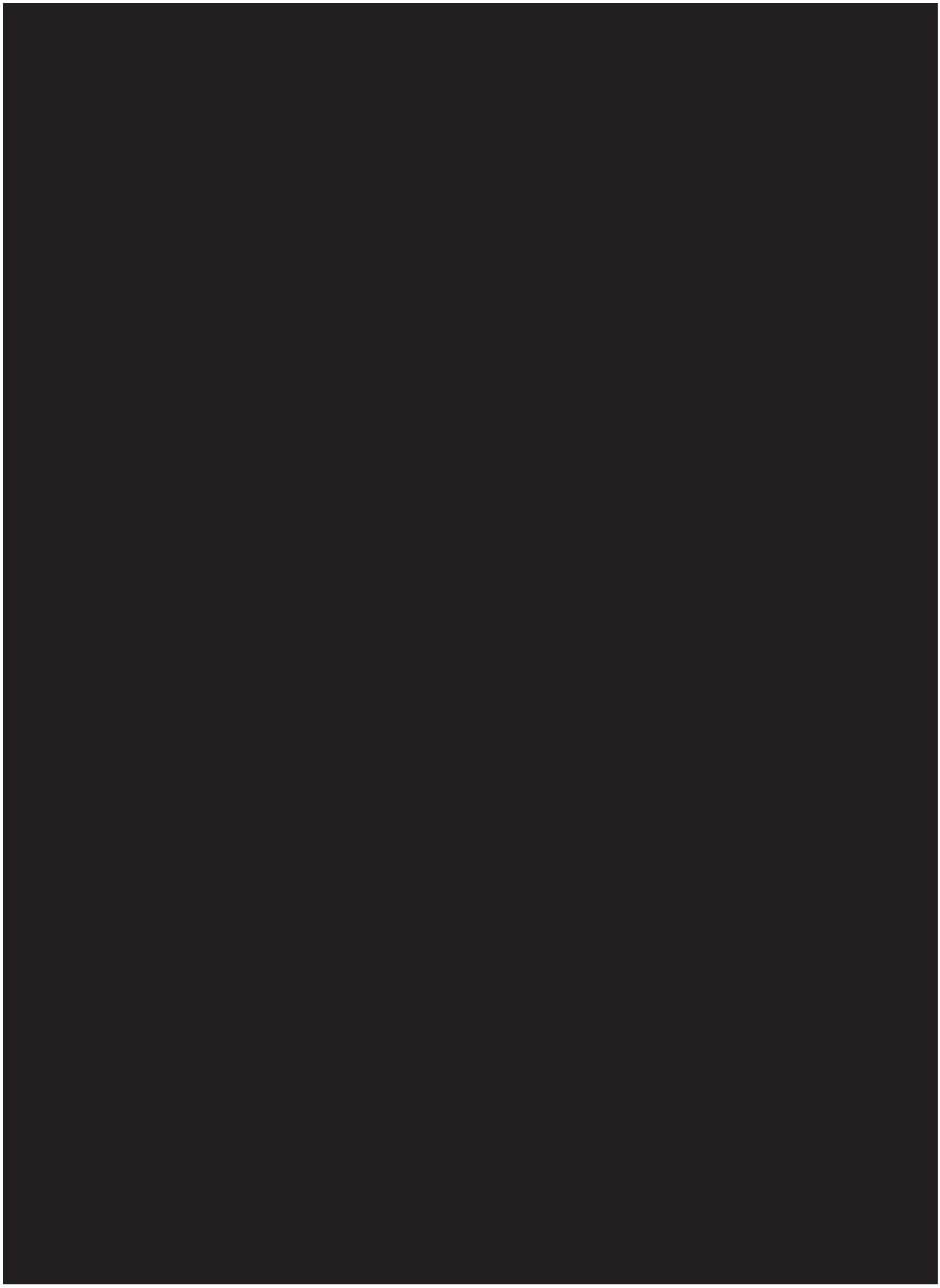

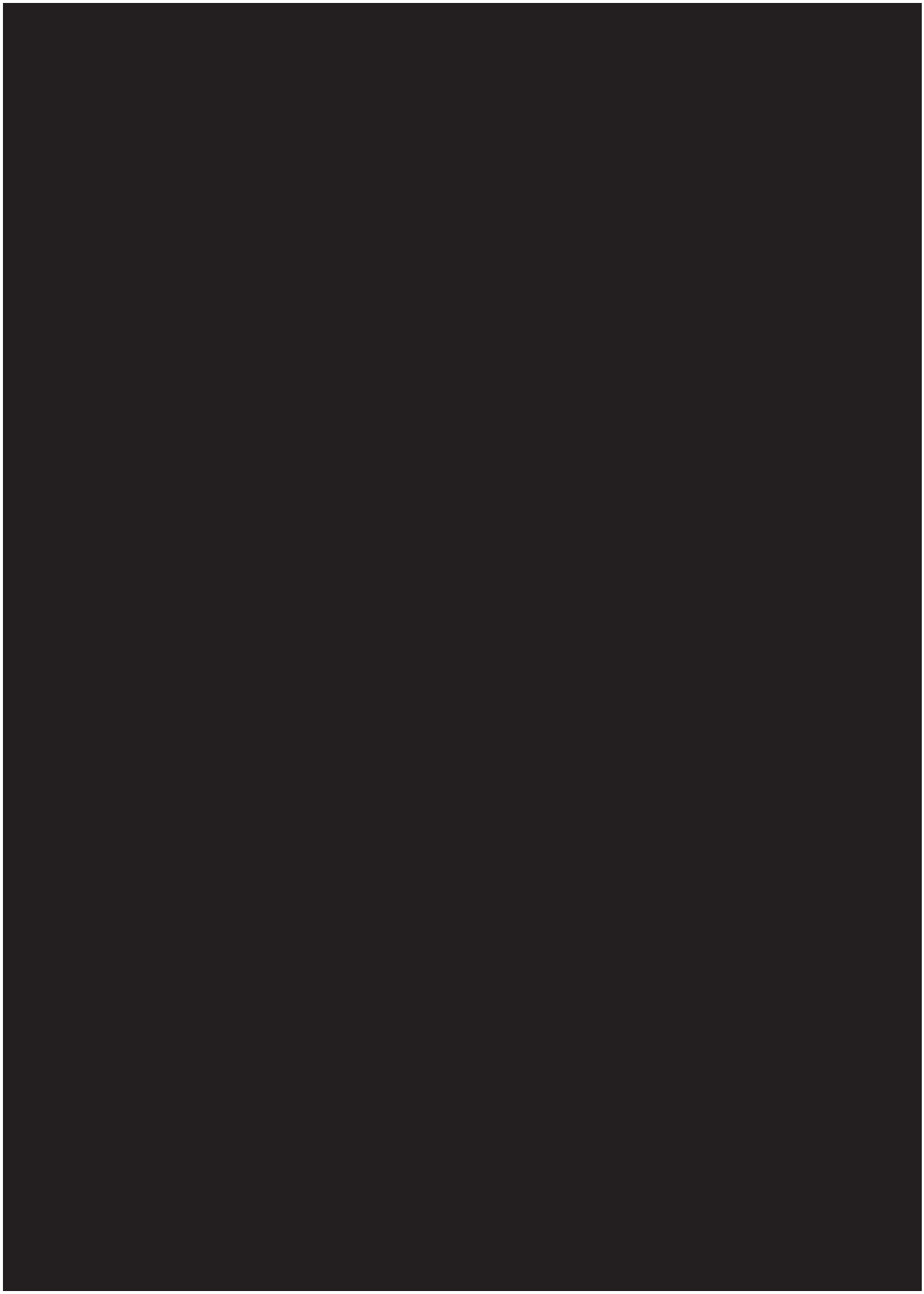

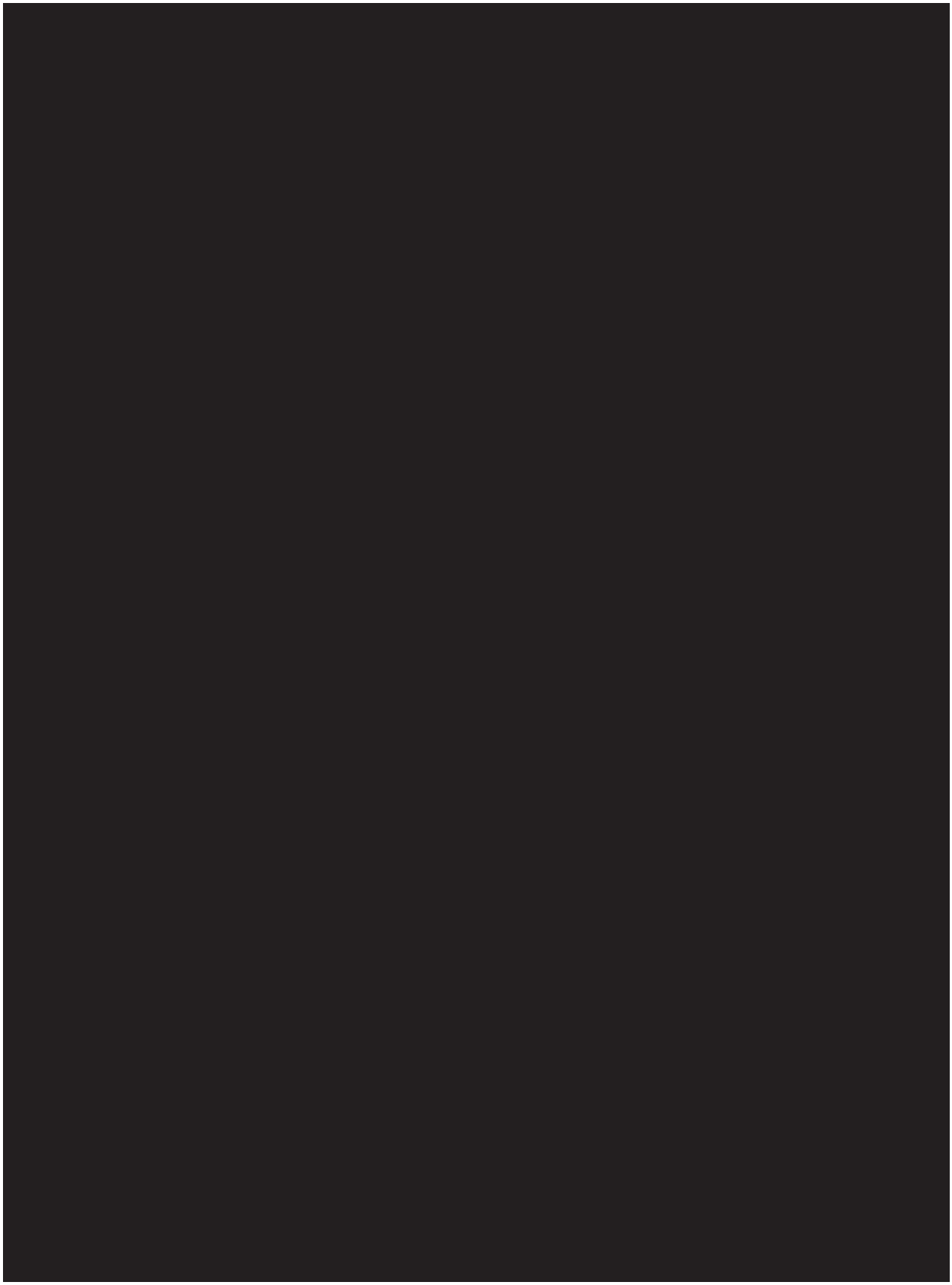

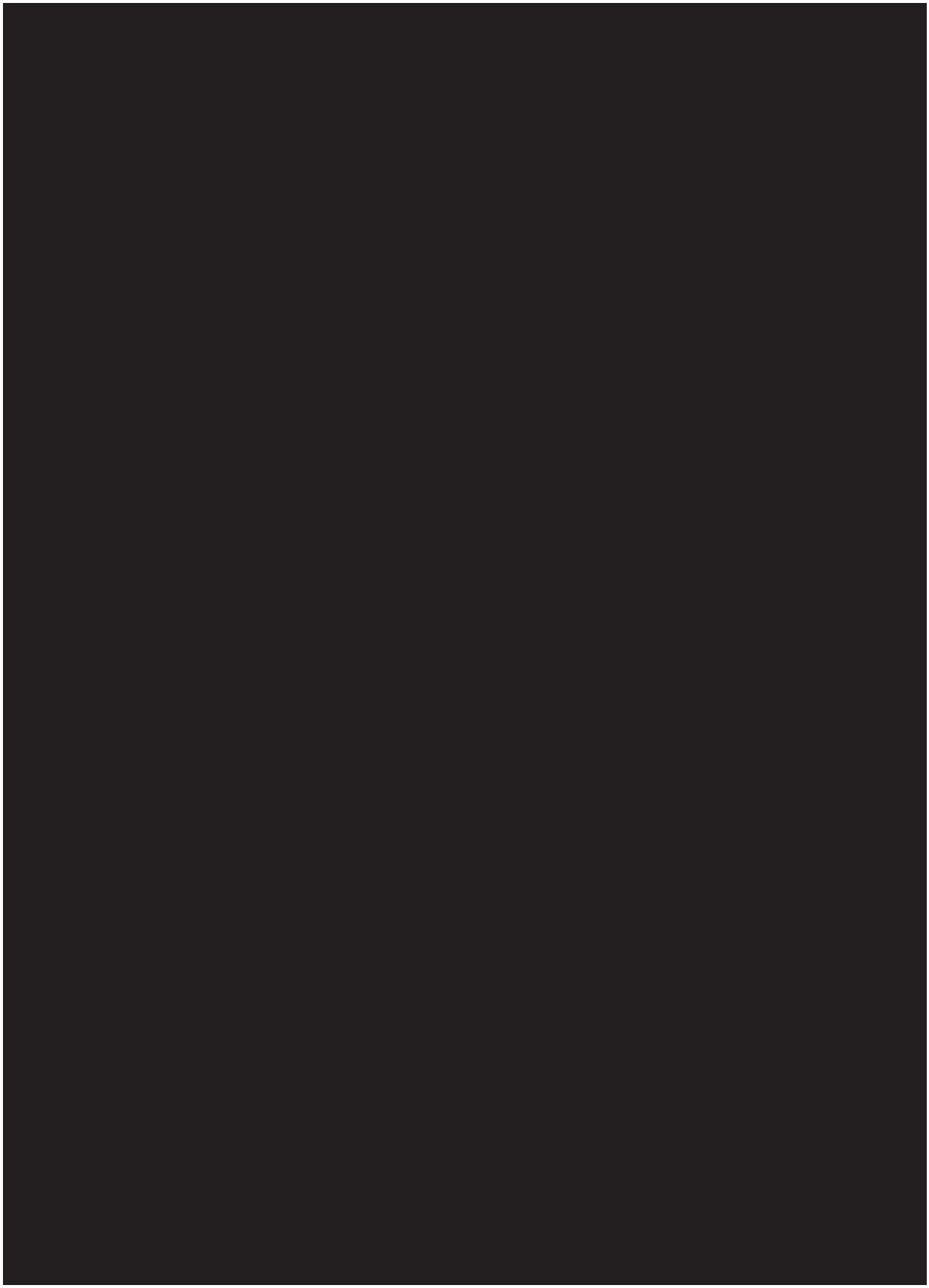

10 HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP:

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**11-JUN-16**	[redacted]	None	This is the final TSAP.
Revised	**28-SEP-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 PK, immunogenicity, biomarkers 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

APPROVAL / SIGNATURE PAGE

Document Number: c02577053 **Technical Version Number:2.0**

Document Name: 8-01-tsap

Title: A Phase Ib/II, Multicentre, Open Label, Randomised Study of BI 836845 in Combination With Enzalutamide, versus Enzalutamide alone, in Metastatic Castration-Resistant Prostate Cancer (CRPC) Following Disease Progression on Docetaxel-Based Chemotherapy and Abiraterone

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval–Clinical Monitor	[redacted]	28 Sep 2017 16:46 CEST
Author-Trial Statistician		28 Sep 2017 16:46 CEST
Approval-Project Statistician		28 Sep 2017 16:47 CEST
Author-Trial Clinical Pharmacokineticist		28 Sep 2017 17:10 CEST
Approval-Project Statistician		29 Sep 2017 12:10 CEST
Approval-Medical Writer		04 Oct 2017 08:10 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed