Trial Statistical Analysis Plan

c17168379-02

BI Trial No.:	1280.18
Title:	An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts. Including Protocol Amendment 8 [c09049566-09]
Investigational Product(s):	Xentuzumab (BI 836845)
Responsible trial statistician(s):	[redacted] Tel.: [redacted]
Date of statistical analysis plan:	25 Oct 2021 SIGNED
Version:	2.0

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2 LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
BI	Boehringer Ingelheim
CR	Complete response
COVID-19	Coronavirus Disease 2019
CTL	Clinical Trial Leader
DC	Disease control
ECG	Electrocardiogram
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IPD	Important Protocol Deviation
ITT	Intent-to-Treat
KM	Kaplan-Meier
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
OR	Objective response
OS	Overall Survival
PD	Progressive Disease
PD	Protocol Deviation
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial response
RP2D	Recommended Phase II Dose
RS	Randomised Set
SAE	Serious Adverse Event

Term	Definition / description
SD	Stable Disease
SDL	Subject Data Listings
SIR	Synoptic Interim Report
SOC	System Organ Class
SOP	Standard Operating Procedure
TSAP	Trial Statistical Analysis Plan

3 INTRODUCTION

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

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

The trial consists of three parts. Part 1 includes a dose finding cohort A and part 2 includes three dose finding cohorts B, C and D and one expansion cohort E. Part 3 includes cohort D1, D2 and F.

The TSAP describes the analysis for all the cohorts of the trial. After each of dose finding cohort (cohorts A, B, C and D), safety analyses were performed and documented.(see Section 9.1).

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

The following additions/new analyses to the statistical methods described in the CTP and subsequent amendments are detailed in this TSAP:

- Where considered appropriate, the potential impact of Coronavirus Disease 2019 (COVID-19) on the study will be assessed by producing additional summaries of disposition, protocol deviations, treatment exposure and adverse events (AEs). The start date for COVID-19 having an impact on the trial will be taken as the earliest date of a COVID-19 related protocol deviation, discontinuation due to COVID-19, onset of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related AE or COVID-19 related global BI recruitment hold (17 MAR 20).

4.2 CHANGES

Not applicable.

4.3 CLARIFICATIONS

The following points warrant further clarification:

- The terms “progression”, “progressive disease” (PD) and “disease progression” will be used interchangeably within this document.
- The terms “treatment cycle” or “treatment course” will be used interchangeably throughout this document.
- The terms “study medication” and “trial medication” will be used interchangeably throughout this document.
- If not stated otherwise, date of randomisation will be replaced by first treatment administration of any study medication in the outputs (i.e. including the run-in period)

5 ENDPOINTS

5.1 PRIMARY ENDPOINTS

5.1.1 Cohorts A, B, C, and D:

The primary endpoint is the maximum tolerated dose (MTD) of trial medications based on the occurrence of dose limiting toxicity (DLT) during the first treatment course. The planned treatment course consists of 28 days.

MTD:

The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being above 33%. The MTD evaluation period is defined as the time from the first administration of any study medication up to start of cycle 2. That means that the exact duration of this period will be derived for each patient. If the patient experiences any delay after planned 28 days of cycle 1 but prior to the start of cycle 2, this delay will be also considered as MTD evaluationperiod.

5.1.2 Cohort E

The primary endpoint for the expansion part cohort E is objective response (OR).

Objective response (OR)

OR is defined as best overall response of complete response (CR) or partial response (PR), where best overall response is determined according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 from date of first treatment administration until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

Best overall response

An adequate RECIST tumour assessment includes an assessment of target lesions (only for patients with measurable disease at baseline), as well as radiological tests to evaluate non-target lesions if any and to search for new lesions. In case no RECIST tumour evaluation has been performed, the assessment will be set to missing.

Best overall response is calculated based on the “overall” visit response from each assessment. Best overall response represents the best response a patient has had during his/her time in the study until progression, last evaluable assessment in the absence of progression or the start of subsequent anti-cancer therapy. For patients whose progression event is death, best overall response will be calculated based on data until the last evaluable RECIST assessment prior to death. (note that no confirmation is required for best overall response)

The following categories of best overall response will be derived:

- Complete response (CR)
- Partial response (PR) – possible only for patients with measurable disease at baseline
- Stable disease (SD) – possible only for patients with measurable disease at baseline

  - Subcategory “SD >= Week 24” for breast cancer and “SD>=6 weeks” for NSCLC: calculated from randomization/treatment start until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy. Here SD >= Week 24 includes SD >=161 days taking into account allowable CTP window.

- Non-CR/Non-PD – possible only for patients with non-measurable disease at baseline
  - Subcategory “Non−CR / Non−PD >= Week 24” for breast cancer and “Non−CR / Non−PD >= 6 weeks” for NSCLC: calculated from randomization/treatment start until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy. Here Non−CR / Non−PD >= Week 24 includes Non−CR / Non−PD >=161 days taking into account allowable CTP window.
- Progressive disease (PD) in the absence of CR or PR or SD or Non-CR/Non-PD
- Not evaluable (NE) - means no evidence of CR or PR or SD or Non-CR/Non-PD or PD
  - Subcategory ‘Missing post-baseline image’: in case no post-baseline image has been performed.

The Week 24 tumour assessment was chosen to coincide with the minimum required duration of SD or Non-CR/Non-PD (24 weeks), in order to include all Week 24 assessments allowable per protocol the cut-off of >=161 days has been implemented.

5.1.3 Cohorts D1 and D2

The primary endpoint for expansion part cohort D1 and D2 is Progression-free survival (PFS) status at 18th month (PFS18).

PFS18 is defined as the PFS status of a patient who is alive without disease progression at 18 months after first treatment administration, where progression is determined according to RECIST 1.1.

PFS is defined as the time from first treatment administration until tumour progression according to RECIST 1.1 or death from any cause, whichever occurs earlier.

Tumour assessments will be performed at screening and then every 8 weeks after start of the first treatment course until week 48 and every 12 weeks thereafter.

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

For details on the imaging process and RECIST evaluation, see Section 5.2 and Section 10.4 of the CTP.

<u>Derivation of endpoint PFS</u>

Derivations below are described in days. However, the endpoints below will be presented in months in the statistical tables produced for the Clinical Trial Report (CTR).

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

- PFS [days] = date of outcome - date of the first treatment administration + 1.

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

- PFS (censored) [days] = date of outcome - date of the first treatment administration + 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, PR, CR or NE, the latest of multiple assessment dates will be taken to censor the patients.

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

Table 5.1.3: 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 of randomisation (or first treatment administration, in non-randomised trials)

Situation	**Outcome (event or censored)**	**Date of outcome**
Death prior or on the second planned radiological assessment	Event	Date of death
Death beyond the second planned radiological assessment	Censored	Date of 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
Death without progression, but two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments

Situation	Outcome (event or censored)	Date of outcome
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent-anti cancer therapy started prior to a death	Censored	Date of randomisation (or first treatment administration, in non-randomised trials)

In order to identify that consecutive imaging time-points are missing for a given patient, a nominal time point [8, 16, 24, 32, 40, 48, and then every 12 weeks thereafter] will be assigned to each and every image. This is achieved by creating windows for every RECIST assessment. The windows are defined in Table 6.7.2: 1.

5.1.4 Cohort F

The primary endpoint for the expansion part cohort F is disease control (DC).

Disease control (DC)

DC is defined as best overall response of complete response (CR) or partial response (PR) or confirmed stable disease (SD) (i.e. lasting till at least Week 24, 161 days taking into account allowable CTP window) where best overall response is defined according to RECIST version 1.1 from first treatment administration until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Other secondary endpoints

5.2.2.1 Cohorts A, B, C, and D

There are no secondary endpoints.

5.2.2.2 Cohorts E, F, D1 and D2

Time to OR

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

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

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

Duration of OR

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

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

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

For patients without disease progression or death:

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

The censoring rules for duration of OR are given in Table 5.2.2.2: 1.

Table 5.2.2.2: 1 Derivation rules for Duration of Objective Response

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

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, no more than one consecutively missed radiological assessments prior to start of subsequent anti-cancer therapy	Censored	Date of last radiological assessment before initiation of subsequent anti-cancer therapy

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

Disease control (DC) (Cohorts E, D1 and D2 only)

For breast cancer, DC is defined as best overall response of CR or PR, or SD ≥Week 24 (>=161 days taking into account allowable CTP window), or **Non-CR/Non-PD for ≥**Week 24 (>=161 days taking into account allowable CTP window) where best overall response is defined according to RECIST version 1.1 from date of randomisation until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

For NSCLC, DC is defined as best overall response of CR or PR, or SD ≥6 weeks, or Non−CR / Non−PD >= 6 weeks where best overall response is defined according to RECIST version 1.1 from date of randomisation until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

Duration of DC

Duration of disease control is defined as the time from first treatment administration until the earliest of disease progression or death, among patients with disease control.

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

- Duration of disease control [days] = date of outcome – date of the first treatment administration + 1.

For patients without disease progression or death:

- Duration of disease control (censored) [days] = date of outcome – date of the first treatment administration + 1.

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

Table 5.2.2.2: 2 Derivation rules for Duration of Disease Control

Situation	**Outcome (event or censored)**	**Date of outcome**
With baseline and post-baseline radiological assessments BUT no other anti-cancer therapy		
Alive and not progressed, no more than one consecutively missed radiological assessments	Censored	Date of last radiological assessment
Alive and not progressed, two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, zero or one missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, but two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessments
Death but no progression, zero or one missed radiological assessment prior to death	Event	Date of death
Death without progression, but two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent anti-cancer therapy started prior to a death	Censored	Date of randomisation (or first treatment administration, in non-randomised trials)

Progression-free survival (PFS)

The derivation of endpoint PFS refers to Section 5.1.3.

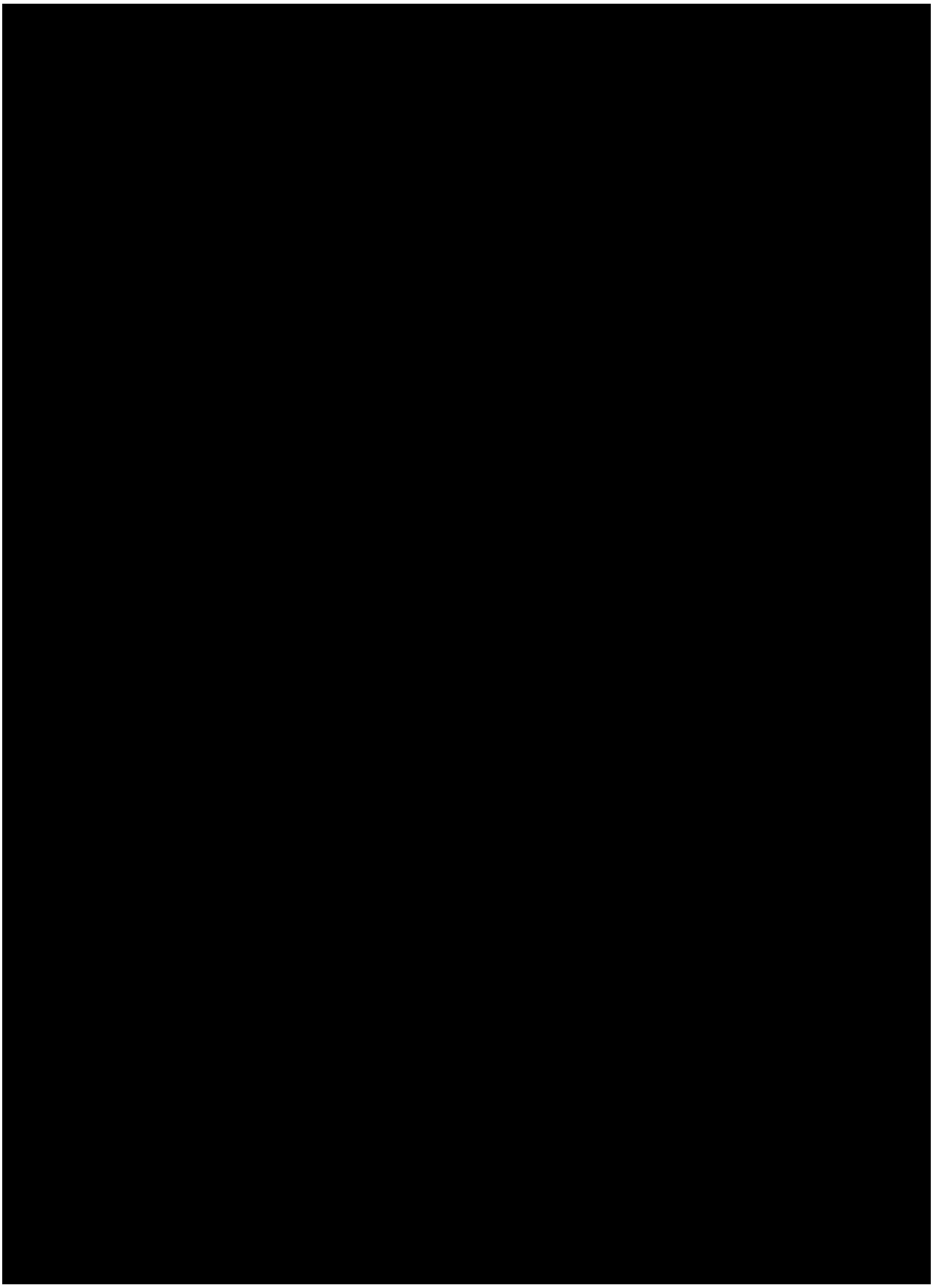
Last evaluable imaging

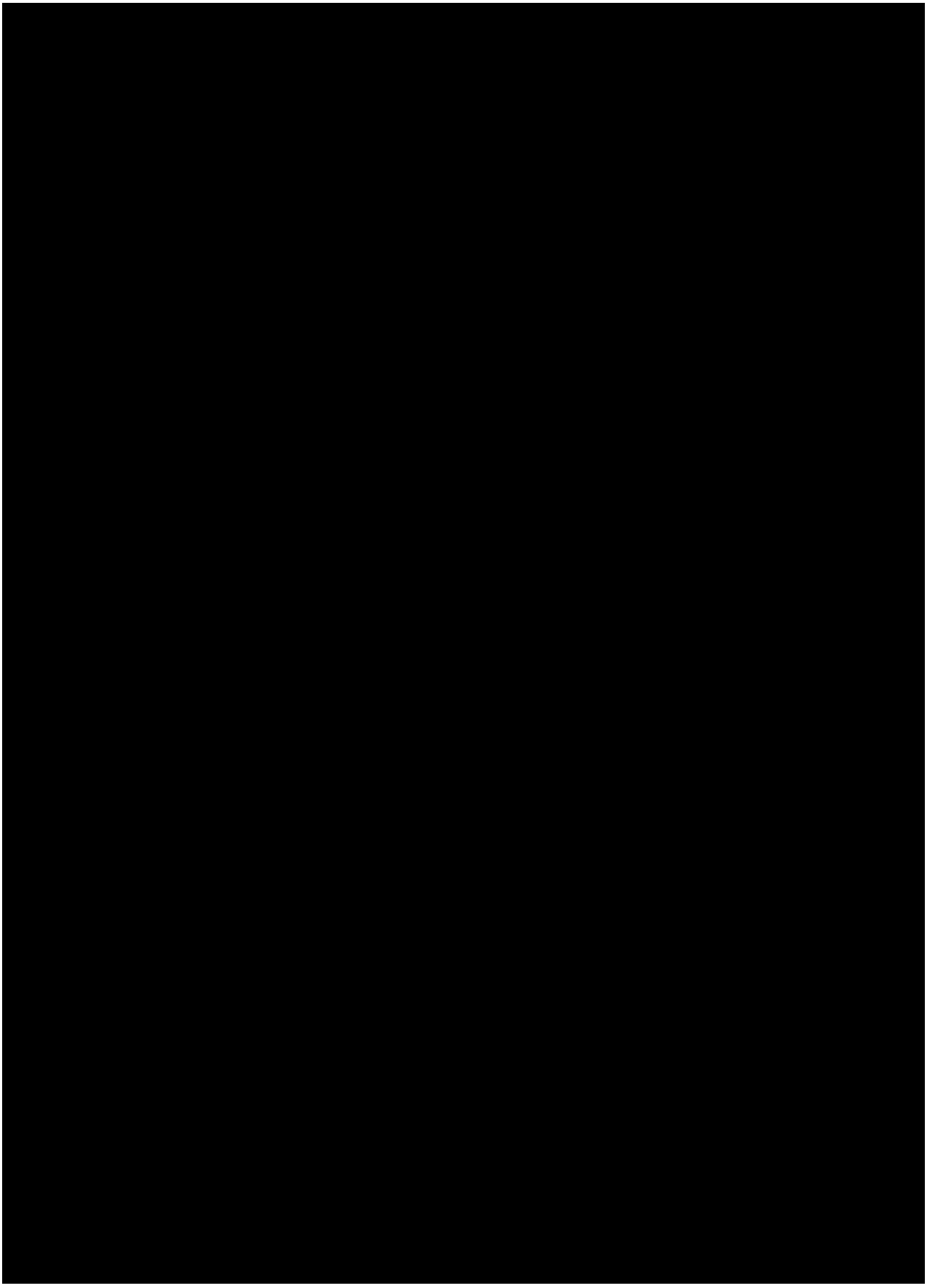
An evaluable radiological image for the censoring of PFS is an image for which an overall response assessment of SD, Non-CR/Non-PD, PR or CR has been assigned. This is used for censoring of patients without progression at end of trial, or censoring prior to missed assessments, or censoring prior to subsequent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

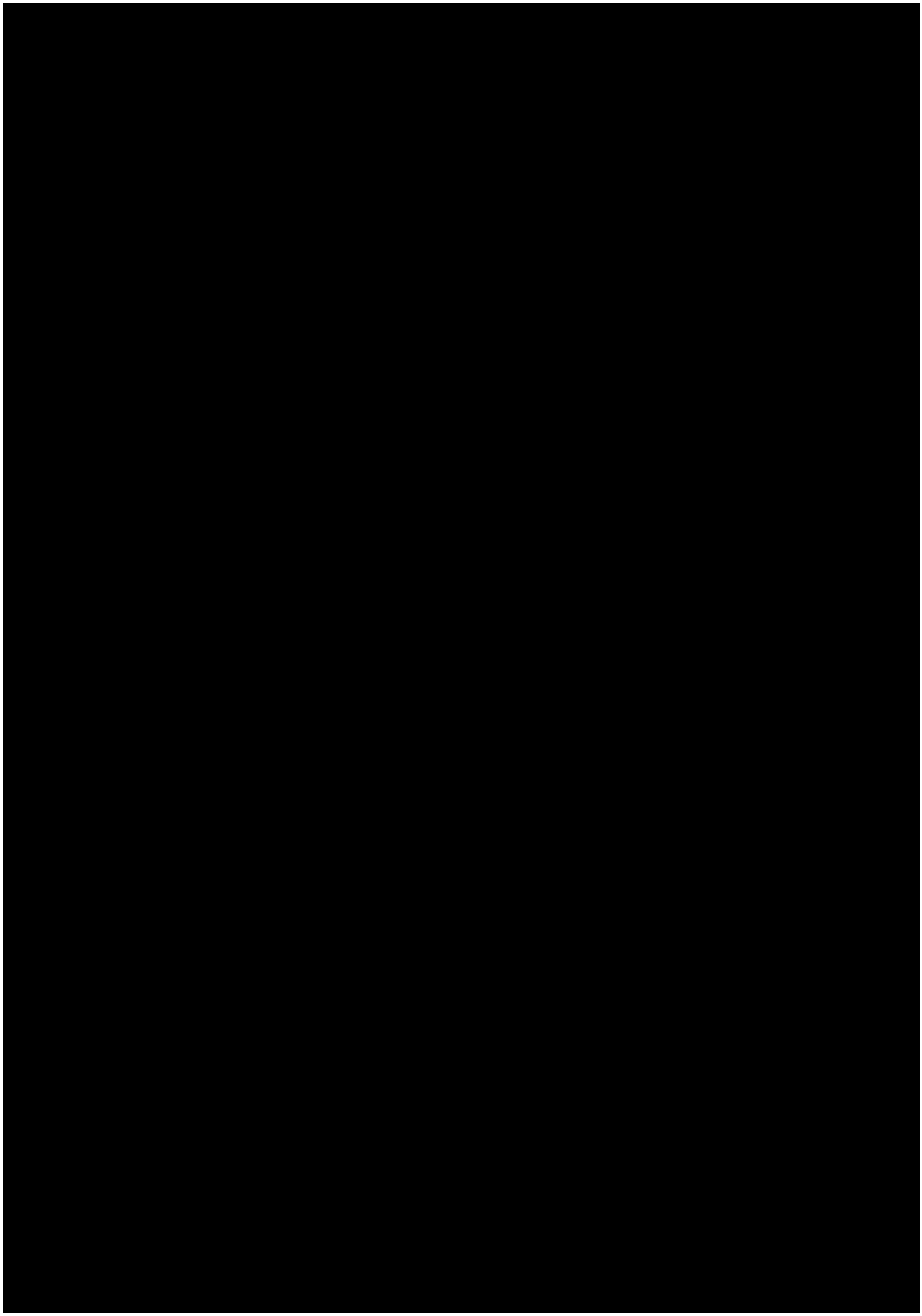
Objective response (OR) (Cohorts F, D1 and D2 only)

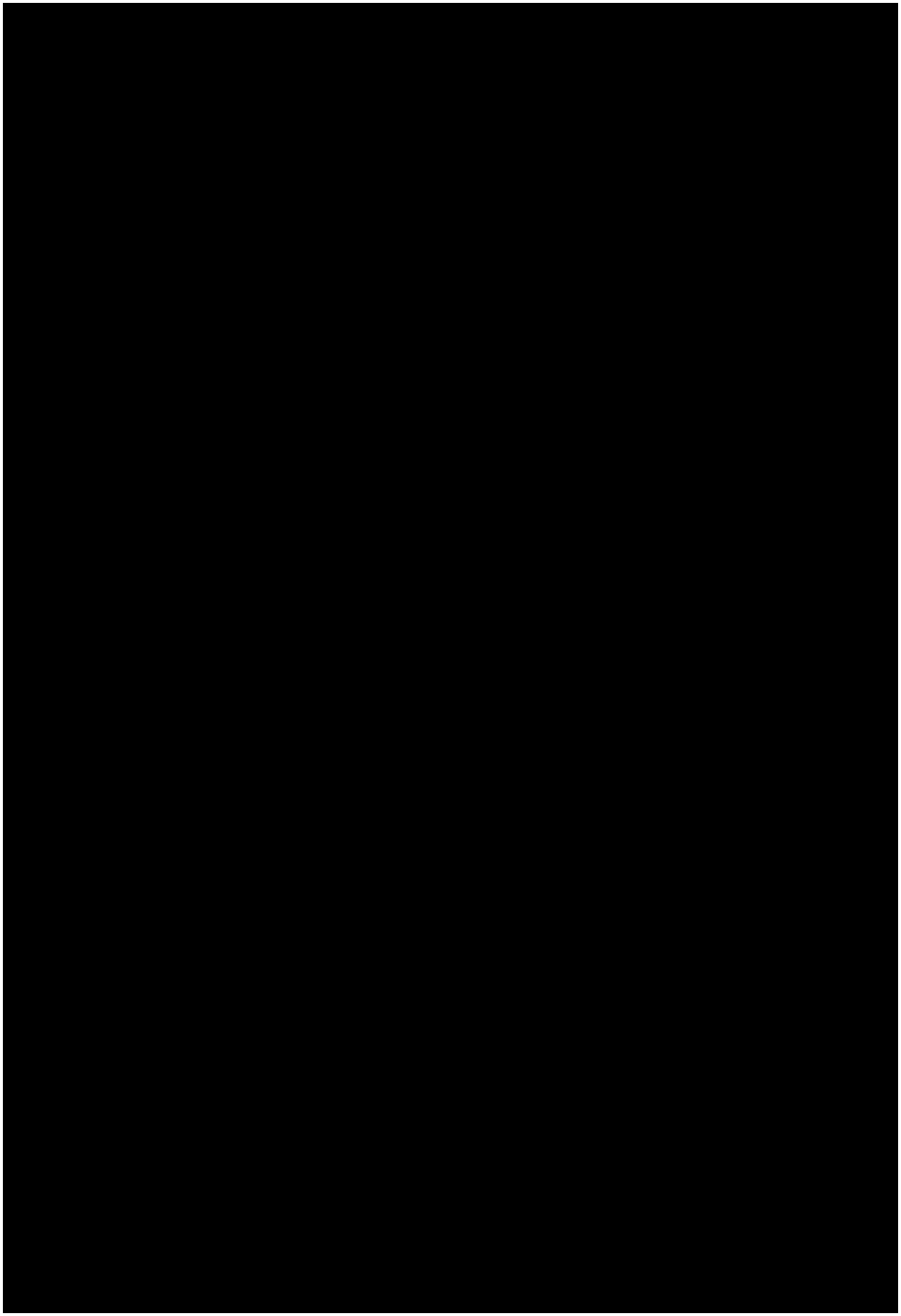
The definition for OR is the same as the primary endpoint for cohort E , refer to Section 5.1.2.

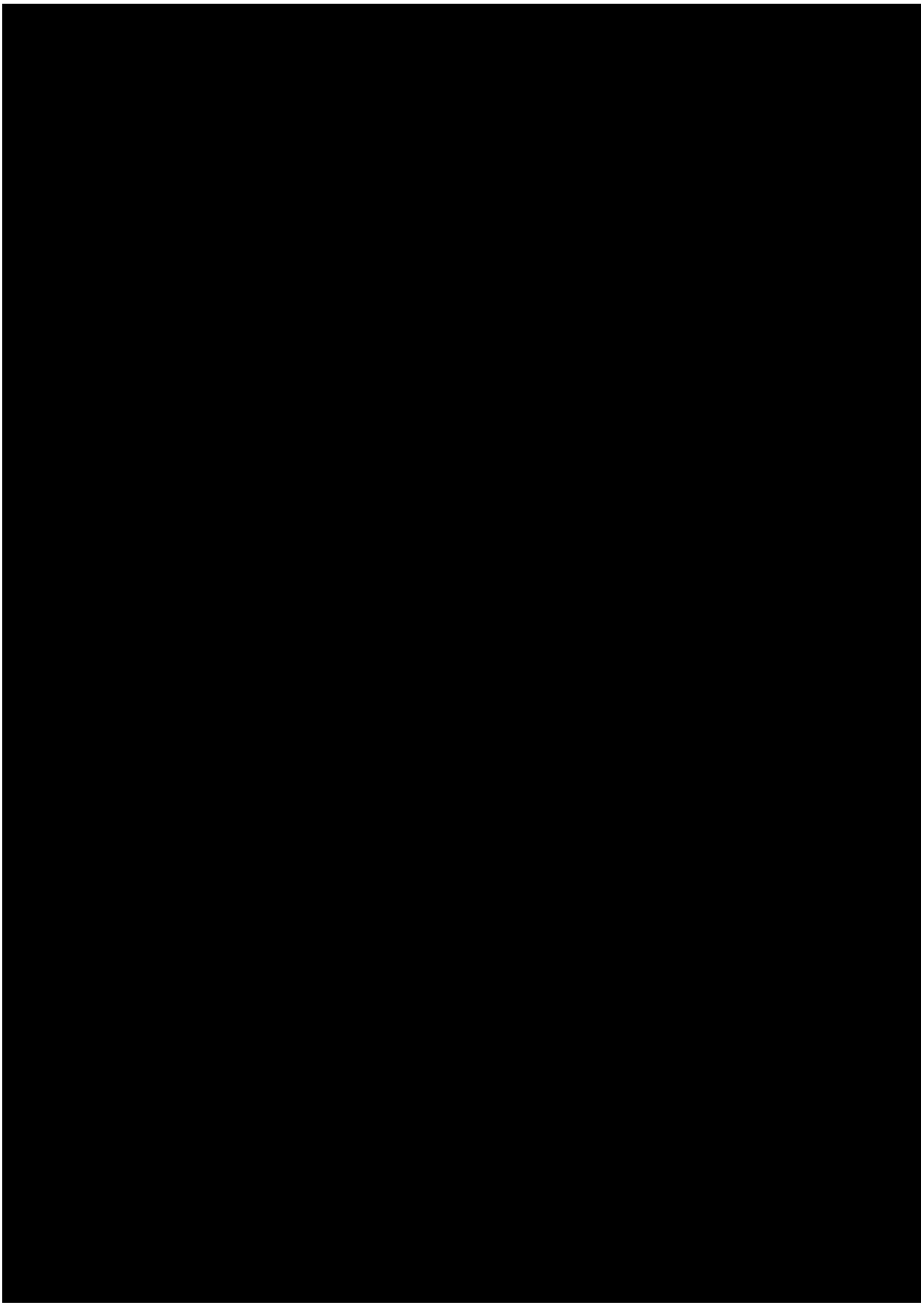
[redacted]











6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For all cohorts: 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 database lock).

For Cohort A, B, C and D, different dose levels of Xentuzumab and Abemaciclib will arise. The data will be presented for all cohorts separately. To justify the MTD determination, DLTs occurring during the MTD evaluation period will be presented separately from those occurring during the complete on-treatment period.

For the on-treatment period and the MTD evaluation period, the initial trial medication assigned at the beginning of the first treatment cycle will be used as label of the analysing treatment.

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

The actual study periods and treatment codes are defined in a document entitled “4-12-01-sdtm-trial-arms-trial-elements-trial-visits”, which can be found in Data Management and Statistics (DMS) folder, Section 4, within BIRDS.

Patients in cohorts E and F are on continuous daily abemaciclib for a 9-days run-in period. For these patients, the on-treatment period is considered to the start of run-in period.

6.2 IMPORTANT PROTOCOL DEVIATIONS

No per protocol set (PPS) analysis will be performed for this study, hence, no patient will be excluded from the analyses (except those with missing informed consent or not adhering to age limit). However patients with potentially important protocol deviations (IPDs) will be documented. The following list of potentially IPDs 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 database lock for the primary analysis). Potentially important protocol deviations will be handled according to BI standards (8).

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).

A frequency table of the iPDs will be produced. In addition, a frequency table of all COVID-19 related non-important and important PDs will be produced.

Table 6.2: 1 Important PDs

Category /Code		**Description**	**Requirements**	**Excluded from**
A [1]		**Entrance criteria not met**		
	A1	Diagnosis of trial disease questionable	Cohort A and E: Inclusion criteria IN6 is not met. or Cohort B, C, D, F, D1 and D2: Inclusion criteria IN6-8 is not met.	None

Category /Code		Description	Requirements	Excluded from
	A2	Prohibited baseline condition, diagnosis or treatment	All Cohorts: Inclusion criteria IN3-5 is not met or Cohort A: Inclusion criteria IN7-8 is not met or Cohort B, C, D, F, D1 and D2: Inclusion criteria IN9-12 is not met or Cohort E: Inclusion criteria IN7-9 not met or Cohort F: Inclusion criteria IN13-14 not met or All cohorts: At least one of exclusion criteria EX1, EX3, EX5-6, EX10, EX12-13, EX15-19, EX21, EX25 is met. or Prohibited medication use (or surgery) before the treatment period of the trial, that is, All cohorts: At least one of exclusion criteria EX4, EX7-9, EX11, EX20, EX22-24 is met	None
	A3	Laboratory result indicating inadequate organ function at screening	All cohorts: Exclusion criteria EX14 is met or Both screening and baseline (defined in Section 6.7 of this document) laboratory results are missing.	None

Category /Code		Description	Requirements	Excluded from
B [1]		**Legal Criteria**		
	B1	Informed consent not available / not done	Written informed consent is not available/done	All
	B2	Informed consent too late	Inclusion criterion IN2 is not met.	None
	B3	Age limit for patient inclusion not adhered to	Inclusion criterion IN1 is not met.	All
C [2]		**Trial medication and randomisation**		
	C1 **[2]**	Time window deviation for procedures performed at screening	Assessment at screening not within 28 days prior to first treatment. Create listing, decision at MQRM / RPM.	None
	C2 **[2]**	Trial medication not given according to protocol	Dose reduction scheme not followed (see CTP Section 4.1.4.2); 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 letrozole, anastrozole, fulvestrant or abemaciclib with associated comments) Please note: This excludes the investigational treatment given outside the boundaries specified in the CTP (covered in Category C3).	None

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 deviation 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 allocated to	None
	C4.1	Randomisation not followed	This dose not apply for this trial	None
	C4.2	Treatment allocation not followed	Patients do not receive the initial treatment they were allocated to	None
D [2]		**Concomitant medication**		
	D1	Prohibited treatment during trial conduct phase	All cohorts: At least one of exclusion criteria EX2, EX26-27 is met or Indicated by medical review of concomitant therapy use during study treatment.	None
E [2]		**Missing Data**		
	E1	Imaging assessments not done according to CTP instructions	Imaging assessment should be performed at screening and several time points thereafter (see TSAP Section 6.7.2).	None
	E2	Pregnancy test not done according to CTP instructions	Only for Studies where pregnancy tests are required	None

Category /Code		Description	Requirements	Excluded from
F [2]		**Trial Specific protocol deviations**		
	F1	Other protocol deviations affecting patient rights or safety	Manual PDs will be collectively captured.	None
Q [2]		Non-important COVID-19 related		
	Q1	Missed examination	With inactived forms or records, but without inactived visit date	None
	Q2	Missed visit	With inactived visit date	None

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

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 (including run-in period).

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

- MTD Set (MS)

The MTD set defines the set of patients in the dose-finding cohorts (cohorts A,B,C and D) 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 for dose-finding cohorts, this is specified in the technical TSAP.

Patients in the TS who were replaced within the MTD period in the dose-finding cohorts (cohorts A,B,C and D) of the trial will be excluded from the determination of the MTD. Patients in the TS who entered in an expansion cohorts will be also excluded from the determination of the MTD. Replacement of patients in the dose-finding cohorts of the study is defined in Section 3.3.5 of the CTP. The final list of replaced patients is supplied by the Clinical Trial Leader (CTL) no later than the last report planning meeting before the database lock for the safety analysis.

- Pharmacokinetic set (PKS)

This patient set includes all patients in the treated set who have at least one valid drug plasma concentration available. The decision whether a concentration is considered valid or not will in general be made at the RPM before Database Lock (DBL) or URPM and documented within the respective meeting minutes. Values to be excluded from analyses identified during analysis would be documented within the respective QC forms. The PKS will be used for the PK analyses of the trial.

No per protocol population will be used for analyses.

[redacted]

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

Missing dates that affect the evaluation of endpoints specified in previous sections of this TSAP will be imputed utilising a "worst case" approach, which will be applied on a case-by-case basis (depending on the affected endpoint) and agreed to by the trial team members at the final BRPM before database lock at the latest.

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

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

Date	**Imputation rule**
Date of birth	In case only the year is given: 1st of January
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 end of treatment (only for patients still ongoing at time of snapshot/interim DBL)	Date of snapshot If date of death before this date, use date of death

6.6.1 Adverse events

Missing or incomplete AE dates are imputed according to BI standards (5).

6.6.2 Laboratory values at baseline

For missing laboratory data at Cycle 1 Visit 1 of Cohort A, B, C, D, D1, D2 and F or at Day 1 Run-in period of Cohort E (before the very first administration of study medication) data from preceding visits will be used.

6.6.3 PK parameters

Missing data and outliers of PK data are handled according to BI standards (2) and as described in Section 7.5 of the clinical trial protocol.

6.7 BASELINE, TIME WINDOWS, AND CALCULATED VISITS

6.7.1 Baseline

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

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

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

Laboratory values:

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

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

6.7.2 Time windows for every RECIST assessment

In order to identify whether consecutive imaging time-points are missing for a given patient, a nominal time point [8, 16, 24, 32, 40, 48, 60 weeks and every 12 weeks thereafter] will be assigned to each and every image. This is achieved by creating windows for every RECIST assessment. The windows are defined in Table 6.7.2: 1 below. Day 1 corresponds to the date of first drug intake of any trial medication (excluding run-in period).

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

Nominal time-point [weeks from start of therapy]	**Due date of scans [days]**	**Window [days]**
8	57	1 to =< 85
16	113	86 to =< 141
24	169	142 to =< 197
32	225	198 to =< 253
40	281	254 to =<309
48	337	310 to =<379
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/she will be said to have 'missed an assessment' for that time-point. In case a patient has more than one assessment in one window, the assessment with the latest outcome will be used for the analysis unless a PD has been recorded earlier then PD will be used.

7 PLANNED ANALYSES

The labelling and display format of statistical parameters will follow BI standards (9).

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

Descriptive statistics for continuous variables will generally contain N (number of patients in that patient set with non-missing values), Mean, Standard Deviation, Minimum (Min), Q1 (25th percentile), Median, Q3 (75th percentile), Maximum (Max). In general, means, standard deviations, medians, Q1 and Q3 will be presented to one more decimal place than the raw data. Minima and maxima will be presented to the same number of decimal places as the raw data.

For time-to-event analysis tables, the set of statistics is: number of patients [N (%)], Number of patients with event [N (%)], Number of patients censored [N (%)], <Time to event> [months] followed by P25 (25th percentile), Median, P75 (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.

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 not be displayed for post-baseline displays. Tables that display the status of patients for a primary or secondary endpoint with number of events and number censored will contain a total column.

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

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

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.1.1 Disposition of patients

For patient disposition the standard descriptive table from the EOT catalogue will be populated. Additionally, patients with discontinuations by initial treatment and the reasons will be listed and tabulated, overall and for each treatment separately. The same output will also contain an overview of discontinued and non-discontinued, as well as completed and non-completed patients (see CTP Section 6.2.3.3).

7.1.2 Important protocol deviations

A table and a listing of patients with important protocol deviations based on Table 6.2: 1 will be created in Section 10.1.3 and Appendices 10.10.3 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 Medical Dictionary for Regulatory Activities (MedDRA) version. Concomitant therapies will be coded according to World Health Organisation - Drug Dictionary (WHO-DD). Concomitant therapies (CT) will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorise CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level-three category will be counted more than once; footnotes will clarify this possible double counting in tables.

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

7.3 TREATMENT COMPLIANCE

Compliance will not be analysed separately, but assessed in terms of exposure (including dose intensity). Refer to Section 7.7 for further details on exposure analysis.

7.4 PRIMARY ENDPOINTS

7.4.1 Cohorts A, B, C, and D

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 5.3.7 for definitions of DLT) which occurred during the MTD evaluation period and the on-treatment period will be provided for each dose cohort.

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

The analysis of the MTD is based on a BLRM guided by the escalation with overdose control principle. The MTD is defined as the highest dose for a given schedule that is expected to cause less than 25% risk of the true DLT rate being above or equal to 33% during the MTD evaluation period. Estimation of the MTD during the dose escalation phase of the study will be based upon the estimation of the posterior probability of the incidence of DLT in toxicity categories during the MTD evaluation period for all evaluable patients. The model to be used is specified in CTP Section 7.

The posterior probabilities that the toxicity rates of each dose level fall into the categories specified in CTP Section 7 will be displayed.

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

7.4.2 Cohort E

Objective response (OR)

OR as assessed by investigators is defined as a best overall response of CR or PR and will be analysed. Descriptive statistics including number of treated patients, number of patients with objective response as best overall response and the corresponding percentages will be presented and evaluated.

7.4.3 Cohorts D1 and D2

PFS status at 18th month (PFS18)

PFS18 is defined as the PFS status of a patient who is alive without disease progression at 18 months after first treatment administration, where progression is determined according to RECIST 1.1.

Descriptive statistics including number of treated patients, number of patients being absence of disease progression or death at 18th month and the corresponding percentages will be presented and evaluated.

Kaplan-Meier (KM) estimates will be used to display the distribution of PFS for cohort D1 and D2 separately on a KM curve. To support the plot, estimated survival probabilities at specific time points of interest (6 months, 12 months and 18 months) will be tabulated. In addition, the survival distribution will be used to provide estimates of the median, 25th and 75th percentiles.

7.4.4 Cohort F

Disease control (DC)

DC as assessed by investigators is defined as a best overall response of CR or PR or SD and will be analysed. Descriptive statistics including number of treated patients, number of patients with objective response as best overall response and the corresponding percentages will be presented and evaluated.

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 Cohorts A, B, C and D

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

7.5.2.2 Cohorts E and F, D1 and D2

Disease control (Cohorts E, D1 and D2 only)

Disease control (DC) is defined as best overall response of complete response (CR) or partial response (PR) or stable disease (SD) (defined in Section 5.2.2.2). Only descriptive statistics are planned for this section of the report.

Time to OR

For patients with objective response, time to objective response will be shown on patient level. A set of summary statistics for time to objective response on cohort level will also be produced.

Duration of OR

KM estimates will be calculated for each treatment group to provide estimates of the median, 25th and 75th percentiles and their corresponding 95% CIs.

Duration of DC

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

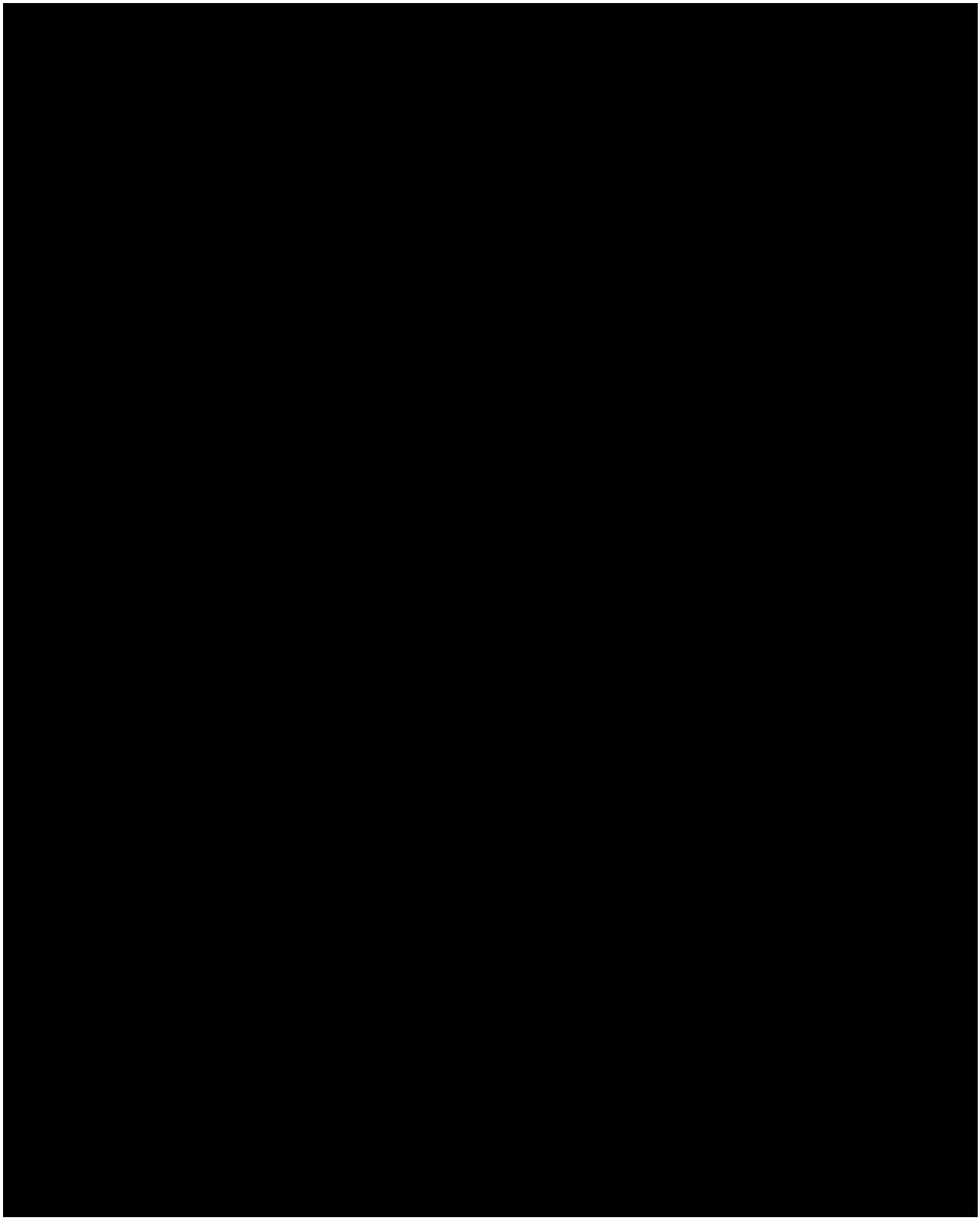
Progression free survival

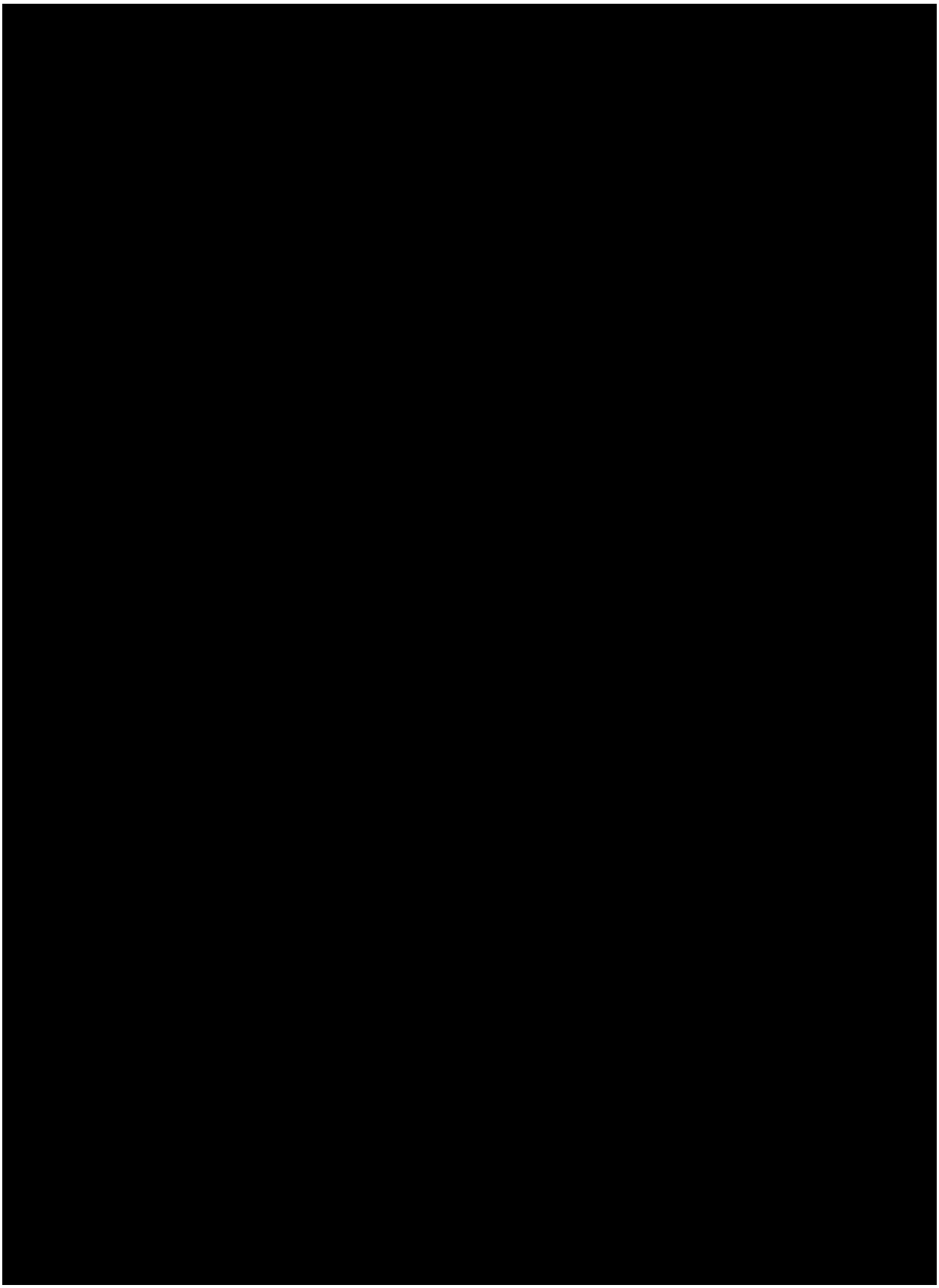
Kaplan-Meier estimates and 95% CIs (based on Greenwood's method) will be calculated. Furthermore progression free survival times on patient level will be shown and if applicable descriptive statistics including, but not limited to, the lower quartile (P25), Median and the upper quartile (P75) will be computed.

Objective response (Cohorts F, D1 and D2 only)

OR as assessed by investigators is defined as a best overall response of CR or PR and will be analysed. Descriptive statistics including number of treated patients, number of patients with

objective response as best overall response and the corresponding percentages will be presented and evaluated.





[redacted]

7.7 EXTENT OF EXPOSURE

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

Appropriate summaries of exposure before and from the start of the COVID-19 disruption will also be produced.

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 dose finding cohorts who were replaced within or before the first treatment cycle will be excluded from the determination of the MTD.

7.8.1 Adverse events

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

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

- All AE attributes are identical (Lowest Level Term (LLT), Common Terminology Criteria for Adverse Events (CTCAE) grade, action taken with trial medication, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)

For further details on summarisation of AE data, please refer to (5) and (6).

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

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

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Similar summaries will be produced for the BIcMQ SARS-COV-2-infections.

Separate tables will be provided for patients with drug-related adverse events, adverse events leading to dose reduction, adverse events leading to discontinuation, serious adverse events, serious drug-related serious adverse events, adverse events leading to death, other significant adverse events, adverse events of special interest, and adverse events fulfilling the DLT definition.

Sorting order:

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

Reporting of CTCAE grades in tables:

In tables showing AEs by worst CTCAE grade, AEs with missing CTCAE grade will only be displayed under the category "All grades", but no category "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 16.1.13.1, the categorisation “All grades”, “Grade 1/2”, “Grade 3/4/5”, will be used.

Listings of adverse events

Adverse events will be reported with start and end day as calculated from the first day of treatment with study medication. This includes the run-in period for the Cohort E and F.

Incidence and severity of adverse events

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

Other significant adverse events

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

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

AEs leading to dose reduction or permanent discontinuation will include:

- AEs leading to dose reduction of xentuzumab
- AEs leading to dose reduction of abemaciclib
- AEs leading to permanent discontinuationof xentuzumab
- AEs leading to permanent discontinuationof abemaciclib

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 Adverse Events of Special Interest (AESI)

Protocol-specified AESIs are specified in the CTP Section 5.3.6.1. Their incidence will also be reported. DLTs are considered as AESIs only in the dose finding cohorts.

Adverse events by user defined AE categories (UDAEC)

User defined adverse events categories (UDAEC) as defined on project level by the pharmacovigilance working group will be derived and the latest version will be used for the analysis. Details of the current version are presented below in the table below.

Table 7.8.1: 1 Adverse events by user defined AE categories

SSC	Group[#]
Hepatic impairment	Drug related hepatic disorders – comprehensive search (SMQ)
Hyperglycaemia narrow	Hyperglycaemia/new onset diabetes mellitus (SMQ) - narrow
Infusion related reaction	Hypersensitivity (SMQ) - broad
Non-infectious pneumonitis	Interstitial lung disease (SMQ) - narrow
Renal insufficiency	Acute renal failure (SMQ) - broad and narrow; Proteinuria (SMQ)-broad and narrow; Glomerulonephritis and nephrotic syndrome:HLT
Weight loss	Weight loss (BIcMQ) – broad and narrow
Neutropenia	Haematopoietic leukopenia (SMQ) – narrow
Stomatitis	Stomatitis (BIcMQ) – broad and narrow
Asthenia	MedDRA PTs: Asthenia, Fatigue, Lethargy, Malaise, and Decreased activity
Haemorrhage	Haemorrhage laboratory terms (SMQ)-narrow; Haemorrhage terms (excl laboratory terms) (SMQ)-broad and narrow
Anemia	Haematopoietic erythropenia (SMQ) – broad and narrow
Thrombocytopenia	Haematopoietic thrombocytopenia (SMQ) - narrow
Thromboembolism	Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)-broad and narrow
Bradycardia	Torsade de pointes/QT prolongation (SMQ), PT of Bradycardia
Rash	BIcMQ: Skin eruptions (subsearch2: Skin rash potentially related to drug use [broad and narrow])

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

The incidence of AE by UDAEC will be analysed.

7.8.2 Laboratory data

7.8.2.1 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (7). The same on-treatment periods as considered for the analysis of adverse events will be applied for laboratory values except for that the baseline laboratory value will be included in the 'on-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 (11). 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" (7), Reference Document 9.

7.8.2.2 Laboratory values of special interest

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

These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of ALT and/or AST > 3ULN with total bilirubin ⩾ 2ULN and 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 5.3.6.1 of the CTP), including flags of true DILI cases, are created in accordance with the Food and Drug Administration (FDA) DILI guidance (10). Tabulations of hepatic enzyme elevations and liver laboratory values (see Section 5.3.6.1 of the CTP), including flags of true DILI cases, are created in accordance with the Food and Drug Administration (FDA) DILI guidance (10).

7.8.3 Vital signs

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

8 REFERENCES

1 *001-MCG-160_RD-06:* "Trial Statistical Analysis Plan - Template", current version; IDEA for CON.

2 *001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics (3.0)", current version; IDEA for CON.

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5 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

6 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.

7 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

8 *001-MCS-50-413*: “Handling of Protocol Violations in Clinical Trials and Projects”, current version; IDEA for CON.

9 *001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.

10 Guidance for industry: drug-induced liver injury: premarketing clinical evaluation U.S. Departement of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), 2009.

11 Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (2010)

10 HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	28-APR-17	[redacted]	None	This is the initial TSAP describing treatment setup and IPD.
1.0	12-APR-18		All sections	Core TSAP
2.0	25-Oct-21		All sections	Update for cohorts D1, D2 and interim CTR