TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c44359225-01**
BI Trial No.:	**1397-0013**
Title:	A randomised, double-blind, placebo-controlled, parallel group trial evaluating safety, tolerability, pharmacodynamics and pharmacokinetics of BI 1291583 one tablet once daily over 12 weeks versus placebo in adult patients with cystic fibrosis bronchiectasis (Clairafly™) revised protocol version 4 (c40742178-04)
Investigational Product(s):	BI 1291583
Responsible trial statistician(s):	
Date of statistical analysis plan:	17 OCT 2024
Version:	1.0
	Page 1 of 37

Proprietary confidential information
© 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved.
This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

1. TABLE OF CONTENTS

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

[redacted]

[redacted]

[redacted]

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

LIST OF TABLES

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
AUC	Area under the curve
[redacted]	
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
[redacted]	
CFB	Cystic Fibrosis Bronchiectasis
CFTR	Cystic fibrosis transmembrane conductance regulator
CFTR-MT	Cystic fibrosis transmembrane conductance regulator modulator therapy
[redacted]	
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum measured concentration of the analyte in plasma
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
[redacted]	
CTP	Clinical trial protocol
CTR	Clinical trial report
[redacted]	
DBL	Database lock
DDR	Data Delivery Request
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

Term	Definition / description
eCRF	Electronic case report form
EDMS	Electronic document management system
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EoS	End of study
EoT	End of treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
[redacted]	
HR	Hazard ratio
ICE	Intercurrent event
ICH	International Conference on Harmonisation
iPD	Important protocol deviation
[redacted]	
KM	Kaplan Meier
[redacted]	
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
LPLT	Last patient last treatment
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MMRM	Mixed model with repeated measurements
NCFB	Non-Cystic Fibrosis Bronchiectasis
NE	Neutrophil elastase
[redacted]	
PD	Pharmacodynamics
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter set

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

Term	Definition / description
PN	Preferred name
[redacted]	
PT	Preferred term
pt-yrs	patient-years
Q1	First quartile
Q3	Third quartile
[redacted]	
REML	Restricted maximum likelihood
REP	Residual effect period
RS	Randomised set
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
[redacted]	
SI	Système international d'unités
SMQ	Standardised MedDRA Query
SOC	System organ class
[redacted]	
SS	Screened set
TEAE	Treatment-emergent adverse event
TMF	Trial master file
[redacted]	
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range
[redacted]	
WHO-DD	World Health Organization – Drug Dictionary

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

3. INTRODUCTION

As per ICH E9 (9.1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the 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 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, randomisation.

This is a randomised, double-blind, placebo-controlled, parallel group trial evaluating safety, tolerability, pharmacodynamics and pharmacokinetics of BI 1291583 5 mg qd over 12 weeks versus placebo in adult patients with cystic fibrosis Bronchiectasis (Clairafly™). [redacted]

Unless otherwise noted, SAS® Version 9.4 will be used for all analyses.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

[redacted]

4.2 CLARIFICATION

The terms ‘subject’ and ‘patient’ will be used interchangeably in this document.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is the occurrence of any treatment-emergent adverse event (TEAE), up to 16 weeks after first drug administration. Details on the concept of TEAE are described in Section 7.8.1.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

5.2.2.1 Relative change from baseline in neutrophil elastase (NE) activity in sputum at Week 8 after first drug administration

This endpoint will be derived based on NE activity levels at pre-specified visits over 12 weeks using log10 transformed values. The relative change from baseline in sputum NE at Week 8 will be estimated as described in Section 7.5.2.1.

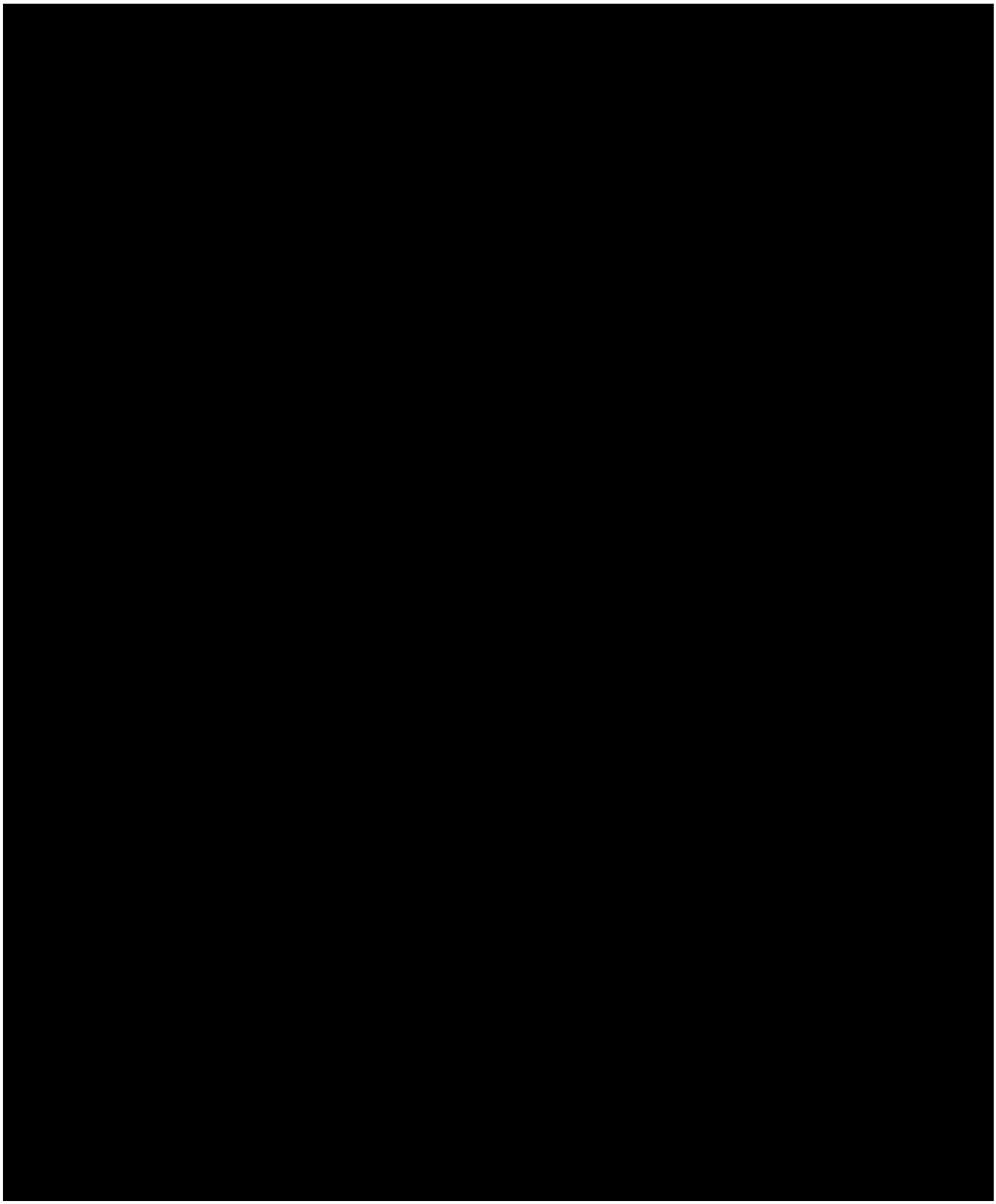
5.2.2.2 Pharmacokinetic endpoints

The following pharmacokinetic endpoints are assessed for BI 1291583 5 mg only.

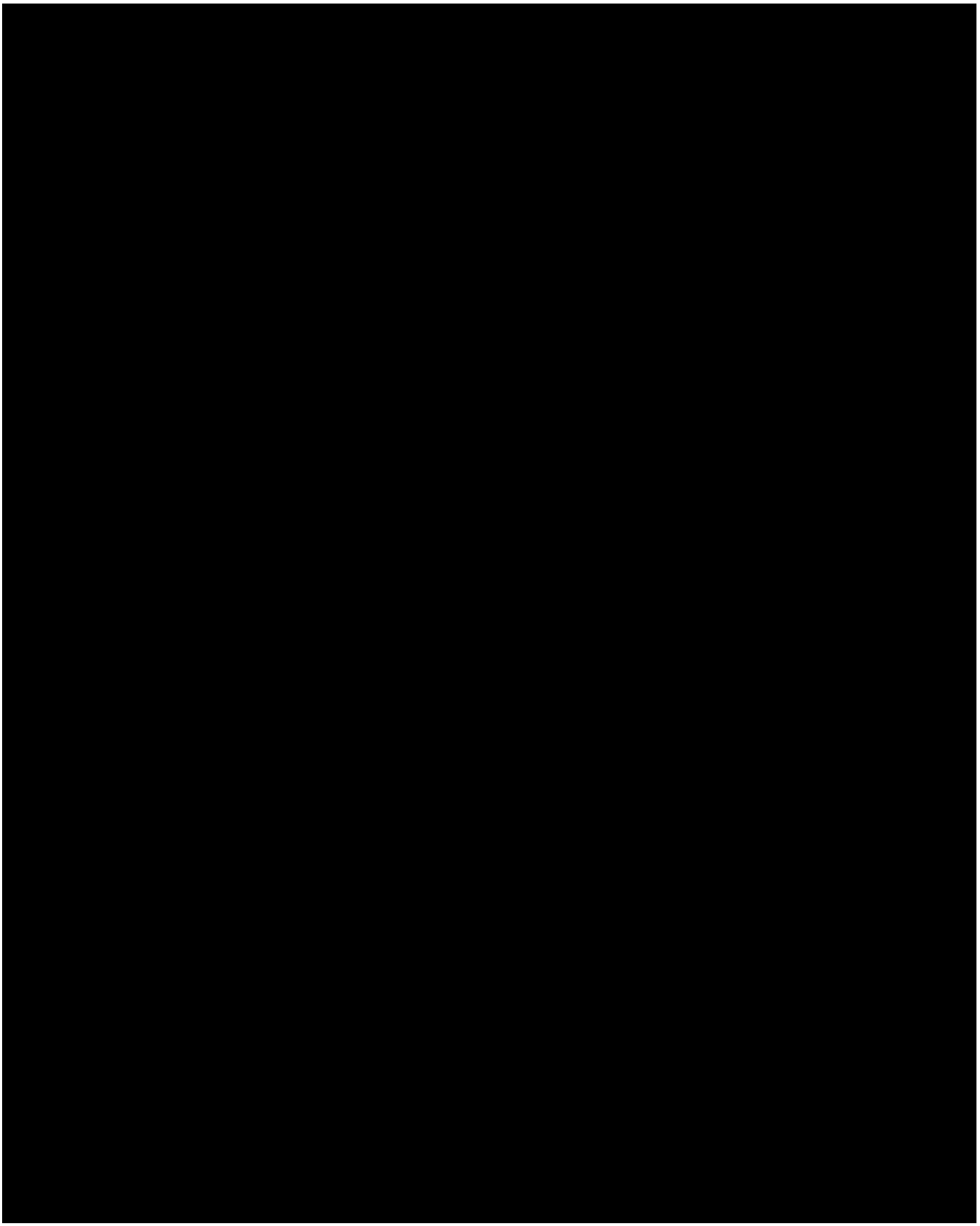
- AUCτ: AUC (area under the curve) over a dosing interval for the first dose
- Cmax: maximum concentration for the first dose
- AUCτ,ss: AUCτ at steady state after multiple dosing of BI 1291583 5 mg qd
- Cmax,ss: Cmax at steady state after multiple dosing of BI 1291583 5 mg qd

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

Pharmacokinetic endpoints from the population PK analysis and/or Population PK/PD analysis will be defined in the Population PK Analysis Plan. Refer to Section 7.2.4.2 of the CTP for details of the analyses of the pharmacokinetic endpoints.



Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.



Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

6.1.1 Analysis phases

For safety analyses, data collected between first drug intake up to the end of residual effect period (REP) will be considered as "on-treatment" period for the evaluation.

Table 6.1.1: 1 Analysis phases

Study analysis phase	Label	Start (included)	End (excluded)
Screening	**Screening**	Date of informed consent at 12 a.m.	Date/time of first drug administration
Treatment	**Placebo** **BI 5 mg** respectively	Date/time of first administration of study drug	12:00 a.m. on day after last drug administration, or 12:00 a.m. on day after last contact date (whichever occurs first)
Residual effect period	**Residual effect period**	12:00 a.m. on day after last administration of study drug	12:00 a.m. on day after last administration of study drug + REP (28 days)
Follow-up [1]	**Follow-up**	12:00 a.m. on day after last administration of study drug + REP (28 days)	12:00 a.m. on day after last contact date

[1] This phase exists only in those subjects whose last contact date is more than 28 days after last trial drug administration.

6.1.2 Treatment grouping

All analyses will be conducted on the TS, with subjects grouped by randomised treatment assignment.

Subjects that received wrongly assigned kits during study will be reviewed shortly after unblinding and any decision to assign these subjects to different treatment arms compared to the above rules will be documented in the decision log (9.2).

6.2 IMPORTANT PROTOCOL DEVIATIONS

Protocol deviations identified during the trial will be discussed at the clinical quality monitoring meetings or at the report planning meeting prior to DBL. Handling of important protocol deviations (iPDs) in analysis is included in the DV domain specifications and stored within the Trial Master File (TMF) in Electronic Document Management System (EDMS). An overview of the number of patients with iPDs will be presented to demonstrate the adherence to the CTP.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

The process of identification of iPDs is according to "Identify and Manage Important Protocol Deviations (iPD)" (9.3).

6.3 INTERCURRENT EVENTS

The expected intercurrent events (ICE) of interest are:

1. Treatment discontinuation
2. Initiation of macrolides for chronic use during trial
3. Initiation of cyclic doses of antibiotic treatment for chronic use during trial
4. Initiation or change of CFTR-MT during the trial

ICE #1 will be collected as disposition data in eCRF; ICE #2, #3 and #4 will be reported as iPDs and confirmed prior to unblinding. The number and percentage of patients reporting each type of intercurrent event will be summarized by treatment group.

In general, analysis strategies to address ICEs that reflect the treatment effect estimation are following ICH E9 (R1) (9.4). The primary objective analysis will be based on while-on-treatment strategy, where data collected up to the end of residual effect period (REP) will be included for the primary endpoint analysis.

For secondary objective analysis, ICEs will be handled using the treatment policy strategy, i.e., data collected regardless of intercurrent events will be used when analyzing secondary endpoints.

6.4 SUBJECT SETS ANALYSED

- Screened set (SS):
  This subject set includes all subjects who signed informed consent.
- Randomised set (RS):
  This subject set includes all randomised subjects, whether treated or not.
- Treated set (TS):
  This subject set includes all subjects who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
- PK parameter analysis set (PKS):
  This subject set includes those subjects in the TS with at least one valid plasma concentration value available.
- [redacted]

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

Table 6.4: 1 Planned analysis per subject set

Class of analysis	Subject set			
	SS	TS	PKS	[redacted]
Disposition	X			
Demographic & baseline characteristics		X		X
Safety & treatment exposure		X		
PK			X	
Efficacy		X		
[redacted]				

Note that the number of subjects with available data for an endpoint may differ.

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, missing data will not be imputed. For specific analysis, technical details of missing data handling rules are as follows:

Primary objective analysis

Missing or incomplete AE dates are imputed according to BI standards (9.5).

Secondary objective analysis

- Missing data will not be imputed for biomarker endpoints. BLQ is not considered as missing data, however, it will be imputed as half of Lower Limit of Quantitation (LLOQ).
- Missing data and outliers of PK data are handled according to BI standards (9.6).

[redacted]

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For all parameters (except for biomarkers), baseline is defined as the last non-missing value prior to first administration of trial medication, or on the same date of first drug administration, if assessment times are not collected (e.g., vital signs, laboratory tests).

For specific assessments, multiple measurements are planned prior to first drug intake (e.g., at Visit 1 or 2). To derive the baseline, specific rules will apply as shown in Table 6.7: 1.

According to CTP Section 5.4.1.3.2 Sputum sample collection at site, if sputum samples do not meet the sputum collection criteria as defined in the ISF/Lab Manual, it is generally possible that the patient returns the next day to provide the sputum sample. Baseline sputum measurement could be on or prior to the first drug administration + 1 day.

Table 6.7: 1 Derivation of baseline for assessments with multiple measurements prior to first drug administration

Parameter	**Baseline value derivation**
Biomarkers based on sputum	Mean of all available valid measurements collected up to date of first study drug administration + 1 day
Murray sputum colour chart	Last valid measurement collected up to date of first study drug administration + 1 day
NEATstik®	Mean of all available valid samples collected up to date of first study drug administration + 1 day

Measurements taken after first administration of trial treatment will be considered either on- or off-treatment values based on the definition in Table 6.1.1: 1. Visit windowing will be performed as described in the tables below, in order to assign data to the relevant study visit based on the actual day of the assessment. Data will be analyzed using the re-calculated visits in the statistical tables. However, in the listings, all visits performed will be displayed (even if outside time-window), along with the re-calculated visit. The date of first treatment intake will be used as Study Day 1 for the time windowing. If more than one value is available within one time window the one which is closest to the planned time/day is used for analysis. In case two values are equidistant from the planned time/day, then the last one will be picked.

Analysis of AE data (including findings in 12-lead ECG assessments or physical examinations), potentially clinically significant abnormal laboratory values, concomitant medication or non-drug therapies will not be based on visits and thus no assignment to time windows is necessary. For this type of data, a safety analysis ‘on-treatment’ concept will be used depending on their actual onset dates.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

Table 6.7: 2 Time windows for assignment of safety assessment – laboratory

Visit number (CTP)	Visit label (analysis)	Planned Day	Time window [days]		
			Window per CTP	Start (analysis)	End (analysis)
V1	**Screening**	-42	≥7d prior to V2	All pre-baseline measurements	
V2	**Baseline**	1	± 0	NA	Date/time of first administration of study drug
V3	**Week 1**	8	± 3	Start of on-treatment phase[1]	18
V4	**Week 4**	29	± 3	19	43
V5	**Week 8**	57	± 3	44	71
V6	**Week 12**	85	± 3	72	End of on-treatment phase[1]
EoS	**Follow-up**	113	+ 7	All post-treatment measurements after last drug intake + REP	

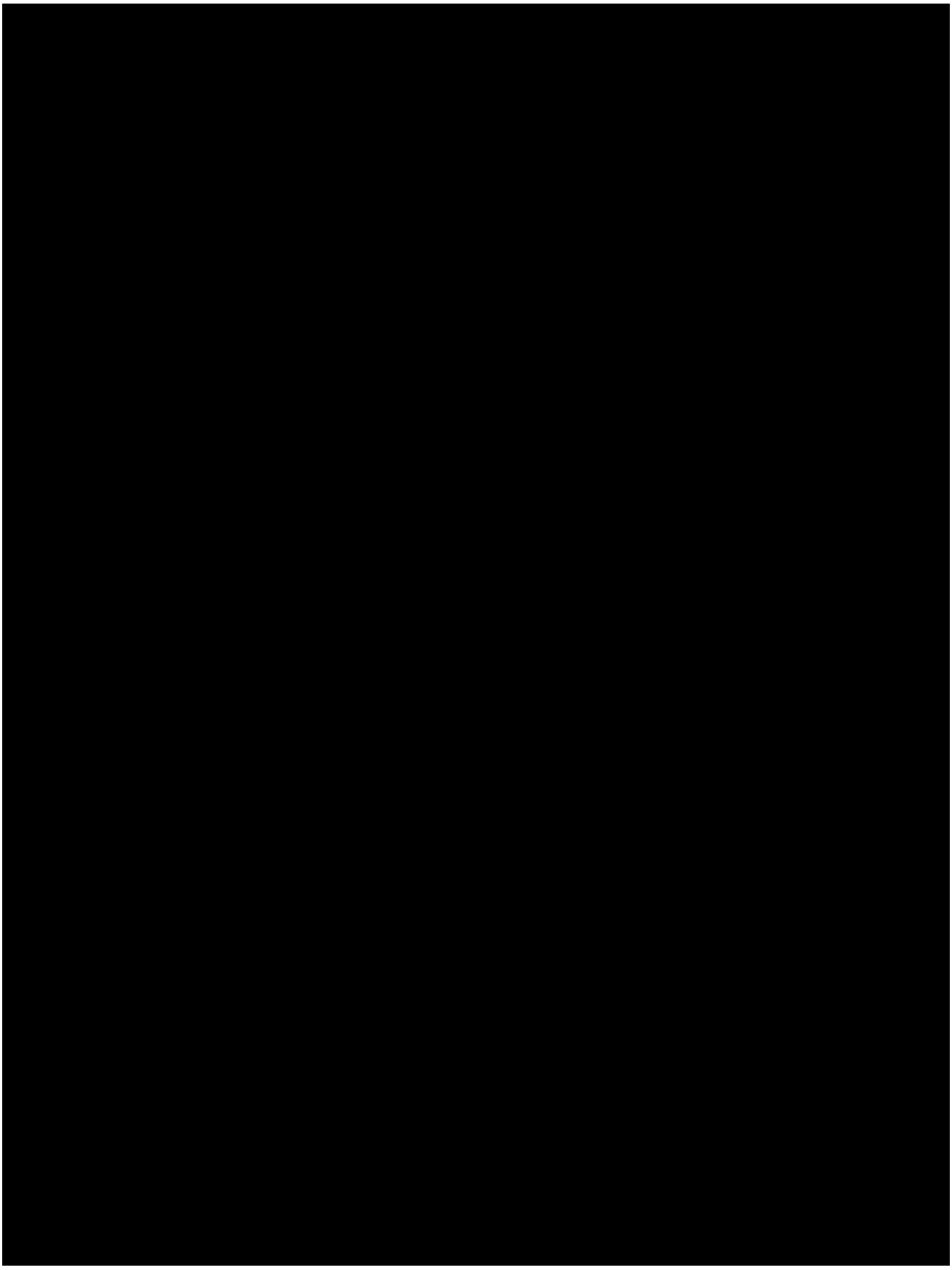
[1] As defined in table 6.1.1: 1.

Table 6.7: 3 Time windows for assignment of biomarkers assessed in sputum

Visit number (CTP)	Visit label (analysis)	Planned Day	Time window [days]		
			Window per CTP	Start (analysis)	End (analysis)
V1	**Screening**	-42	≥7d prior to V2	All pre-baseline measurements	
V2	**Baseline**	1	± 0	NA	Date/time of first administration of study drug
V3	**Week 1**	8	± 3	Start of on-treatment phase[1]	18
V4	**Week 4**	29	± 3	19	43
V5	**Week 8**	57	± 3	44	71
V6	**Week 12**	85	± 3	72	Last drug administration
EoS	**Safety Follow-up**	Last drug administration + 28		All measurements after last drug administration + 1	All measurements before last drug administration + 36

[1] As defined in table 6.1.1: 1.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.



Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

For all variables with a sparse sampling schedule that does not match the schedules in the above tables, the screening, baseline and follow-up phase will follow the same rules, while the start and end days of the on-treatment time windows will be equidistant from the planned visit day.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow BI standards (9.7). For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max. In descriptive statistics tables, mean, SD and median will be rounded to one additional digit than the raw individual value. In case extreme data outside of the expected range are observed, quartiles and percentiles will be presented additionally.

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 (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

A table in the CTR will present the number of subjects screened, randomised and treated. The number of subjects prematurely discontinuing their study treatment will be shown with the reasons for discontinuation.

Descriptive statistics will be provided for demographics and baseline disease characteristics, presented by treatment group and overall total, based on the TS.

7.1.1. Demographics

- Age [years]
- Sex
- Race
- Ethnicity
- Country
- Region
- Weight [in kg]
- Height [in cm]
- BMI: Body mass index (BMI) [kg/m^2]: Weight [kg] / (Height [m] × Height [m])
- History of Cigarette Use (Never, Current, Former)
- Smoking Pack Years (continuous variable)
- Smoking Pack Years (<20, 20-40, >40)

[redacted]

7.1.2. Baseline disease characteristics

- Number of exacerbations requiring antibiotics in the past 12 months (categories [1, ≥2] and [1, 2, 3, ≥ 4])
- Treatment with cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy (yes vs no) based on concomitant therapy information
- *P. aeruginosa* status (positive vs negative) based on actual lab results

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

7.1.5. Baseline sputum assessment

- Neutrophil Elastase in sputum (continuous variable and categorical: <25th percentile, 25th – 75th percentile, ≥75th percentile)
- NEATstik score
- Murray sputum colour

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diagnosis and relevant medical history as well as non-drug therapies will be included as coded items using the current Medical Dictionary for Regulatory Activities (MedDRA) version in use at BI at the time of database lock. They will be summarized by MedDRA system organ class (SOC) and preferred term (PT) and will be descriptively presented by treatment group and overall total, based on TS. The CTR table will show the counts of patients with a Baseline condition in each SOC present (SOC sorted by standard European Medicines Agency [EMA] order) and then the conditions (PTs) under that SOC in descending order of overall prevalence.

Concomitant medication is defined as:

- Ongoing at the start of trial medication intake
- Starts within the on-treatment period (see CTP Section 6.2 for a definition of study phases)

Concomitant medications will be coded according to the most recent version of the World Health Organization – Drug Dictionary (WHO-DD) at the time of database lock. Concomitant medication use will be summarized by ATC and preferred name (PN) will use the ATC3 code, and will be sorted by alphabetical ATC class and decreasing frequency of PN in all patients within ATC class. Concomitant medications will cover the whole study duration and will be

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

presented by treatment group and overall total. Separate tables will be prepared for concomitant medications were ongoing at the start of trial medication intake, or started within the on-treatment period.

7.3 TREATMENT COMPLIANCE

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

Treatment compliance (yes/no) will be based on the adherence to the expected range of 80-120% for the number of tablets actually taken vs. the number of tablets which should have been taken as directed by the investigator, see CTP Section 4.3. Number of subjects with or without treatment compliance will be summarized by treatment group per visit and overall.

7.4 PRIMARY OBJECTIVE ANALYSIS

The primary objective is to estimate the number and percentage of patients who have at least one TEAE during the trial. The assessment will be performed on TS.

7.4.1 Main analysis

The main analysis is the same as safety analysis of patients who have at least one TEAE during the trial. Refer to Section 7.8.1 for more details.

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

7.5.2.1 Relative change from baseline in NE activity in sputum at Week 8 after first drug administration

The analysis of this endpoint will be based on the TS and will be performed on log10-transformed data.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

Baseline NE activity in sputum is defined as the mean value of Screening and Week 0 prior to the first treatment intake. Baseline NE activity will be summarized as continuous variable, as well as presented by categories as: <25th percentile, 25th-75th percentile, and >75th percentile.

Descriptive statistics for absolute NE activity on log10 transformed scale will also be presented by timepoint and treatment group.

% inhibition analyses

The assessment of NE activity will further comprise the analysis of the % inhibition of NE activity. For the purpose of descriptive analysis, for each time point including baseline, % inhibition will be calculated as:

$$NE\ inhibition_t = \frac{NE\ activity_{baseline} - NE\ activity_t}{NE\ activity_{baseline}} \times 100$$

Descriptive statistics for absolute % inhibition by timepoint and treatment group will be presented. Maximum % inhibition (on patient level during the trial) will be summarized by treatment group. The median % inhibition of NE activity per treatment group over time will be plotted. All timepoints will be taken into account, analysis windows will be applied to the % inhibition of NE activity.

Change from baseline analyses

Change from baseline in log10-transformed NE activity in sputum up to Week 12 after first drug administration will be analysed by descriptive statistics and graphical representations across all visits. Descriptive statistics of change from baseline will be presented by timepoint and treatment group.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

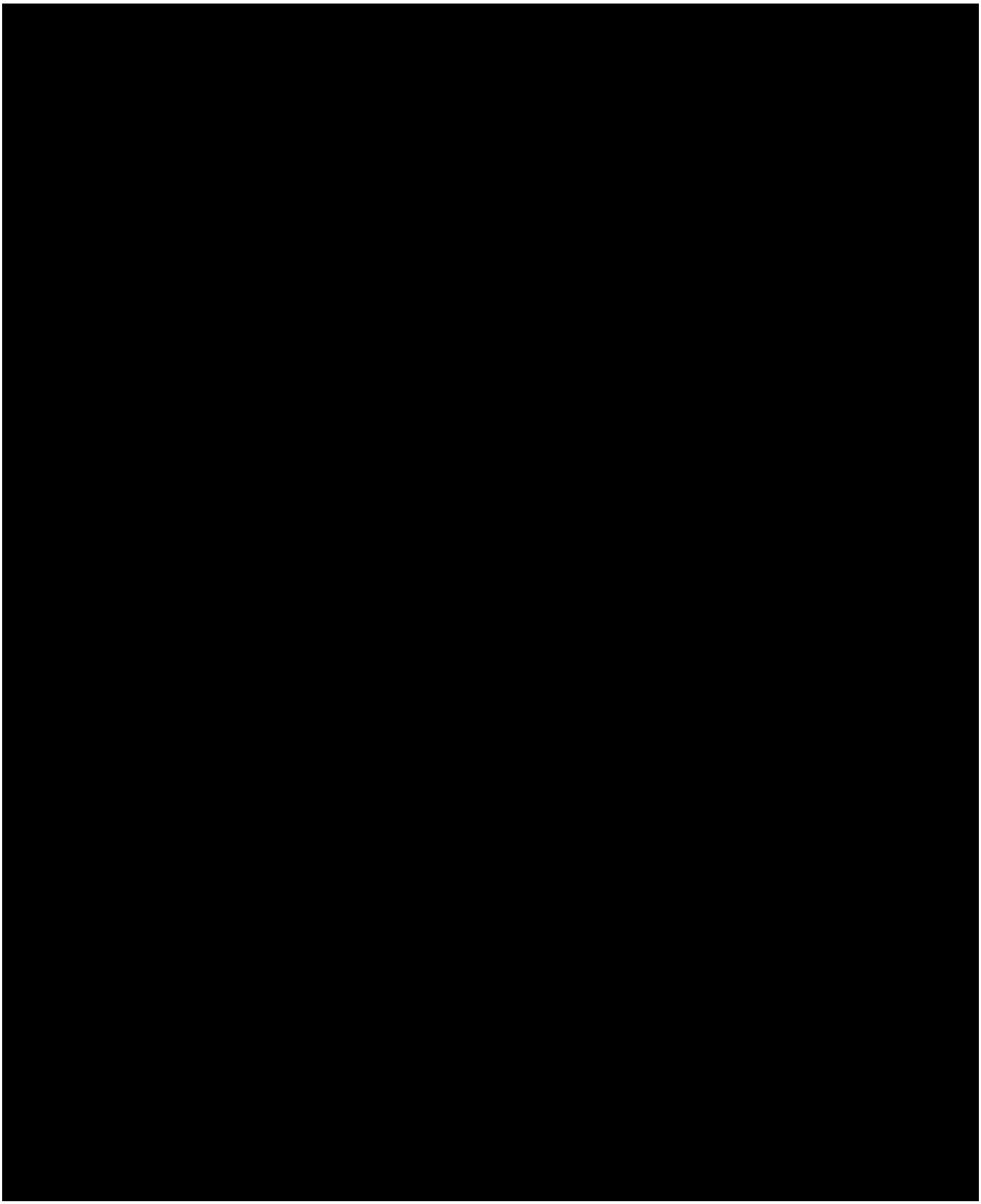
[redacted]

7.5.2.2 Pharmacokinetic endpoints

The analyses of PK parameters AUCτ, Cmax, AUCτ,ss and Cmax,ss are performed according to (9.8) based on the PKS. AUCτ and Cmax for the first dose as well as at steady state (AUCτ,ss and Cmax,ss) will be summarized for the active treatment group.

[redacted]

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.



Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

[redacted]

7.7 EXTENT OF EXPOSURE

The date of first drug administration is recorded at Visit 2 (Day 1). The following parameters will be calculated to assess extend of exposure:

Duration of exposure [months] = (date of last administration – date of first administration +1 day) / 30.5

Duration of exposure in categories: ≤1 months (31 days); >1 months (31 days) to ≤ 2 months (62 days); > 2 months (62 days) to ≤3 months (91 days)

Total dose [mg]: Duration of exposure [days] × actual dose [mg]

Finally, first dose and last dose administration, and the reason for premature treatment discontinuation will be listed for each subject.

[redacted]

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

7.8 SAFETY ANALYSIS

All safety analyses will be presented by randomised treatment and overall total, based on the TS.

7.8.1 Adverse Events

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

The analysis of AEs will be based on the concept of TEAEs. All AEs occurring between first drug intake and end of REP, a period of 28 days after the last drug intake will be assigned to the on-treatment period for evaluation. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after last drug intake + REP of 28 days will be assigned to 'follow-up' (for listings only). For details on the treatment definition, see Section 6.1.1.

According to ICH E3 (9.9), 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious AE that led to an "action taken = study drug withdrawn".

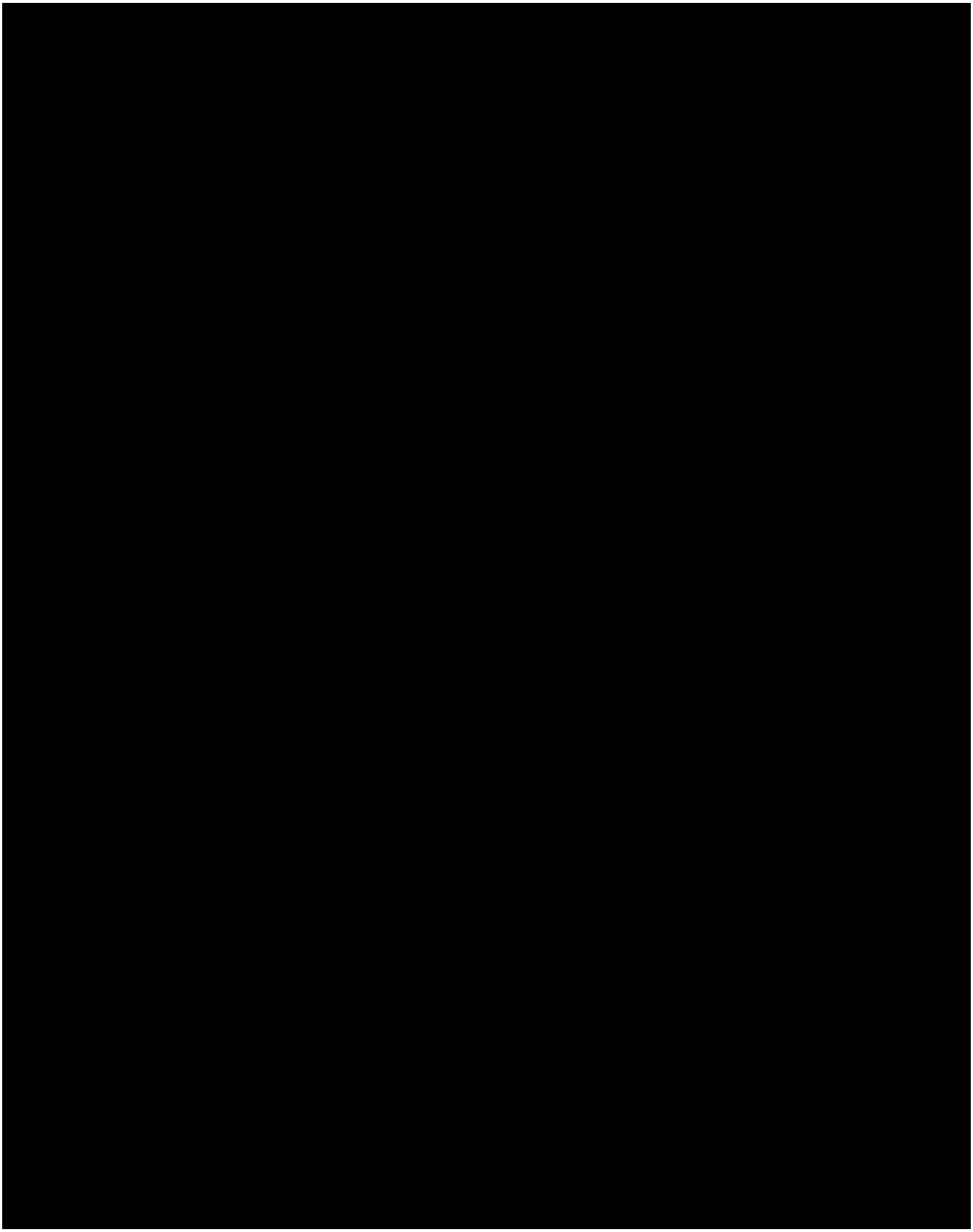
An overall summary of TEAEs will be presented by treatment group. In addition, the following displays will be provided:

- Patients with any AE
- Patients with AEs by worst intensity
- Patients with severe AEs
- Patients with serious AEs (reason for seriousness included as per CRF)
- Patients with investigator reported drug-related AEs
- Patients with AEs leading to death
- Patients with adverse events of special interest
- Patients with AEs leading to discontinuation of study treatment
- Patients with other significant AEs

The frequency of subjects with AEs will be summarized by treatment, primary SOC and PT (MedDRA version used will be displayed in the tables).

The SOC will be presented in descending frequency of the total number of AEs for each system organ class in all patients. The PTs within each SOC will be ordered by descending prevalence in all patients. Cases with multiple occurrences of the same PT will be counted only once under that PT. Patients with AEs in several PTs within the same SOC will be counted only once at the SOC level.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.



Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

7.8.2 Laboratory data

The analyses of laboratory parameters will be descriptive in nature and will be based on the BI guidance "Handling, Display and Analysis of Laboratory Data" (9.10).

For continuous safety laboratory parameters, normalized values will be derived. Normalization means transformation to a standard unit and to a standard reference range. The process of normalization, 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. All analyses considering multiple times of the ULN will be based on standardized values. For continuous safety laboratory parameters, differences to baseline will be calculated.

Only subjects 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 of the normal reference range will be flagged.

For quantitative safety laboratory parameters, descriptive statistics of laboratory values over time and change from baseline will be based upon normalized values and provided by analysis visit, including summaries of the last value on treatment, the minimum value on treatment and maximum value in the treatment period.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on standardized lab values, i.e., using SI units. Frequency tables will summarize the number of subjects with potentially clinically significant abnormalities.

Subjects having an abnormal lab value at baseline will be presented in a listing separately. A separate listing will present all subjects with potentially clinically significant lab values. In addition, a summary table will be prepared for the values outside of the clinically significant reference range including frequency and percentage of subjects with abnormal values for will be presented by treatment group.

A graphical analysis of the ALT and total bilirubin during the on-treatment period will also be performed according to the BI guidance, the so-called eDISH plot. For cases whose total bilirubin and ALT values meet the criteria for Hy's Law (maximum total bilirubin two or more times the ULN for the parameter, and the maximum ALT value three or more times its ULN) at any individual visit will be presented in a listing, showing the constituent values plus the associated alkaline phosphatase value at that time and the full course of available values for that case obtained during the study.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. The analysis of vital signs (aural body temperature, pulse rate, systolic and diastolic blood pressure) and physical examination results (height, body weight) are assessed according to time windowing rules described in Section 6.7.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

7.8.4 ECG

Clinically relevant abnormal findings in ECG will be reported as AEs by the investigator. No separate listing or analysis of ECG data will be prepared.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study / Follow-up visit and all data has been entered and cleaned as defined in the “Data Ready to be Unblinded and / or Final Trial Closure Notification” (RUN) form.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

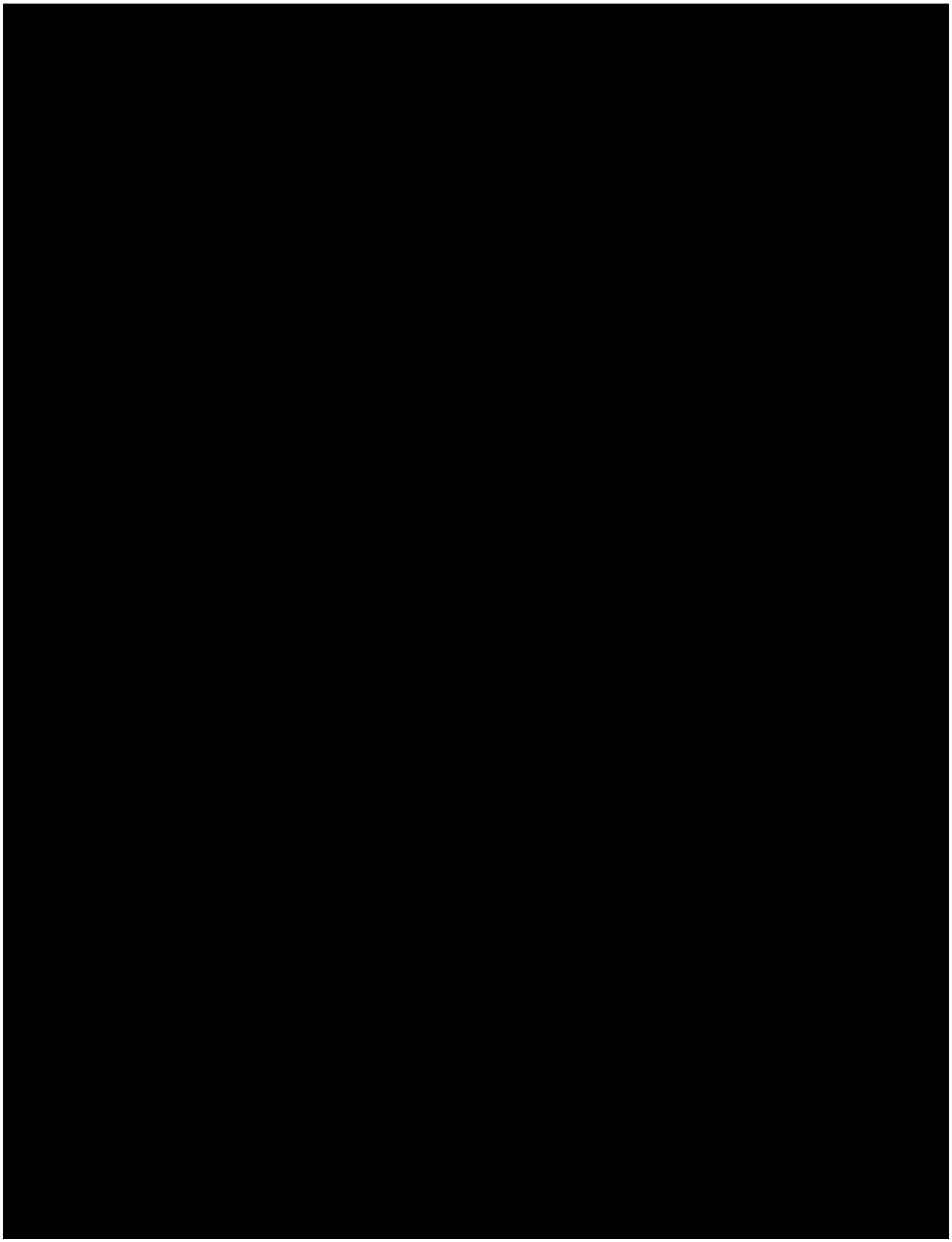
9. REFERENCES

9.1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
9.2	*BI-VQD-12682-S-G_50-415_AD-03:* "Clinical Trial Analysis Decision Log (template)", current version, group / owning department "Med Biostatistics & Data Sciences", DMS for controlled documents.
9.3	*BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, group / owning department "Med Clinical Development & Operations", DMS for controlled documents.
9.4	EMA/CHMP/ICH/436221/2017: "ICH E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials", European Medicines Agency, 2020
9.5	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version, group / owning department "Med Biostatistics & Data Sciences", DMS for controlled documents.
9.6	*BI-KMED-TMCP-HTG-0025*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, group / owning department "Med Translational Medicine Clinical Pharmacology", DMS for controlled documents.
9.7	*BI-KMED-BDS-HTG-0045*: "Standard for Reporting of Clinical Trials and Project Summaries", current version, group / owning department "Med Biostatistics & Data Sciences", DMS for controlled documents.
9.8	*BI-KMED-TMCP-MAN-0014:* "Noncompartmental PK/PD Analyses of Clinical Studies", current version, group / owning department "Med Translational Medicine Clinical Pharmacology", DMS for controlled documents.
9.9	*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, EMA webpage.
9.10	*BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version, group / owning department "Med Biostatistics & Data Sciences", DMS for controlled documents.

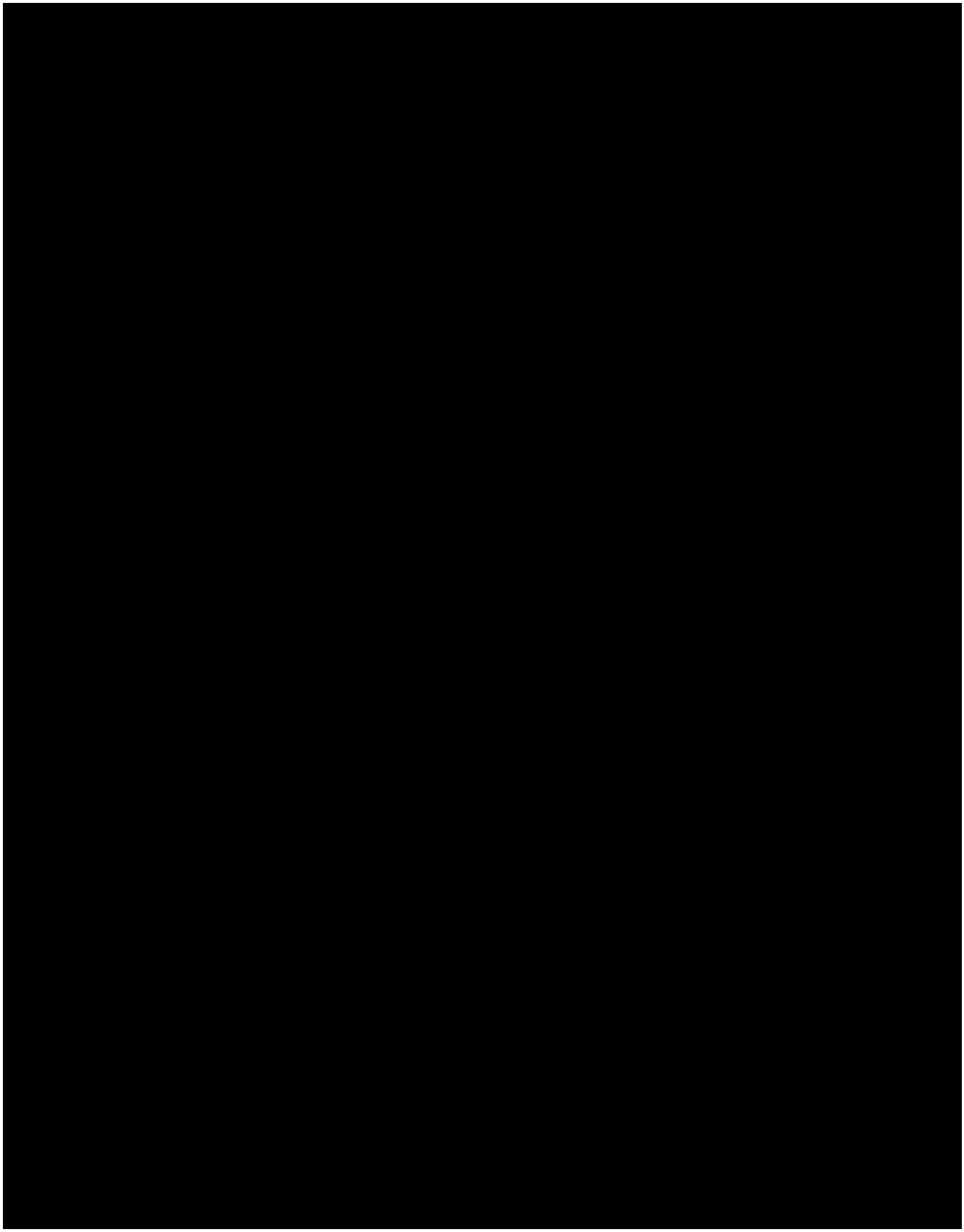
Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

9.11	[redacted]
9.12	
9.13	
9.14	
9.15	
9.16	
9.17	

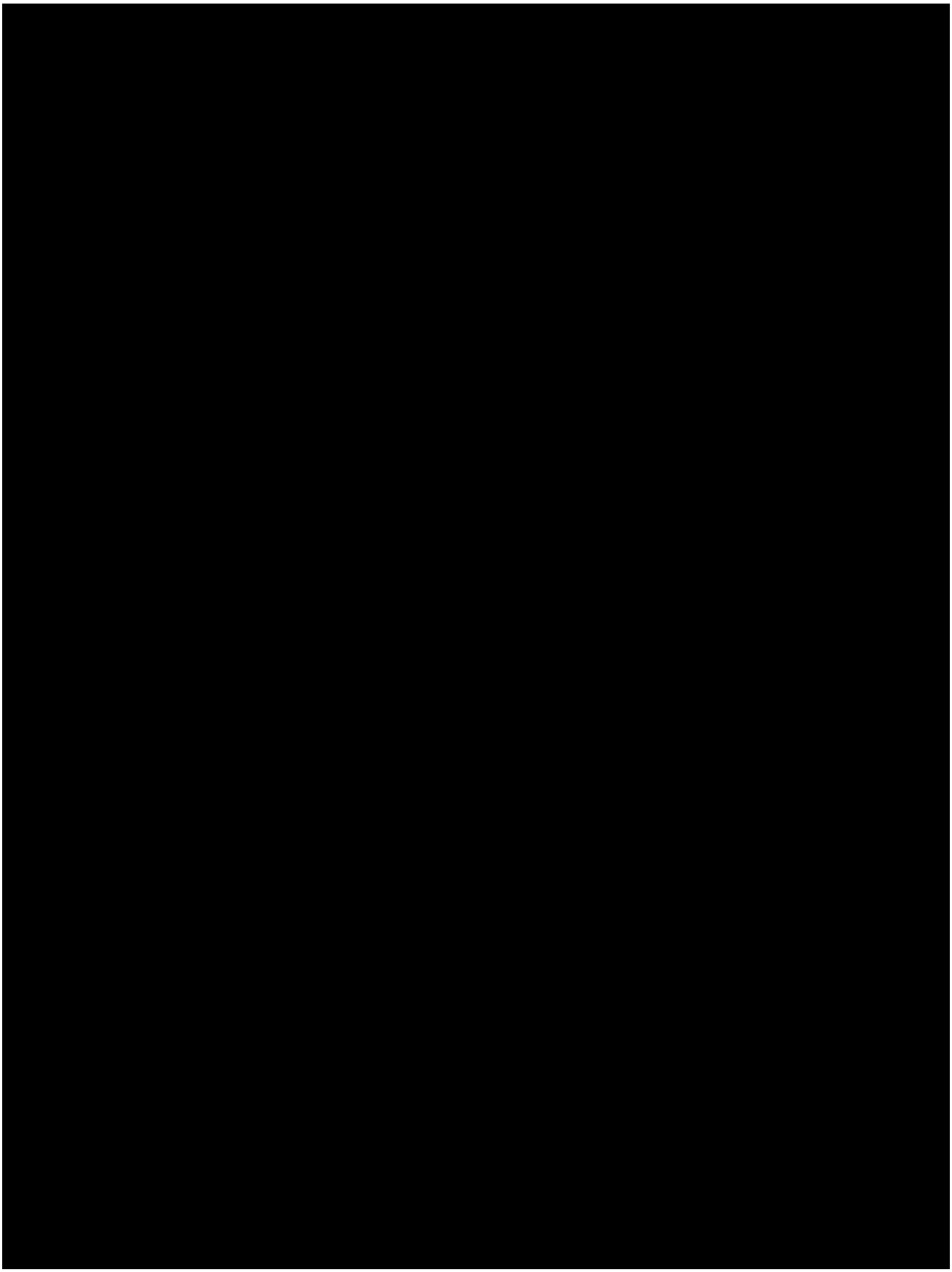
Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.



Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.



Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.



Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date	Author	Sections changed	Brief description of change
1.0	17-OCT-2024	[redacted]	Not applicable	This is the final TSAP.