Trial Statistical Analysis Plan

c23715112-04

BI Trial No.:	1368.17
Title:	Trial Statistical Analysis Plan An open label, long term safety trial of BI 655130 treatment in patients with moderate to severely active ulcerative colitis who have completed previous BI 655130 trials Including Protocol Amendment 6 [include c18806983-06]
Investigational Product:	BI 655130
Responsible trial statisticians:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	13 JAN 2021 SIGNED
Version:	4.0 (Revised TSAP)

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2. LIST OF ABBREVIATIONS

Term	Definition / description
[redacted]	[redacted]
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALQ	Above limit of quantification
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
BRAVE	BI RAVE®
RPM	Report Planning Meeting
BSA	Body surface area
CARE	Clinical data analysis and reporting environment
CR	Clinical remission
CRF	Case report form
CRP	C-reactive protein
CS	Systemic corticosteroids
CTC	Common Terminology Criteria
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study

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Term	Definition / description
EOT	End of treatment
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials
FLF	Faecal lactoferrin
F/U	Follow-up
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	Interleukin
IPD	Important protocol deviation
IRT	Interactive response technology
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
MCS	Mayo Clinical Score
MedDRA	Medical Dictionary for Regulatory Activities
mESS	Modified Endoscopic Subscore
MQRM	Medical quality review meeting
NRI	No response imputation
OC	Observed cases
OC-IR	Observed cases including values after rescue medication
OR	Original results
PD	Pharmacodynamic(s)
PGA	Physician Global Assessment
[redacted]	[redacted]
PMR	Partial Clinical Remission
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
RBS	Rectal Bleeding Subscore
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual effect period

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Term	Definition / description
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDL	Subject data listing
SFS	Stool Frequency Score
SI	Système international d'unités
SMQ	Standardised MedDRA query
SOC	System Organ Class
CTL	Clinical Trial Lead
SAF	Safety Analysis set
SAF-RT	Safety Analysis set for Re-induction Treatment
SAF-MT	Safety Analysis set for Maintenance Treatment
SAF-FT	Safety Analysis set for Flare Treatment
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range
ULOQ	Upper limit of quantification
VAS	Visual analogue scale

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3. INTRODUCTION

As per International Conference on Harmonisation (ICH) E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the CTP and its amendments, 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). In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “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.

For other biomarkers not specified as endpoints, a separate document will complement this TSAP.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

Since the primary aim of this study is to collect long-term safety and efficacy data on the use of spesolimab (BI 655130) in this population, multiple interim analyses will be done over the 7-year conduct phase of this trial in order to support, for example, regulatory interactions, Clinical Trial Authorizations (CTA), and MAA/BLA submissions, but also to provide important safety and efficacy information to the sponsor to guide further development of the compound, and to the investigators via IB updates and publications. Any data cut-off to be used for the reporting of trial data at interim will be presented in either a separate data cleaning plan, or in an appendix to this TSAP. If considered appropriate, an access plan may be developed at the time of the interim which describes those personnel who will be allowed access to the results of the interim data analysis.

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4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The population label for Treated Set (TS) is updated to be Safety Analysis set (SAF) based on current project definition. Thus the TS-RT for re-induction treatment becomes SAF-RT, and TS-MT for maintenance treatments becomes SAF-MT.

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5. ENDPOINTS

For handling of missing data and the occurrence of inter-current events, unless otherwise specified, see section 6.6.

Baseline for safety data, unless otherwise specified, is the last value prior to initiation of the re-induction treatment (for the re-induction period), or the maintenance treatment (for the pre-flare treatment period and post-flare treatment period), or the disease flare treatment (for the disease flare treatment period).

For the summary of all efficacy data, only those observations which were collected during the on-treatment period (i.e. first dose of spesolimab through to the last dose of spesolimab + 16 weeks) will be used.

Regarding the analyses of the change from baseline by visit for continuous efficacy endpoints, the baseline in current study is used, which refers to the last value prior to initiation of

- the re-induction therapy (i.e. baseline of re-induction period, denoted as R-baseline, corresponding to the week 12 assessment on the prior induction trial),
- or the maintenance therapy (i.e. baseline of the maintenance trial part, denoted as M-baseline, corresponding to the week 12 assessment on the prior induction/re-induction trial part).

For the specification of baseline definition for derivation of the applicable binary MCS endpoints, i.e. clinical response:

- the baseline is defined as the last non-missing value reported prior to the first dose of study drug on the preceding induction study, i.e., the definition of efficacy baseline from the parent trial.

However, for binary MCS endpoints after a disease flare treatment (specifically for disease flare treatment period), the baseline is defined as the last value prior to initiation of each disease flare treatment (i.e. baseline of disease flare treatment period, refers to data from flare confirmation visit with endoscopy or regular maintenance visit with endoscopy before administration of each disease flare treatment, denote as Fx-baseline, ‘x’ represents disease flare occurrence).

5.1 PRIMARY ENDPOINT(S)

- Exposure adjusted rate of patients reporting a treatment emergent adverse event (TEAE) up to week 336 of maintenance treatment

Please refer to section 7.8.1 for the description of the calculation of exposure-adjusted adverse event incidence rates.

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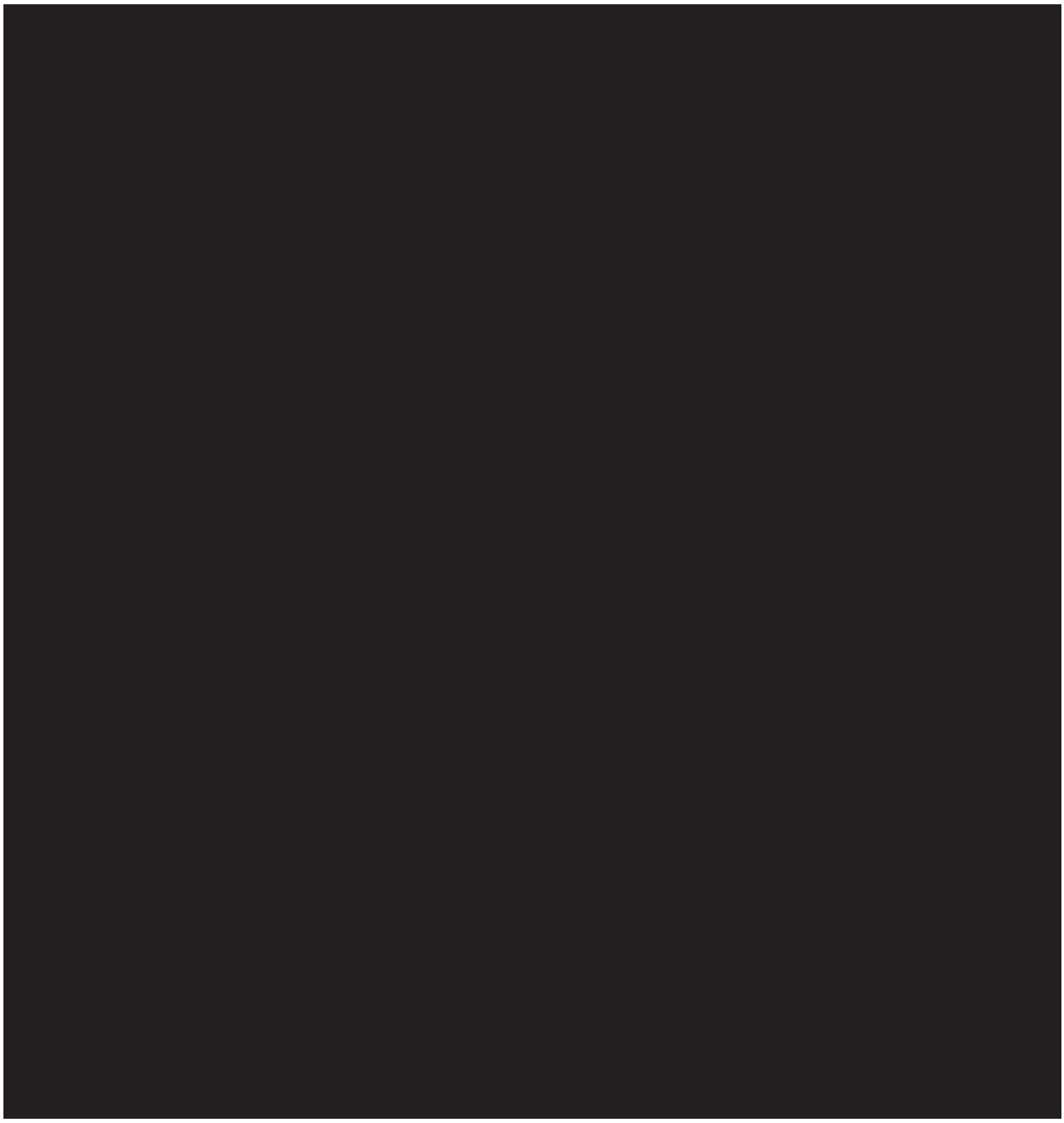
5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable. No key secondary endpoints have been specified in the CTP.

5.2.2 Secondary endpoint(s)

Proportion of patients with clinical remission (CR) at week 336 of maintenance treatment (as defined in Table 9.1.1: 1)



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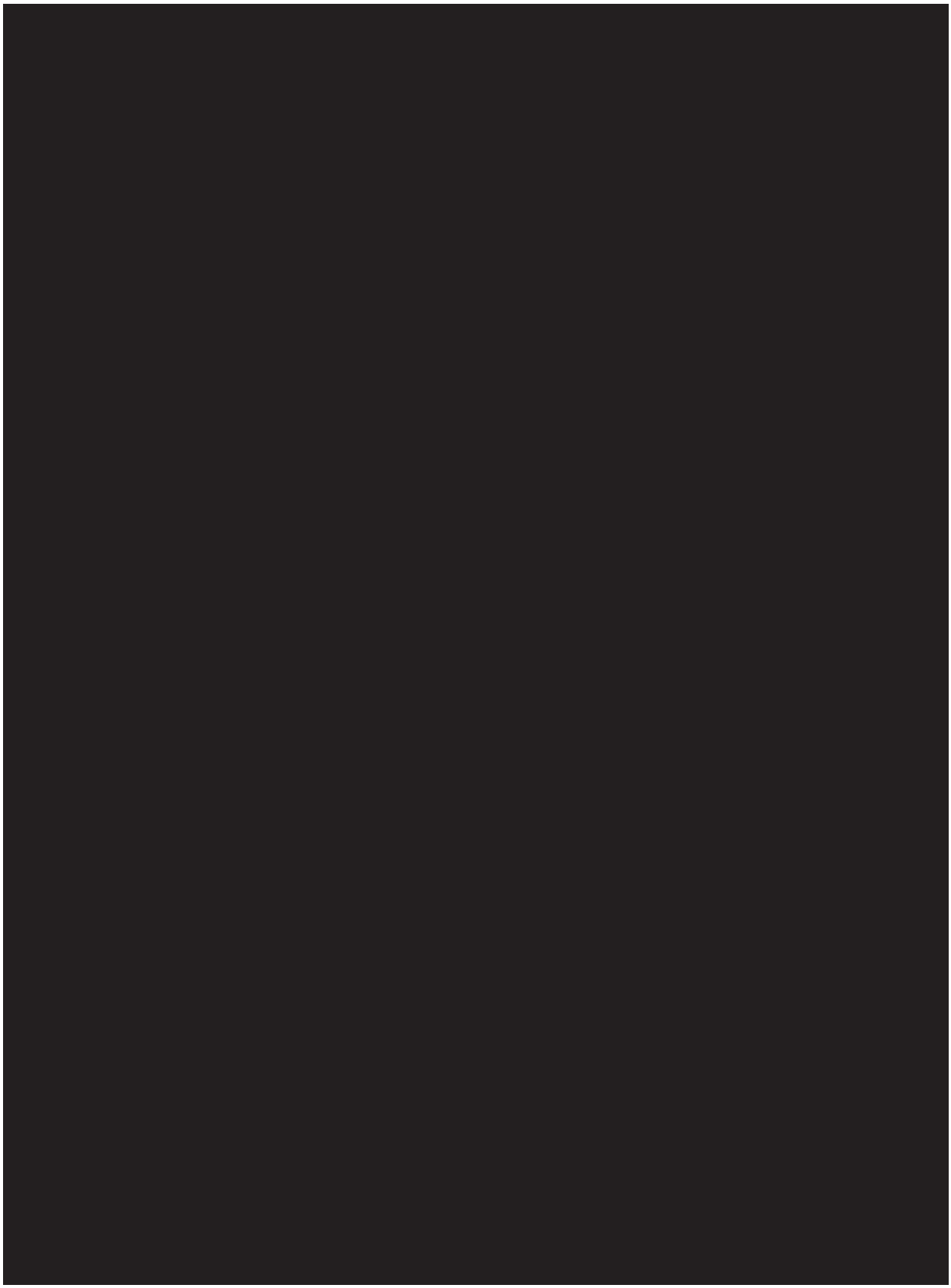

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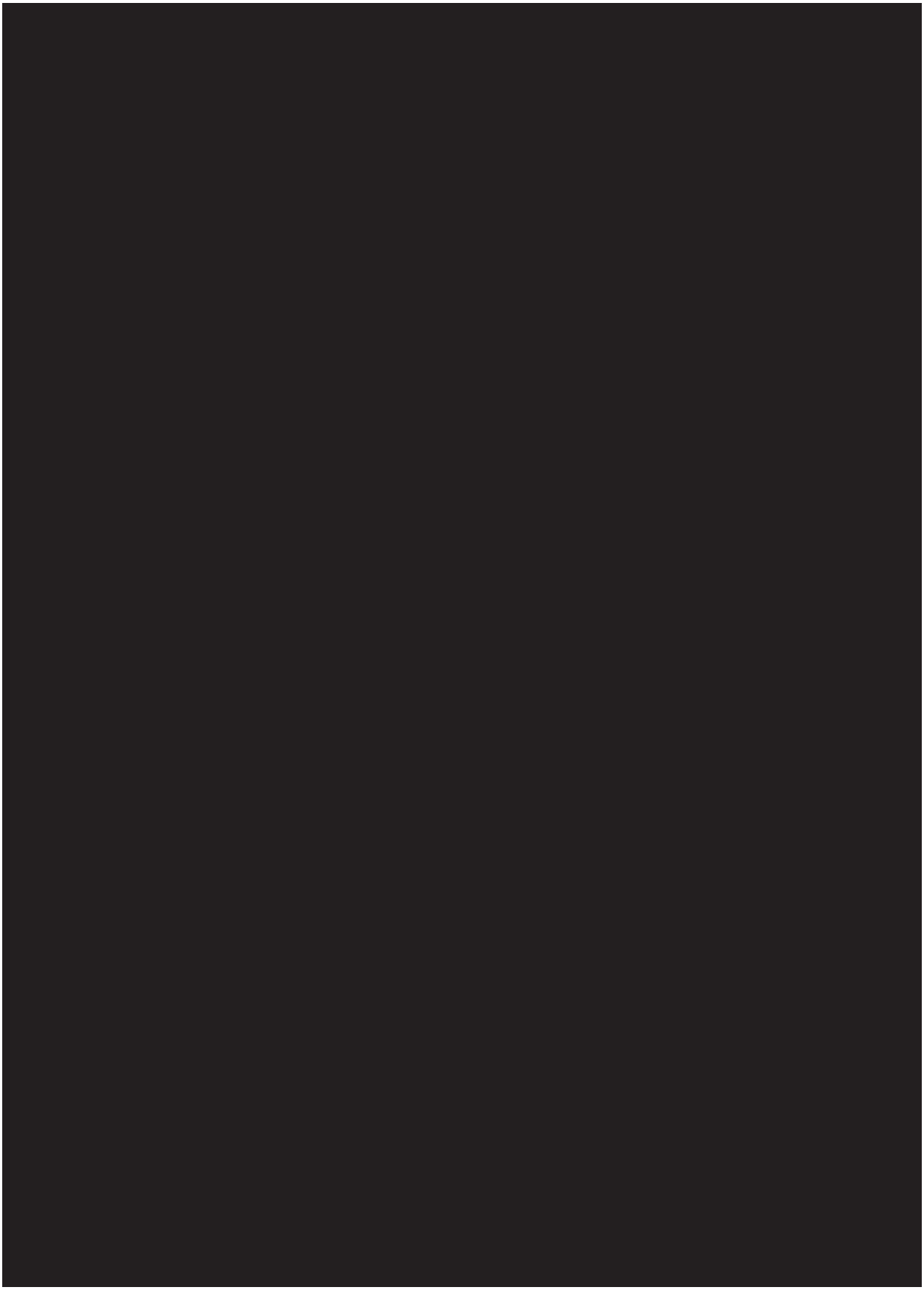

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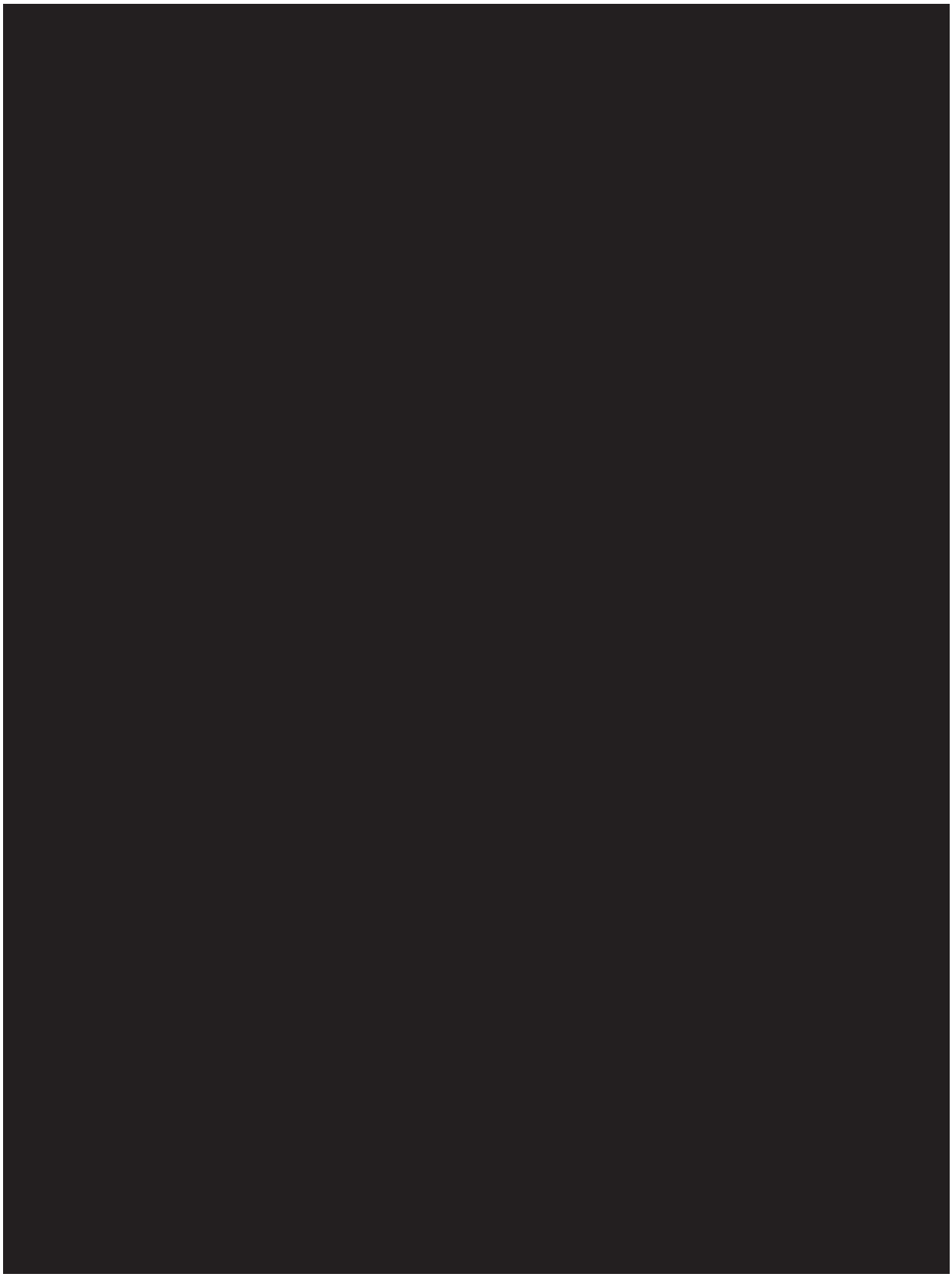

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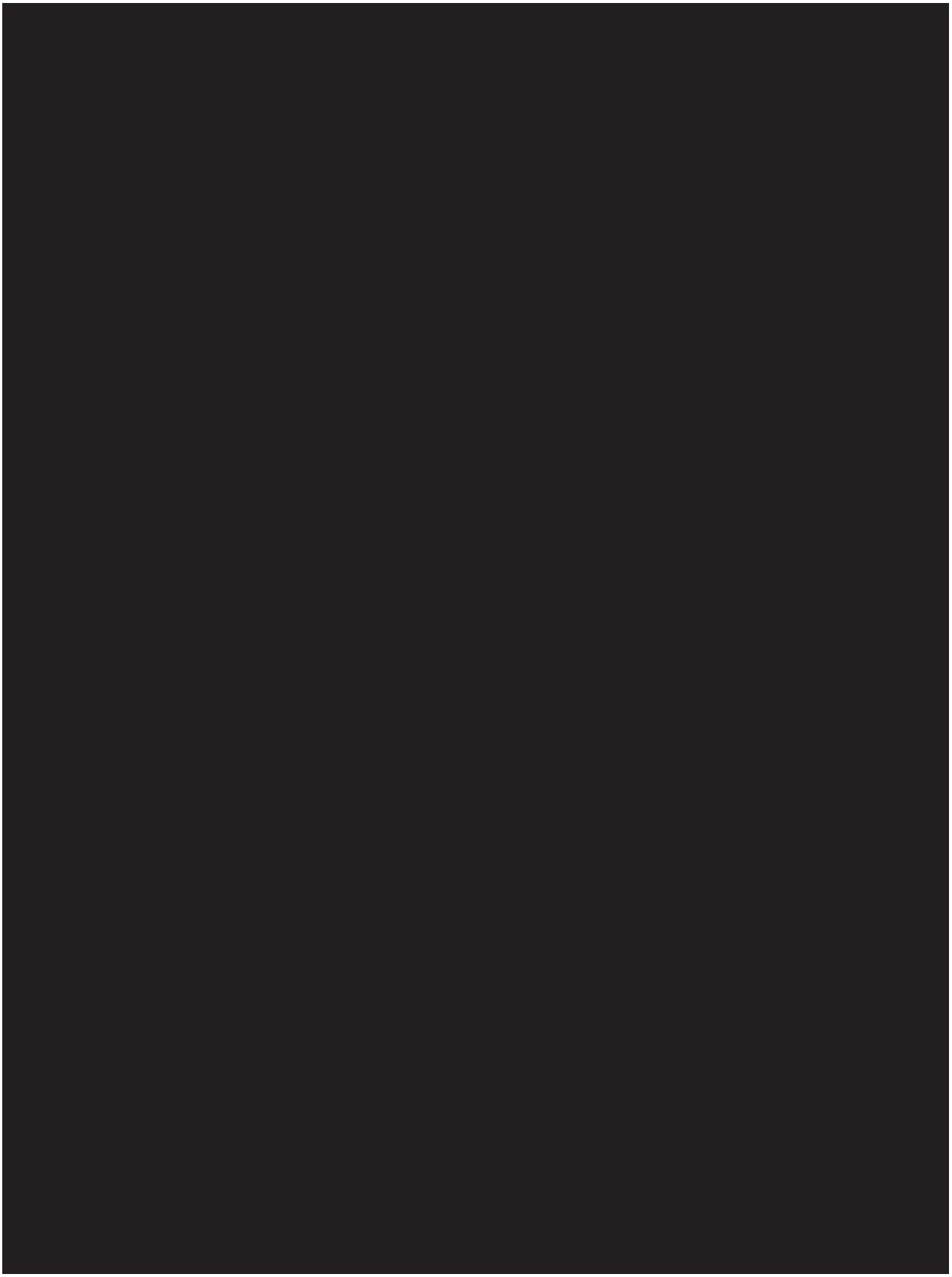

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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

The following treatment options are planned in this study:

- For patients who complete treatment in the previous induction study but who do not have a clinical response at week 12 (EoT):
    - Multiple active doses of intravenous spesolimab 1200 mg q4w are administered for 12 weeks (re-induction); responders at week 12 will subsequently receive subcutaneous spesolimab 300 mg q4w as maintenance treatment for up to 7 years;
- For patients who complete treatment in the previous induction study and who have a clinical response at week 12 (EoT):
    - Subcutaneous spesolimab 300 mg q4w as maintenance treatment for up to 7 years.

Note that patients entered into the trial according to CTP version 4.0 or earlier who initially received subcutaneous spesolimab 300 mg q12w as maintenance treatment will be switched to treatment with spesolimab 300 mg q4w per CTP amendment 5.0.

Patients who experience a disease flare during maintenance treatment (as defined in Table 9.1.1: 1) will be administered a single intravenous dose of spesolimab 1200 mg followed by an intensified subcutaneous maintenance dosing schedule with 600 mg q6w. Note that patients entered into the trial according to CTP version 4.0 or earlier may have received an intensified subcutaneous maintenance dosing schedule with 300 mg q6w; these patients will be switched to 600 mg q6w per CTP amendment 5.0.

The following study phases are defined:

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Re-Induction Period

The analysis phase as described below is applicable to both the efficacy and safety analyses of the re-induction period.

Table 6.1: 1 Flow chart of analysis phases for re-induction period

Study analysis phase	Description	Start (included)	End (included)
Screening phase	Screening	Earliest of (Date of informed consent, first screening procedure)	Date/time of start of infusion of first re-induction study drug minus 1 minute
Re-induction treatment phase & Residual effects period	Re-induction on-treatment period	Date/time of start of infusion of first re-induction study drug (Day 1 for re-induction)	Patient does not participate in maintenance treatment period: Date of end of infusion of last re-induction study drug + 112 days at 11:59 pm; Patient participates in maintenance treatment period[2]: Date/time of injection of first maintenance study drug minus 1 minute
Follow-up[1] phase	Off-treatment period	Patient does not participate in maintenance treatment period: Date of end of infusion of last re-induction study drug + 113 days at 12:00 a.m.	Latest of: i) Date of EOS visit (Week 24 visit); ii) last contact date on End of Study page at 11:59 p.m.

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.

[1] The off-treatment period (i.e. Follow-up phase) only exists if the trial completion date is after the date of end of last infusion + 112 days, and if patient did not continue into the Maintenance period.

[2] This part applies only to patients entering maintenance period after completing re-induction period; it is expected to occur within the period defined by REP. Note that for safety data, i.e., AE where date and time are collected, an event which occurs on the same day of first dose in the following maintenance period, but prior to the administration are assigned to, and reported as a part of the re-induction period.

Assessments done on the same day as the first re-induction treatment dose will be assigned to a study analysis phase based on assessment via date and time. If time is not collected for a particular assessment, then assignment will be to the screening phase.

The period between last intake of re-induction study drug and first intake of maintenance study drug will be considered as a part of the re-induction analysis phase irrespective of the duration. For re-induction treated patients who do not subsequently receive maintenance treatment, the REP will be applied for the purpose of defining the duration of the on-treatment period.

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Pre-Flare Treatment Period

The analysis phase as described below is applicable to safety analyses only of the pre-flare treatment period.

Table 6.1: 2 Flow chart of analysis phases for pre-flare treatment period

Study analysis phase	Description	Start (included)	End (included)
Screening[2] phase	Screening	Earliest of (Date of informed consent, first screening procedure)	Date/time of injection of first maintenance study drug minus 1 minute
Maintenance treatment phase & Residual effects period	Maintenance on-treatment period	Date/time of injection of first maintenance study drug (Day 1 for maintenance)	Without flare treatment: Date of injection of last maintenance study drug + 112 days at 11:59 p.m. With flare treatment[3]: Date/time of infusion of first flare study drug minus 1 minutes
Follow-up[1] phase	Off-treatment period	Without flare treatment: Date of injection of last maintenance study drug + 113 days at 12:00 a.m.	Latest of: i) Date of EOS visit (Week 352 visit); ii) last contact date on End of Study page at 11:59 p.m.

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.
[1] The off-treatment period (i.e. Follow-up phase) only exists if the trial completion date is after the date of end of last injection + 112 days.
[2] The screening phase does not exist for re-induction treated patients who subsequently receive maintenance treatment.
[3] Safety data is censored for reporting following intake of disease flare treatment with spesolimab. Measurements collected with date only on the day of first flare treatment are assigned to the pre-flare treatment period.

Assessments done on the same day as the first maintenance treatment dose will be assigned to a study analysis phase based on assessment via date and time. If time is not collected for a particular assessment, then assignment will be to the previous study analysis phase, i.e. to the screening phase for patients who directly enter the trial into the maintenance period, or to the re-induction phase for patients who directly enter the trial into the re-induction period.

For all subjects who received disease flare treatment with spesolimab during the maintenance period, safety assessments (including adverse events, laboratories, vital signs etc.) which occurred subsequent to such intake will be excluded from presentations according to the actual treatments in a primary approach.

Post-Flare Treatment Period

The analysis phase as described below is applicable to safety analyses only of the post-flare treatment period.

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For the post-flare treatment period of the maintenance period, the analysis phases described below consider the inclusion of data from the following study parts: disease flare treatment with 1200 mg spesolimab single i.v. infusion followed by intensified maintenance dosing with 600 mg s.c. spesolimab q6w, up to the (extended) REP from the last dose of spesolimab (either injection or infusion).

Table 6.1: 3 Flow chart of analysis phases for the post-flare treatment period

Study analysis phase	Description	Start (included)	End (included)
Post-flare treatment phase & Residual effects period	Post-flare treatment period (REP extended)	Date/time of infusion of first flare study drug (Day 1)	Date of end of (infusion or injection) of last administered spesolimab + 112 days at 23:59
Follow-up[1] phase	Off-treatment period (REP extended)	Date of end of (infusion or injection) of last administered spesolimab + 113 days at 12:00 a.m.	Latest of: i) Date of End-of-Study visit; ii) last contact date on End of Study page at 23:59

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.
[1] The off-treatment period (i.e. Follow-up phase) only exists if the trial completion date is after the date of end of last infusion or injection + 112 days.

The post-flare treatment period only applies to those patients who are administered a disease flare treatment with spesolimab. Assessments done on the same day as the first disease flare treatment dose will be assigned to a study analysis phase based on assessment via date and time. If time is not collected for a particular assessment, then assignment will be to the previous study analysis phase, i.e. to the pre-flare treatment period.

Overall Maintenance Treatment Period

The overall maintenance treatment period applies to all patients taking at least one dose of maintenance treatment regardless of flare occurrence. This period will be considered to understand long-term efficacy and safety of spesolimab.

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Table 6.1: 4 Flow chart of analysis phases for overall maintenance treatment period

Study analysis phase	Description	Start (included)	End (included)
Screening[2] phase	Screening	Earliest of (Date of informed consent, first screening procedure)	Date/time of injection of first maintenance study drug minus 1 minute
Maintenance treatment phase & Residual effects period	Maintenance on-treatment period	Date/time of injection of first maintenance study drug (Day 1 for maintenance)	Date of end of (infusion or injection) of last administered spesolimab + 112 days at 23:59
Follow-up[1] phase	Off-treatment period	Date of end of (infusion or injection) of last administered spesolimab + 113 days at 12:00 a.m.	Latest of: i) Date of End-of-Study visit; ii) last contact date on End of Study page at 23:59

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.
[1] The off-treatment period (i.e. Follow-up phase) only exists if the trial completion date is after the date of end of last injection or infusion + 112 days.
[2] The screening phase does not exist for re-induction treated patients who subsequently receive maintenance treatment.

Disease Flare Treatment Period

The analysis phase as described below is applicable to both the efficacy and safety analyses of the disease flare treatment period.

The following phases will be used for assessment on the efficacy and AE safety profile only in patients who take disease flare treatment with 1200 mg spesolimab single i.v. infusion. This analysis phase considers the fixed 12-week duration after administration of a disease flare spesolimab infusion up to the time of the planned endoscopy measurement (Rx-Week 12 defined in Table 6.7: 3).

Table 6.1: 5 Flow chart of analysis phases for disease flare treatment period

Study analysis phase	Description	Start (included)	End (included)
Disease flare treatment phase*	On-treatment period after flare infusion with spesolimab	Date/time of start of infusion of flare treatment (Day 1 for flare treatment)	Date of end of infusion of flare treatment + 98 days at 23:59

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.
*One patient may have multiple disease flare treatment phases if multiple flares happen at different times.

The disease flare treatment period only applies to those patients who are administered a disease flare treatment with spesolimab. Assessments done on the same day as the first disease flare treatment dose will be assigned to a study analysis phase based on assessment via date and time. If time is not collected for a particular assessment, then assignment will be

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to the previous study analysis phase, i.e. to the pre-flare treatment period for first administration of disease flare treatment, or to the post-flare treatment period for subsequent administrations.

The selection of data for presentation in this analysis is described in Tables about time window in Section 6.7.Treatments will be labelled as follows:

- "Re-induction Speso 1200 mg IV q4w" [applicable to the re-induction period]
  Selected tables also by prior parent trial treatment

- "Pre-Flare SC" [applicable to the pre-flare treatment period, i.e., censoring data after intake of first flare treatment, including also the old dosing schedule]
- "Post-Flare IV/SC" [applicable to the post flare treatment period, includes also the old dosing schedule]
- "Overall Maintenance" [applicable to the whole period after maintenance treatment, includes also the old dosing schedule]
  Selected tables also by prior parent trial treatment

- "Disease Flare Speso 1200 mg IV SD" [applicable to the disease flare treatment period]
  Selected tables also by prior parent trial treatment

6.2 IMPORTANT PROTOCOL DEVIATIONS

Each protocol deviation must be assessed to determine whether it is an IPD. For definition of IPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2).

This is an open label, long term safety trial, all analyses will be performed based on the treated population only, i.e., no Full analysis Set or Per Protocol Set will be defined for analyses of efficacy. Since no confirmatory efficacy testing is planned, no efficacy related iPDs leading to exclusion from analysis set are defined. Efficacy, safety and GCP related iPDs are included in Section 4.1 of the Integrated Quality and Risk Management Plan (IQRMP).

Patients with iPD B.01, i.e., informed consent not available/not done, will be excluded from all analyses.

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Table 6.2: 1 Important protocol deviations

Category / Code		Description	Comments	Excluded from
A		**Entrance criteria violated**		
A1		**Inclusion criteria not met**		
	A1.01	Male or female patients, aged ≥18 years	IC01 Also check versus derived age for patient.	None
	A1.02	Women of childbearing potential (WOCBP) must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly.	IC03	None
	A1.03	Have completed treatment and the EOT visit in the previous trial and are willing and able to continue treatment in 1368.17.	IC04	None
A2		**Exclusion criteria violated**		
	A2.01	Have experienced study treatment-limiting adverse events during induction treatment with study drug	EC01	None
	A2.02	Have developed any of the exclusion criteria from the original induction study	EC02, medical review	None
B		**Informed consent**		
	B.01	Informed consent not available/not done	Date of informed consent missing or no signature on patient's "Declaration of Informed Consent"	All analyses
	B.02	Informed consent too late	Date of informed consent not obtained prior to any study related procedure. Minimum requirement for initial informed consent <= date of Visit 1/date of any study procedure	None
C		**Trial medication and randomisation**		
C3		**Administration instruction not followed**		
	C3.01	Administration of potential contaminated drug	Study drug not prepared according to the instruction of administration Medical review	None

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Table 6.2: 1 Important protocol deviations (cont.)

Category / Code	Description	Comments	Excluded from
F	**Study specific analysis**		
F1	**Other trial specific violation**		
F1.01	Incorrect response assessment leads to assignment to wrong trial part (i.e. re-induction or maintenance) or to continuation of intensified maintenance therapy (following disease flare treatment)	Medical review	None
F1.02	Disease flare treatment used without sufficient evidence for a disease flare	Medical review	None
G	**Other safety related violations**		
G1	Pregnancy test not done for woman of child bearing potential, or pregnant during study	Pregnancy test not done at any visit where such is scheduled and the patient did not yet complete follow-up.	None

Source: BI reference document ' Identify and Manage Important Protocol Deviations (iPD)' [001-MCS-40-413] (2).

6.3 PATIENT SETS ANALYSED

From CTP Section 7.3:

There will be 2 main patient populations in this trial for analyses: the Safety Analysis set for maintenance treatment (SAF-MT) and the Safety Analysis set for re-induction treatment (SAF-RT).

Safety Analysis set for Maintenance Treatment (SAF-MT)
This patient set includes all patients who received at least one dose of maintenance treatment in the extension trial. It will be the main analysis set for presentation of safety and efficacy during the maintenance part of the extension trial.

Safety Analysis set for Re-induction Treatment (SAF-RT)
This patient set includes all patients who received at least one dose of re-induction treatment in the extension trial. It will be the main analysis set for presentation of safety and efficacy during the re-induction part of the extension trial.

In addition, the following patient sets are defined for analysis.

Enrolled set (ES)
This patient set includes all patients who sign the informed consent. This set will be used for disposition analyses.

Safety Analysis set (SAF)

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This patient set includes all patients who received at least one dose of study drug in either the re-induction or maintenance periods. This set will be used for presentation of IPDs and patient listings.

Safety Analysis set for Flare Treatment (SAF-FT)
This patient set includes all patients who take at least one dose of disease flare treatment of 1200 mg SD i.v. in the extension trial. This set is the basis for efficacy and safety analysis on both the disease flare, and the post-flare treatment periods.

Note that the constitution of treatment sets will differ depending upon the number of patients entered into the trial at the time of each interim analysis.

Table 6.3: 1 illustrates the data sets which are to be used for each category class of endpoints, as well as treatment periods to be reported for each data sets. For explanation of the different methods of handling missing data, cf. Section 6.6.

Table 6.3: 1 Patient sets and treatment periods analysed

Class of endpoints	ES	SAF	SAF-MT	SAF-RT	SAF-FT
Disposition	X		Overall maintenance TP	Re-induction TP	
Exposure			Pre-flare TP; Overall maintenance TP	Re-induction TP	Post-flare TP; Disease flare TP
IPDs		X			
Demographic/baseline characteristics			X	X	X
Concomitant medication			X	X	X
Secondary endpoint			Overall maintenance TP		
Further endpoint (including biomarker endpoint)			Endpoints defined for overall maintenance TP	Endpoints defined for re-induction TP	Endpoints defined for disease flare TP
Adverse event			Pre-flare TP; overall maintenance TP	Re-induction TP	Post-flare TP; disease flare TP
Safety lab, vital sign			Pre-flare TP; overall maintenance TP	Re-induction TP	Post-flare TP; disease flare TP

Note: MT=Maintenance Treatment; RT=Re-induction Treatment; FT=Flare Treatment; TP= Treatment Period

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6.5 POOLING OF CENTRES

All patients from all centres will be pooled for statistical analysis.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.5 of the CTP describes the handling of missing data.

The original results (OR) approach implies the presentation of data exactly as observed (not using time windows and not setting values to missing).

OR analysis will be performed on parameters and endpoints that are either not affected by patients' rescue medication use (e.g. plasma concentration level of spesolimab, rescue medication use itself, or disease flare related endpoints), or, if it is not meaningful to apply any imputation rule for the replacement of missing values.

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6.6.1 Withdrawals

The reasons for withdrawal from treatment will be reported as indicated on the eCRF.

6.6.2 Efficacy endpoints

From CTP Section 7.5: *With regards to the handling of missing data on those efficacy outcomes derived from the MCS, no missing data imputations are planned to be performed.*

In order to appropriately handle missing data in this trial, it is first necessary to define which are the inter-current events within each trial part, that lead to specific decisions being made upon the respective efficacy endpoint outcome, with such decisions being dependent upon the occurrence and timing of these events.

Any occurrence of the following will represent an inter-current event during both the re-induction and maintenance trial parts:

- Intake of rescue medication (as defined in section 5.4.4).
  Data after occurrence of such an event will be censored, and, handled subsequently according to the applicable missing data strategy described below.

In addition, any occurrence of the following will represent an inter-current event during the maintenance trial part:

- Occurrence of a confirmed disease flare (as defined in Section 5.4.6), or the intake of a dose of disease flare medication with 1200 mg BI 655130 SD.

Data after occurrence of such an event will be included in displays of the efficacy endpoints since treatment with spesolimab i.v. (to treat a disease flare) is not considered to represent a failed treatment outcome in this trial.

Efficacy imputation rules

The following rules apply for all treatment periods with defined efficacy endpoints. Missing data imputation, when performed, will not be done for missing assessments due to implementation of any cut-off date.

The following imputation strategy will be applied to the reporting of continuous efficacy data.

- Observed cases (OC) approach: prior to observing the applicable efficacy endpoint, data will be reported with no imputation performed on the missing data irrespective of whether the data is considered to be randomly missing, or missing due to prior occurrence of an applicable intercurrent event.

The following imputation strategy will be important for the display of binary efficacy data:

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- No Response Imputation [NRI]: prior to observing the applicable binary efficacy endpoint, all missing data will be set to non-response irrespective of whether the data is considered to be randomly missing, or missing due to prior occurrence of an applicable intercurrent event. Only patients continuing at this visit per time window before interim cut-off will be included in the denominator.

The following imputation strategy will be important for the display of, i.e. safety laboratory data:

- Observed cases including values after any use of rescue medication (OC-IR): this approach is an extension of the OC approach which includes all values which were measured both before and after any rescue medication intake. The analysis using the OC-IR approach is then only based on the patients with observed data.

6.6.3 Safety endpoints

From CTP Section 7.5: *For the safety data, including the primary endpoint, no missing data imputations are planned.*

The only exceptions where imputation might be necessary for safety evaluation are AE dates, and start and stop dates for concomitant medications. Missing or incomplete AE dates are imputed according to BI standards (see *KM Asset* BI-KMED-BDS-HTG-0035 (3)).

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[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For patients who are included directly into the maintenance period, measurements reported with date and time, and taken prior to start of administration of trial treatment are considered to be pre-treatment values. Measurements reported with a date only (and no time) and taken on the day of first administration of trial treatment are handled in a similar manner, i.e.

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assigned as pre-treatment values. These pre-treatment values will be assigned to visits according to the nominal visit number as recorded on the eCRF or as provided by the laboratory.

For patients who are included directly into the re-induction period, measurements reported with date and time, and taken prior to start of administration of trial treatment are considered to be pre-treatment values. Measurements reported with a date only (and no time) and taken on the day of first administration of trial treatment are handled in a similar manner, i.e. assigned as pre-treatment values.

Baseline for derivation of the binary MCS efficacy endpoints, as well as for the efficacy endpoint displays over time are defined in Section 5.

For safety endpoints, baseline for different treatment periods are defined in Section 5.

Measurements taken after start of administration of trial treatment will be considered either on- or off-treatment values based on the definition in Section 6.1, and will be assigned to visits for statistical analysis, if applicable, as defined below.

Analysis of AE data, concomitant medication or non-drug therapies, as well as use of rescue medication will not be based on visits. Therefore, no assignment to time windows will be necessary.

For derivation of the last value on treatment, minimum value on treatment, and maximum value on treatment, all on-treatment values (whether or not selected in any time window; see Table 6.1: 1 and Table 6.1: 4 for definition of the on-treatment period) will be considered; these will be derived for analysis of laboratory and vital signs data. For identification of potentially clinically significant abnormal laboratory values, all values (whether or not selected in any time window) within the on-treatment period will be considered.

Safety lab, vital sign, efficacy and biomarker measurements will be assigned to visits based on extended time windows around the planned visit dates, defined relative to the day of first re-induction, maintenance, or disease flare treatment depending on analysis phase. These extended time windows are defined below as well as their planned analyses.

- Re-induction period (Table 6.7: 1): efficacy, safety, and biomarker
- Overall maintenance treatment period (Table 6.7: 2): efficacy, safety, and biomarker
- Disease flare treatment period (Table 6.7: 3): efficacy, and safety

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Table 6.7: 1 Time windows for assignment of efficacy, safety lab, vital signs and biomarker to visits for statistical analysis for re-induction period

Visit number /name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
V1	Screening/ R-baseline*	-7 to -2	n/a				
V1a	Screening	-2 to -1	n/a				
I1	RI-Week 0	Day 1	+/-0	1 [A]	1 [A]	≤1 [A]	1 [A]
Planned On-Treatment Data							
I2	RI-Week 4	Day 29	+/-3	26	32	2	43
I3	RI-Week 8	Day 57	+/-3	54	60	44	71
I4	RI-Week 12	Day 85	+/-3	82	88	72	99[B]
All Data (planned Off-Treatment data)							
Unscheduled	Unscheduled					100	148
EOS[C]	Week 24/EoS	Day 170	+7	170	177	149	Day of last f-up value

Days are counted relative to the day of first i.v. treatment of re-induction period, which is defined as Day 1.
* For derivation of binary MCS based efficacy endpoints, the baseline refers to baseline of parent trial. The R-baseline for efficacy endpoint displays over time refers to EoT of parent trial (V1 of current study).
[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of infusion of trial treatment) via assessment on date and time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.
[B] All data after a patient has taken the first dose in the subsequent maintenance period are not applicable for reporting as a part of the re-induction period.
[C] EOS is only applicable to those patients who do not enrol into the maintenance period.

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Table 6.7: 2 Time windows for assignment of efficacy, safety lab, vital sign and biomarker to visits for statistical analysis for overall maintenance treatment period

Visit number /name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
V1	Screening/ M-baseline*	-7 to -2	n/a				
V1a	Screening	-2 to -1	n/a				
M1	M-Week 0	Day 1	+/-0	1 [A]	1 [A]	≤1 [A]	1 [A]
Planned On-Treatment Data							
M2	M-Week 12	Day 85	+/-7	78	92	2	127
M3	M-Week 24	Day 169	+/-7	162	176	128	211
M4	M-Week 36	Day 253	+/-7	246	260	212	295
…	…	…	…	Planned date-7	Planned date+7	End of extended window of last visit+1	Midpoint of planned days between current visit and next visit
M29/EOT	M-Week 336/EoT	Day 2353	+/-7	2346	2360	End of extended window of last visit+1	Minimum of (2395, LD[B]+112)
All Data (planned Off-Treatment data)							
Unscheduled	Unscheduled					2396	2444
EOS	EoS	Day 2466	+7	2466	2473	Minimum of (2396, LD[B]+113)	Day of last f-up value

Days are counted relative to the day of first s.c. treatment in maintenance period, which is defined as Day 1 for maintenance.

* For derivation of binary MCS efficacy endpoints, the baseline refers to baseline of parent trial. The M-baseline for efficacy endpoint displays over time refers to EoT of parent trial (V1 of current study) for initial responders and visit I4 (RI-Week 12) for responders after re-induction.

[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of injection of trial treatment) via assessment on date and time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.

[B] LD = Day of last treatment received in the overall maintenance treatment period regardless of flare occurrence;

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Table 6.7: 3 Time windows for assignment of efficacy, safety lab, and vital signs to visits for statistical analysis for disease flare treatment period

Visit number/name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
F0y	Fx-baseline*	-5 to -3	n/a				
Fx-Week 0	Fx-Week 0	1	+/-0	1 [A]	1 [A]	≤1 [A]	1 [A]
Planned On-Treatment Data							
Fx-Week 6	Fx-Week 6	Day 43	+/-7	36	50	2	64
Fx-Week 12	Fx-Week 12	Day 85	+/-7	78	92	65	99

Visit number/name: 'x' represents disease flare occurrence.
Days are counted relative to the day of each corresponding flare i.v. treatment, which is defined as Day 1 of disease flare treatment period.
* For clinical response/remission assessment after disease flare treatment based on mayo score related calculation, the baseline refers to data from flare confirmation visit with endoscopy or regular maintenance visit with endoscopy before administration of each disease flare treatment.
[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of infusion of trial treatment) via assessment on date and time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.

Repeated and unscheduled efficacy, safety and biomarker measurements will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement.

Only one observation per time window will be selected for statistical analysis at a particular visit. Generally, the value which is closest to the protocol planned visit day will be selected. For composite endpoints based on MCS subscores, the date of PGA assessment will be used for time window assignment, and the PGA with the most complete components (RBS/SFS/mESS) at the same visit will be identified and then the closest will be selected. If the date of PGA assessment is missing, the date of endoscopy will be used instead for time window assignment and calculation of SFS and RBS, if available. If there are two observations which have the same difference in days to the planned day, the later value will be selected. If there are two observations on the same day, then [for vital signs per nominal time-point] the latest value (according to the date and time) will be selected, [for other endpoints] the worst value will be selected.

Assignment of efficacy observations to visits based on time windows will be based on the non-imputed (observed) data.

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7. PLANNED ANALYSIS

General Remarks

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (001-MCG-159) (7).

The individual values of all patients will be listed, including those collected during the off-treatment period. Listings will generally be sorted by country, centre number, patient number and visit (if visit is applicable in the respective listing). (see Section 7.8.1 below for details).

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Q1	lower quartile
Median	median
Q3	upper quartile
Max	maximum

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Reporting of clinical trials and project summaries" (7).

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 patient set (unless otherwise specified, all patients in the patient set irrespective of whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

Disposition of the patient population for each trial part (re-induction or overall maintenance) will be summarised by presentation of the frequency of patients enrolled, treated, enrolled but not treated, who completed all doses of trial medication as planned, who completed the PE visit (EOT), who completed the trial (EOS), and who were prematurely discontinued, by reason. Additional summaries by the parent trial will be produced, and, summaries of the maintenance period disposition according to whether or not a patient experienced re-induction treatment or not will also be done. The frequency of patients with iPDs will also be presented; the iPDs will be listed per patient.

To better illustrate the long-term efficacy of the overall maintenance treatment (defined in Table 6.1: 4), a summary table regarding patient status over time will be added. The cumulative frequency of patients for the following categories will be displayed based on 12-week interval:

- ongoing on study medication, i.e., without early treatment discontinuation by the time point

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  - Occurrence of a disease flare, or intake of disease flare medication
  - Intake of rescue medication
  - Any of the above

- pre-maturely stopped study medication, i.e., discontinued study medication by the time point
  - Occurrence of a disease flare, or intake of a disease flare medication
  - Intake of rescue medication
  - Death
  - Any of the above

For details on the requirements of the first interim data snapshot of this trial, refer to additional Section 9.2.1. The second interim analysis requirements are specified in Section 9.2.2.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Tables will be displayed for SAF-MT, SAF-RT and SAF-FT respectively.

For the continuous variables described below, the following categories will be defined and presented according to the number and percentage of patients in each category:

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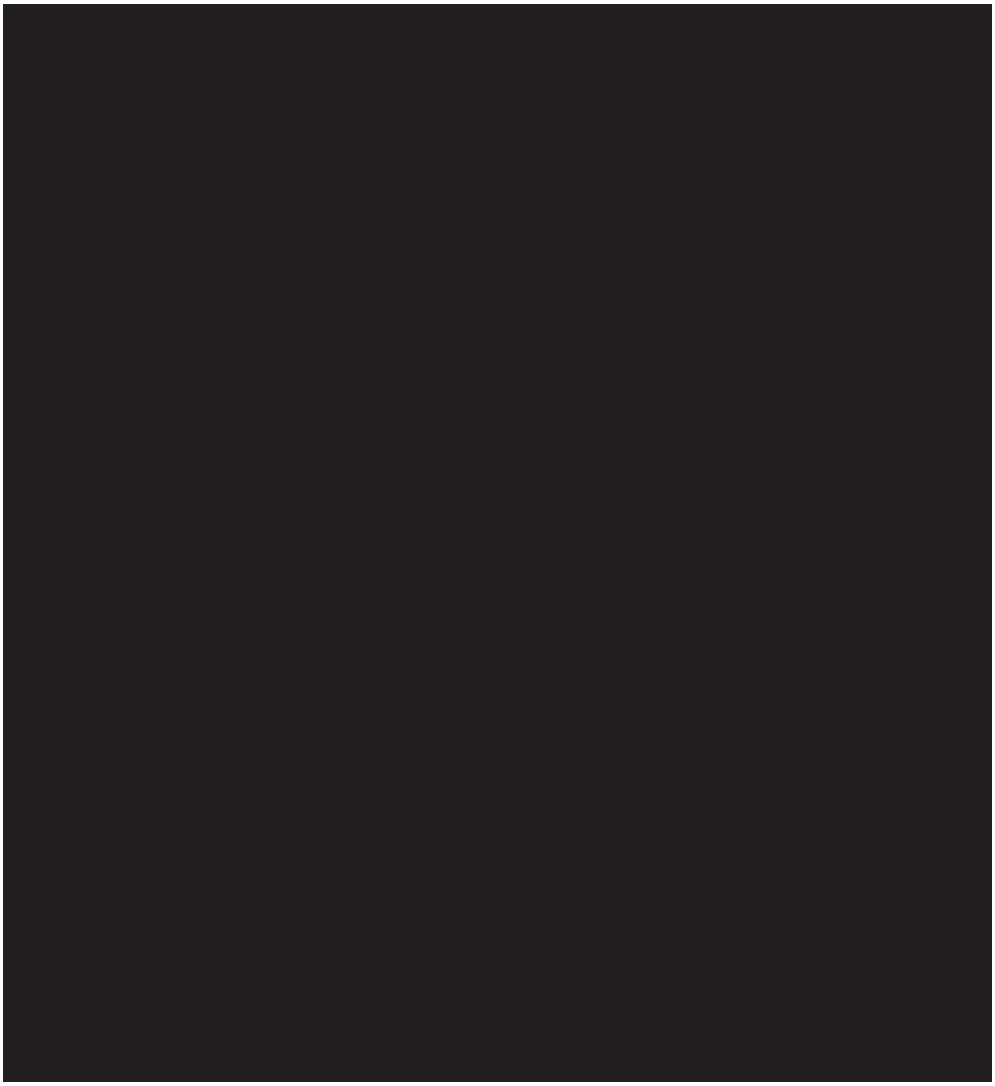

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. The analyses of EIM is defined in Section 7.8.5.2.

Analyses of concomitant diseases and medication will be based on SAF-MT, SAF-RT, and SAF-FT, respectively.

Concomitant diseases (i.e., baseline conditions) will be coded according to the most recent version of MedDRA.

Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Concomitant non-drug therapy will be coded according to the most recent version of MedDRA.

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7.3 TREATMENT COMPLIANCE

Not applicable since the treatment regimens can be different based on patient status and the version of signed informed consent.

7.4 PRIMARY ENDPOINT

Refer to section 7.8.1 for the description for adverse events including the primary endpoint..

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

From CTP Section 7.3.2:

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The evaluation of clinical outcomes based on the MCS, i.e. clinical remission, is based upon the endoscopy results obtained from central reading. Only if the centrally read endoscopy result is missing at a time-point will the locally read result be used instead.

For the stool frequency and rectal bleeding items reported in the patient diary, an average of the last 3 non-missing daily assessments collected within the last 7 days prior to the applicable visit will be used for the determination of clinical outcome. If the patient undergoes bowel preparation for endoscopy on any of the days before a visit, the stool frequency and rectal bleeding subscores on that day(s) should be considered to be missing. In addition, the stool frequency and rectal bleeding subscore will be considered to be missing both on the day of and the day after the endoscopy.

Secondary endpoint will be assessed descriptively.

The pre-defined secondary endpoint is described with the corresponding further endpoint in section 7.6.

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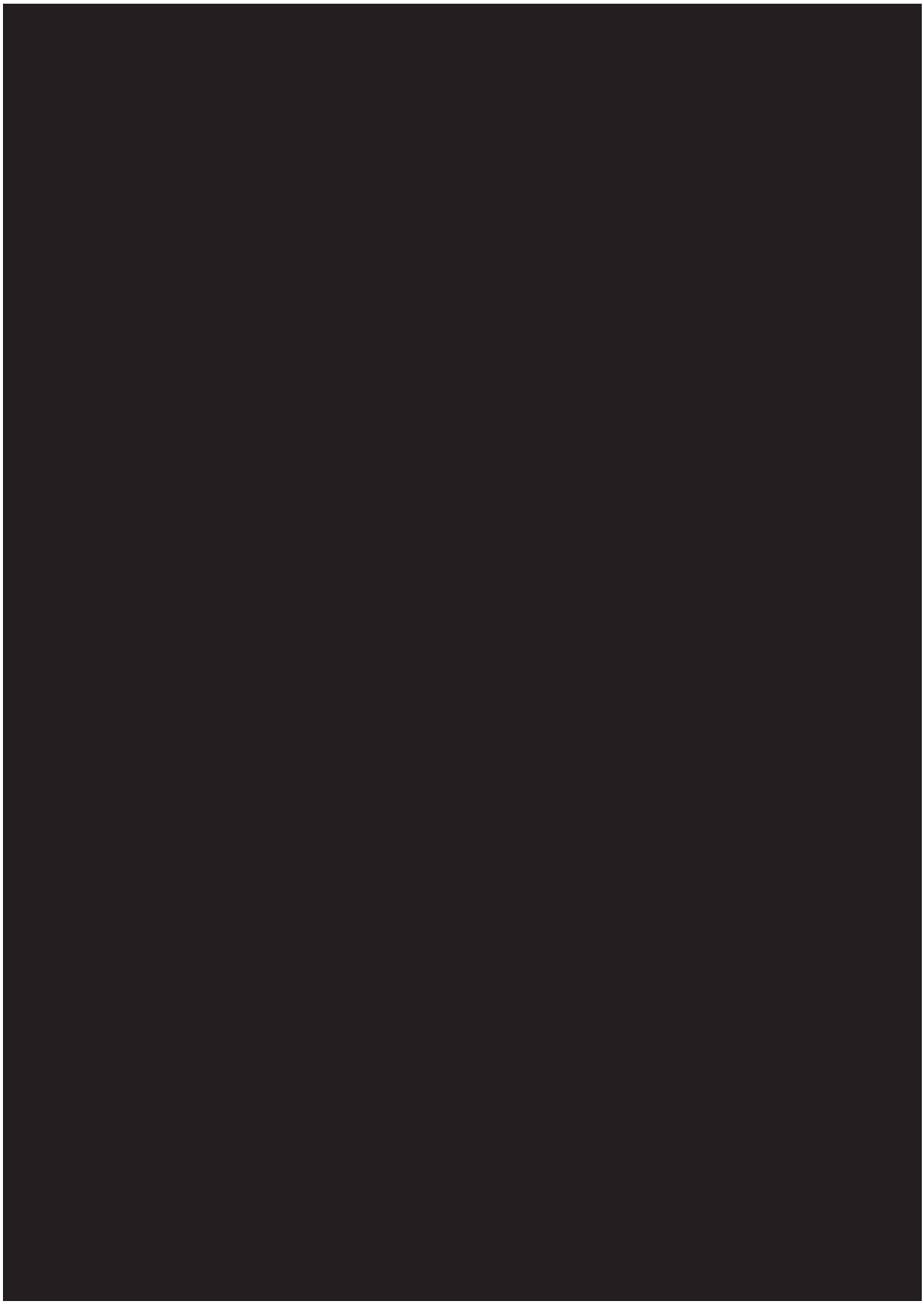

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7.8 SAFETY ANALYSIS

All safety analyses will be performed based on each of the SAF-MT and SAF-RT following BI standards. No hypothesis testing is planned.

The analyses based on SAF-MT will be done for the pre-flare treatment period (as defined in Table 6.1: 2), as well as for the overall maintenance treatment period (as defined in Table 6.1: 4). The analyses based on SAF-FT will be done for the post flare treatment period (as defined in Table 6.1: 3), as well as for the disease flare treatment period (as defined in Table 6.1: 5). For additional analysis on the individual flare safety data based on the SAF-FT, all standard

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safety tables will be provided for each flare occurrence using the analysis phases as defined in Table 6.1: 5.

In addition, a subgroup analysis on the overall maintenance treatment period by the number of flare treatments (without flare treatment, with only one flare treatment, with two or more flare treatments as defined in Section 6.4) will be provided for the following tables based on SAF-MT. Additional subgroup analysis (e.g., by pre-flare regimen) will be considered if necessary.

- Overview on TEAE
- TEAE by SOC, preferred term

7.8.1 Adverse events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. System organ classes (if applicable) will be sorted according to the standard sort order specified by the EMA, preferred terms (if applicable) will be sorted by total frequency (within system organ class).

For further details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (4) [*KM Asset BI-KMED-BDS-HTG-0041*] and "Handling of missing and incomplete AE dates" (3) [*KM Asset* BI-KMED-BDS-HTG-0035].

The analysis of AEs will be based on the concept of treatment emergent AEs. This means that all AEs will be assigned to the screening phase, re-induction on-treatment period (i.e. re-induction treatment phase plus REP), maintenance on-treatment period (i.e. maintenance treatment phase plus REP) or off-treatment period (i.e. follow-up) as defined in Section 6.1. Adverse events occurring in the maintenance and re-induction periods will be separately described. Since only the start date of an AE is collected (without start time), any AE occurrence on the same day as the first re-induction or first maintenance spesolimab administration will be assigned to the respective on-treatment period. For patients who switch directly to maintenance treatment at week 12 of the re-induction period, adverse events occurring on this first day of maintenance treatment will be included in summaries of the maintenance period only. Exposure-adjusted adverse event incidence rates (per the primary endpoint) will be calculated using the following approach:

1) The exposure adjusted incidence rate (per 100 subject years) of a selected treatment emergent adverse event is defined as the number of subjects experiencing the adverse event per treatment group during time at risk divided by the total time of subjects at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 subject years), where:

2) Time at risk [subject years] = (date of onset of AE – study drug start date + 1) / 365.25

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For safety analysis on the post-flare treatment periods: Time at risk [subject years] = (date of onset of AE – first i.v. disease flare treatment start date + 1) / 365.25

For safety analysis on the disease flare treatment period: Time at risk [subject years] = (date of onset of AE – prior i.v. disease flare treatment start date + 1) / 365.25

3) If, for a subject, the selected treatment emergent adverse event didn't occur then the time at risk will be censored at min (date of death, date of end of applicable treatment period per Section 6.1, or date of cut-off if interim analysis performed). For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

4) Incidence rate [1/100 Subject years (pt-yrs)] = 100 * number of subjects with TEAE / Total TEAE-specific time at risk [subject years].

An overall summary of AEs will be presented. This overall summary will include summary statistics for the class of other significant AEs derived according to an adaptation of the ICH E3 (6) and for the class of AESIs.

The following are considered as AESIs (cf. CTP section 5.2.6.1):

- Infusion reactions including anaphylactic reaction
- Severe infections (according to RCTC grading)
- Opportunistic and mycobacterium tuberculosis infections
- Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
a. ALT or AST >5x ULN
b. ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
c. AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample

The investigator identified AESI will be captured from the eCRF and reported in the "Investigator reported AESI" table. In addition, user defined adverse event concepts (UDAEC) identified through specific search criteria will be reported separately (Table 7.8.1: 1).

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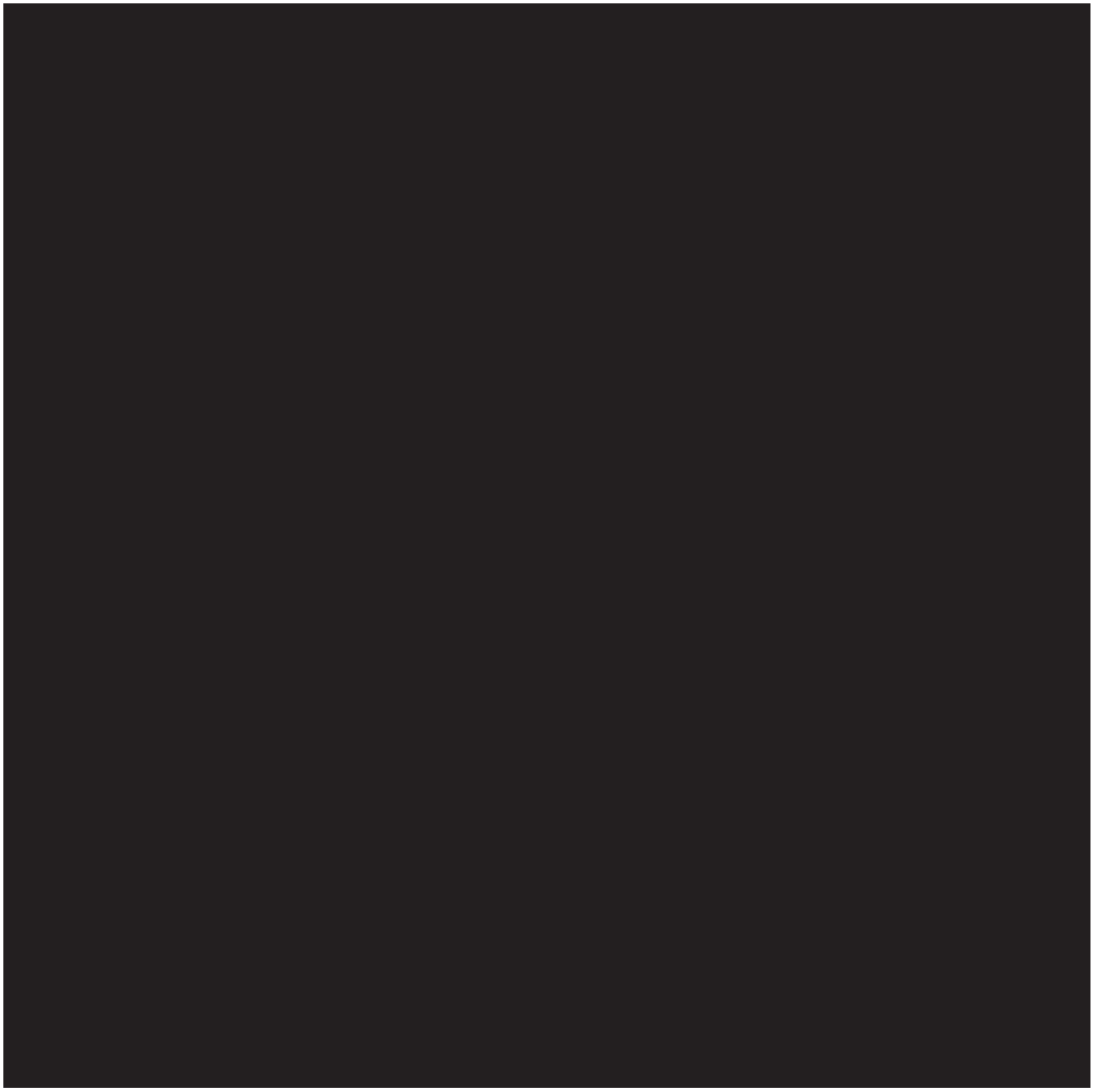

Adverse Events classified as ‘other significant’ will be reported using an adaptation of the ICH E3 (6) and will include those non-serious and non-significant AEs which were reported with ‘action taken = drug withdrawn’ or ‘action taken = reduced’.

The exposure-adjusted incidence rate and frequency of patients with AEs will be summarised by treatment, primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for patients with SAEs, patients with AESIs, patients with AE leading to discontinuation of the trial, patients with other significant AEs and User-defined Adverse Event Concepts (UDAEC) (see Table 7.8.1: 1). AEs will also be summarized by maximum intensity based on the RCTC measure (see Section 5.4.1).”

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For disclosure of AE data on ClinicalTrials.gov, the frequency of patients with non-serious AEs occurring with an incidence of greater than 5% (in preferred terms) will be summarised by primary system organ class and preferred term. The frequency of patients with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of non-serious AEs with an incidence of greater than 5% (in preferred terms) and the frequency of SAEs will be summarised.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5). Note that data from the central Laboratory will be used for all displays described below, unless otherwise specified.

For continuous safety laboratory parameters, normalized values will be derived. Normalisation means transformation to a standard unit and to a standard reference range. The process of normalisation, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (5). All analyses considering multiple times of the ULN (as described below) will be based on standardized and not normalized values. For continuous safety laboratory parameters, differences to baseline will be calculated.

Only patients with at least one available post-baseline value will be included in the analysis of an individual laboratory parameter. All individual laboratory data will be listed. Values outside the reference range will be flagged.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be based upon normalized values and provided by visit, including the last value on treatment, the minimum value on treatment and maximum value on treatment.

Laboratory values will be compared to their reference ranges; shift tables will be provided for the number of patients with a specific RCTC grade at baseline versus the grade at the last measurement on treatment, as well as the worst grade on treatment. These analyses will be based on standardized laboratory values.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on normalized converted lab values, i.e. using SI units. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities. Patients having an abnormal lab value at baseline will be presented separately. A separate listing will present potentially clinically significant abnormal lab values; for each functional lab group all patients' lab values will be listed, if there exists at least one lab value with clinically significant abnormality within the group.

The frequency of patients with AST or ALT elevations ≥ 3xULN, ≥ 5xULN, ≥ 10xULN, and ≥ 20xULN will be displayed based on standardized laboratory values. To support analyses of liver related adverse drug effects, the frequency of patients with AST and/or ALT ≥ 3xULN

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combined with a total bilirubin ≥ 2xULN in a 30 day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase < 2xULN and ≥ 2xULN (a patient can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin elevations).

The start of the 30 day time span is triggered by each liver enzyme elevation above the defined thresholds. This analysis will be based on standardized laboratory values. A graphical analysis of the ALT and total bilirubin during the on-treatment period will also be performed; the so called eDISH plot. In the graph, for each subject, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed for total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph in order to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3xULN and total bilirubin < 2xULN).

An additional display will be produced for the frequency of patients with an elevation of the ALT or AST > 3-fold ULN and with the appearance of one or more of the following TEAE: fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). An occurrence is flagged if, within +/- 7 days of the onset of an AST or ALT elevation > 3-fold ULN (including events which start or are ongoing through this interval), at least one of the following TEAE terms (excluding PT terms on the secondary path) is observed:

- ADAE.AEHLT = "Gastrointestinal and abdominal pains (excl oral and throat)";
- ADAE.AEDECOD in ("Vomiting","Fatigue","Nausea","Pyrexia")
- ADAE.CQ16NAM = "Skin Rash (BIcMQ narrow)

An occurrence is also flagged if a >5% proportion in the ratio of eosinophils to total white blood cells is observed in the same sample as the detected AST/ALT elevation.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate, body temperature, respiratory rate and body weight) will be descriptive in nature.

Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided and will include the last value during on-treatment period, the minimum value during on-treatment period, and the maximum value during on-treatment period (see Table 6.1:1 for definition of the on-treatment period).

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Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

No separate listing or analysis of ECG data will be prepared.

7.8.5 Other

7.8.5.1 Immunogenicity

The frequency and percentage of patients with ADAs to spesolimab will be presented by visit. ADA will be analyzed descriptively. A potential effect of ADA on PK and safety may be evaluated.

7.8.5.2 Extra-intestinal manifestation

During the course of the study's on-treatment period, the frequency and percentage of the presence of pre-defined EIM diagnoses will be summarized over time.

7.9 HANDLING OF DMC ANALYSES

An external DMC, independent of the trial and project teams, will be set-up to review all available un-blinded safety data as well as selected efficacy data at regular intervals following first-patient-in. A separate DMC SAP which describes the analyses required for assessment by the DMC will be produced. Further details are provided in a DMC charter.

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8. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Statistical Principles for Clinical Trials, current version
2	*001-MCS-40-413:* " Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*KM Asset* BI-KMED-BDS-HTG-0035 : "Handling of missing and incomplete AE dates", current version; KMED
4	*KM Asset BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
5	*KM Asset BI-KMED-BDS-HTG-0042:* " Display and Analysis of Laboratory Data", current version; KMED
6	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
7	001-MCG-159: "Reporting of clinical trials and project summaries", current version; IDEA for CON

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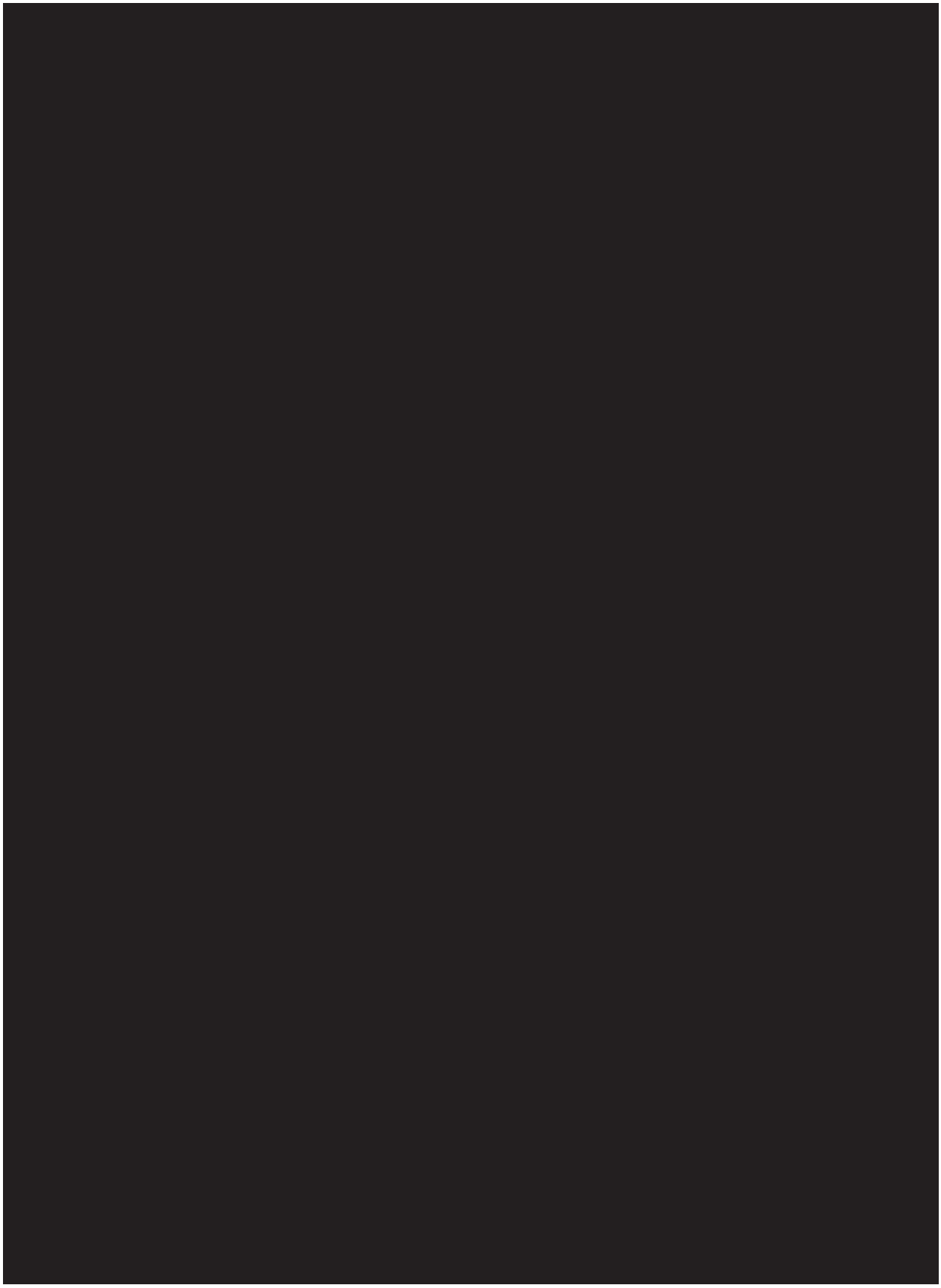

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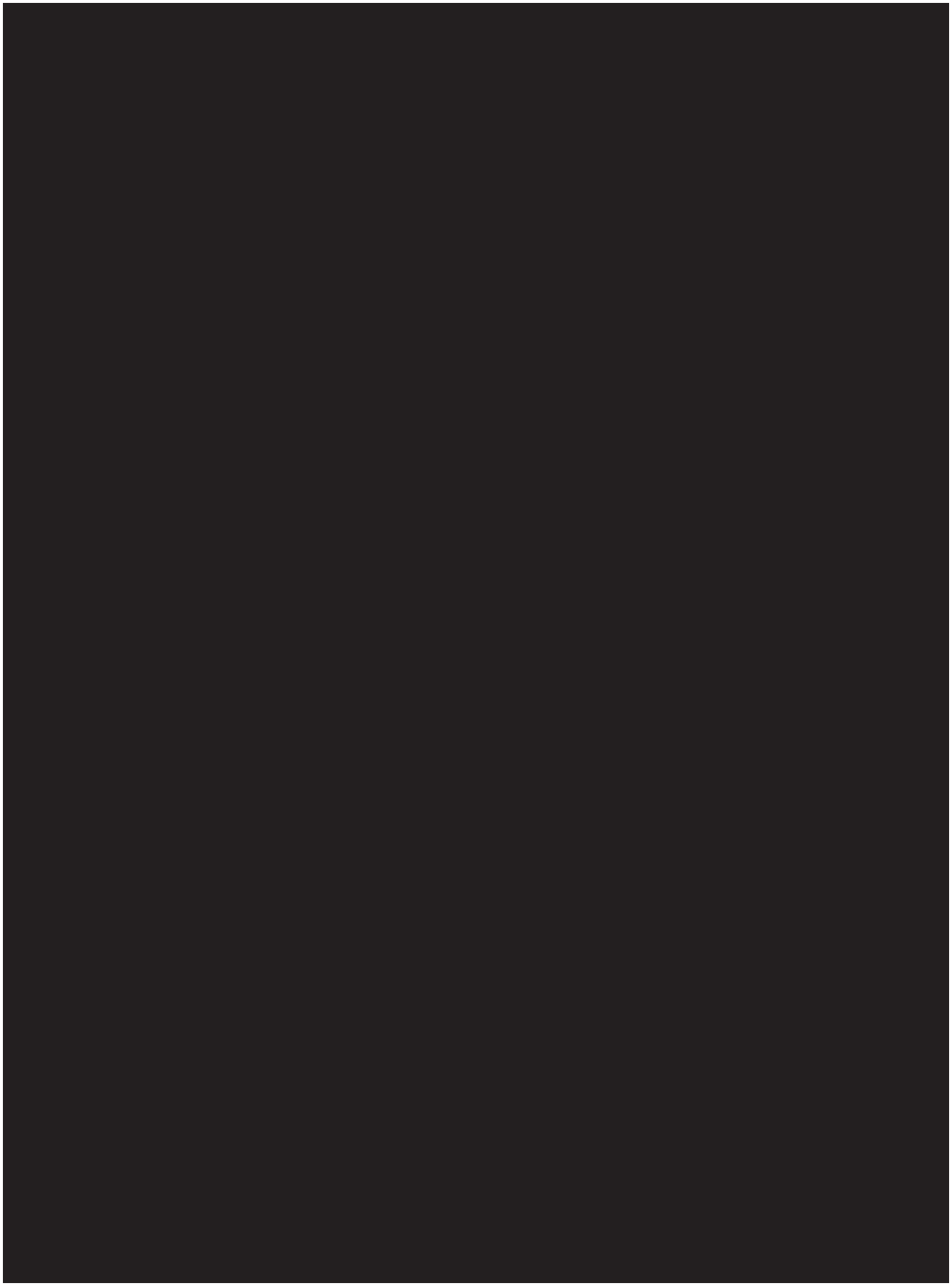

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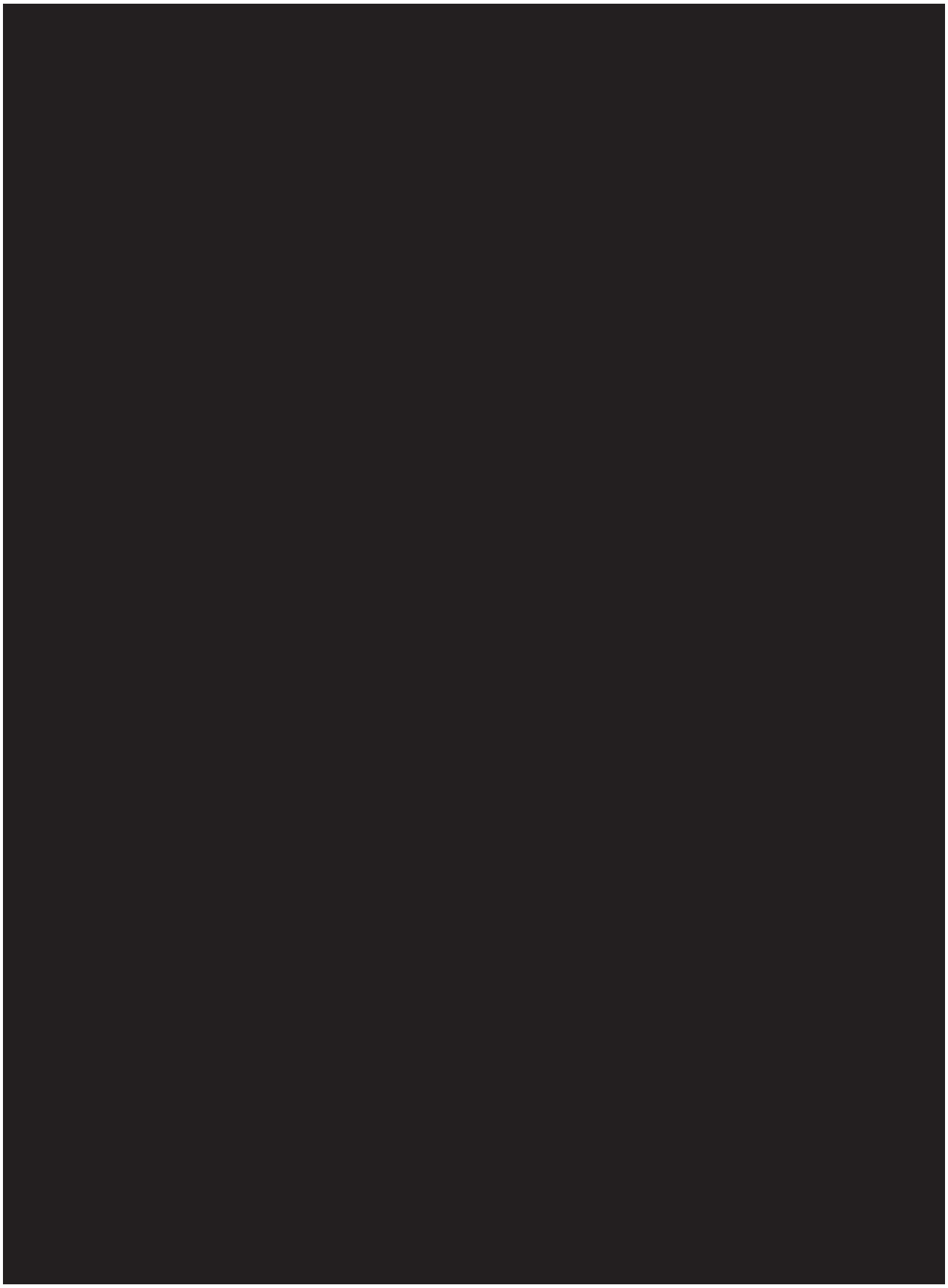

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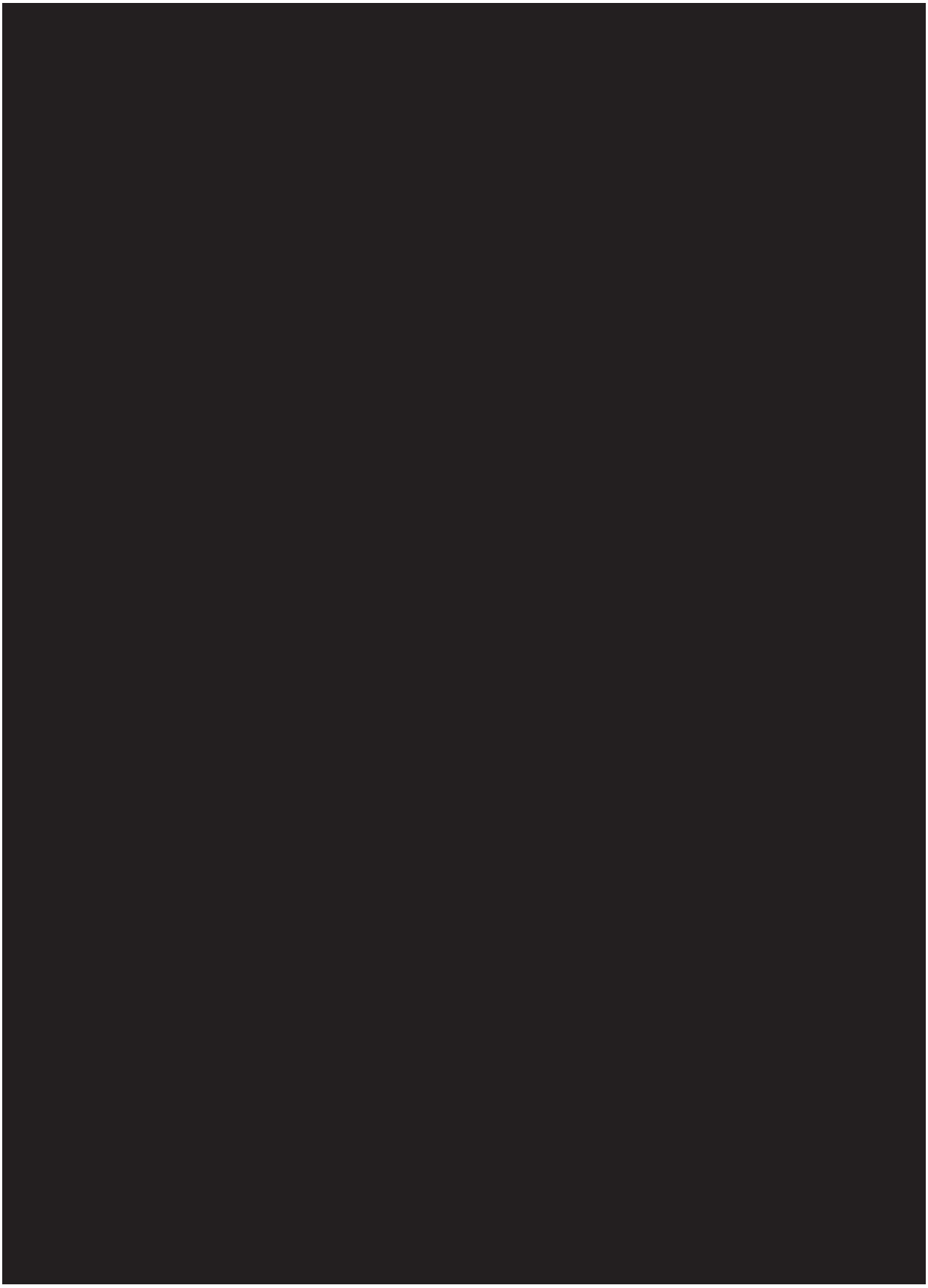

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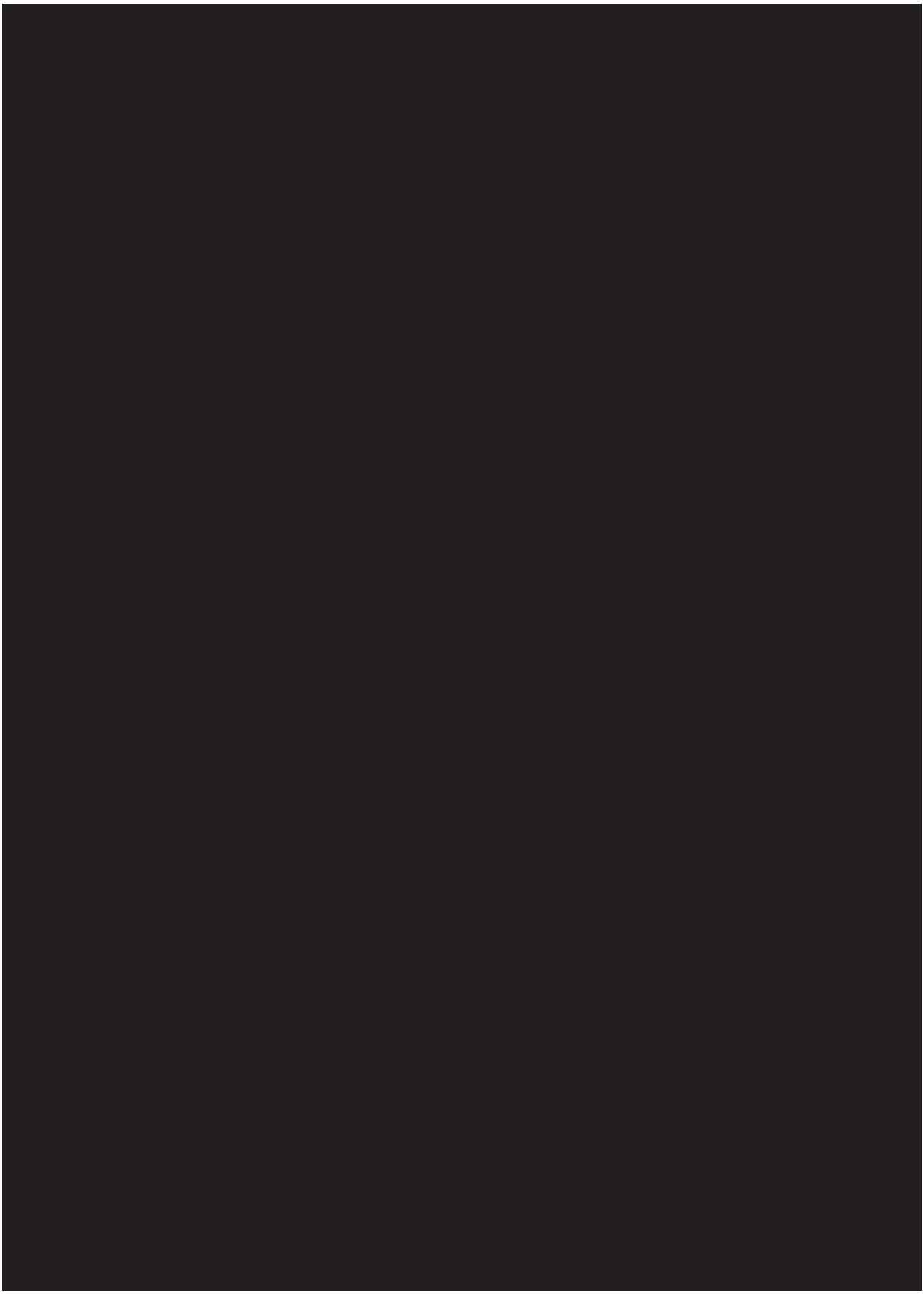

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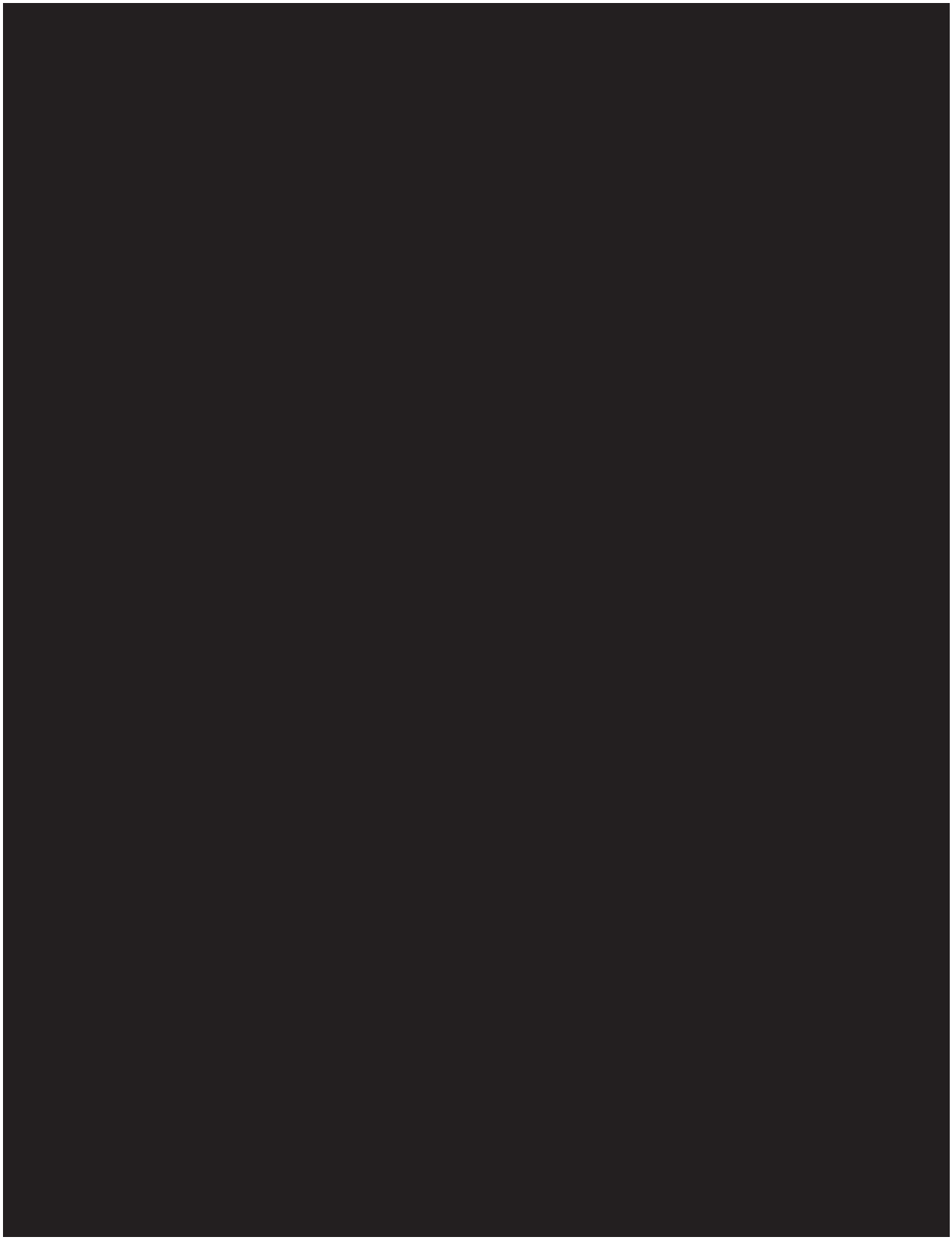

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10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	11-Oct-2018	[redacted]	None	This is the initial TSAP with necessary information for trial conduct.
2.0	25-Feb-2020		None	This is the final TSAP before first interim DBL.
3.0	29-Oct-2020		All	The pre-planned analysis are simplified and updated, including reducing endpoints, deleting compliance analysis, reducing subgroups to be analysed, more clarifications about treatment periods, and missing data handling for binary efficacy endpoints.
			Section 7.8.1	Categories of UDAEC are updated.
			[redacted]	
4.0	13-Jan-2021		Section 6.3	The name of patient set for analysis is updated from Treated set to be Safety analysis set.
			Section 6.7	The safety lab and vital sign over time for maintenance treatment is simplified.
			Section 7.8.1	Categories of UDAEC are updated.