TRIAL STATISTICAL ANALYSIS PLAN

c31353891-01

BI Trial No.:	1418-0001
Title:	Safety, tolerability and pharmacokinetics of single rising intravitreal doses and multiple intravitreal dosing of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled). (including Protocol Amendments No.1-6 [c25843245-07])
Investigational Product:	BI 754132
Responsible trial statisticians:	[redacted] Phone: [redacted] Fax: [redacted] [redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	08 SEP 2022 SIGNED
Version:	1

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LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of BI 754132 in serum over the time interval from 0 to the last quantifiable drug concentration
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve of BI 754132 in serum over the time interval from 0 extrapolated to infinity
BCVA	Best Corrected Visual Acuity
BLRM	Bayesian Logistic Regression Model
BMI	Body mass index
CI	Confidence Interval
C_{max}	Maximum serum concentration of BI 754132 after a single intravitreal dose
CV	Arithmetic Coefficient of Variation
DBLM	Database Lock Meeting
DILI	Drug induced liver injury
DLE	Dose Limiting Event
ENR	Enrolled set
ERG	Electroretinography
ES	Entered set
FAF	Fundus autofluorescence
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
IVT	intravitreal
IQRMP	Integrated Quality and Risk Management Plan
Max	Maximum
Min	Minimum
N	Number non-missing observations
NAION	Nonarteritic anterior optic ischaemic neuropathy
OCT	Optical Coherence Tomography
P10	10^{th} percentile

Term	Definition / description
P90	90th percentile
PKS	PK parameter analysis set
Q1	1st quartile
Q3	3rd quartile
q4w	4-weekly interval
RAGe	Report Appendix Generator system
REP	Residual Effect Period
SD	Standard Deviation
SMC	Safety Monitoring Committee
t_{max}	Time from dosing to maximum serum concentration of BI 754132
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal

3. INTRODUCTION

As per 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 protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP 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.

Study data (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 6.3 or higher, [redacted]).

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).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP. The following changes compared to the protocol will be made:

- The additional analysis set ‘Enrolled set’ was defined, which is used for disposition tables and listings, see Section 6.3.

- The additional analysis set ‘Entered set’ was defined, which is used in disposition tables and listings, see Section 6.3.

- The additional analysis set ‘DLE evaluable set’ was defined for the SRD part, which is used for SMC outputs related to the BLRM, see Section 6.3.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:
SRD part:

- *Number of patients with ocular (in the study eye) and systemic dose limiting events (DLEs) from drug administration until end of trial (EOT).*

For definition of a DLE, refer to Section 7.4.

MD part:

Number of patients with drug-related AEs from drug administration until EOT.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

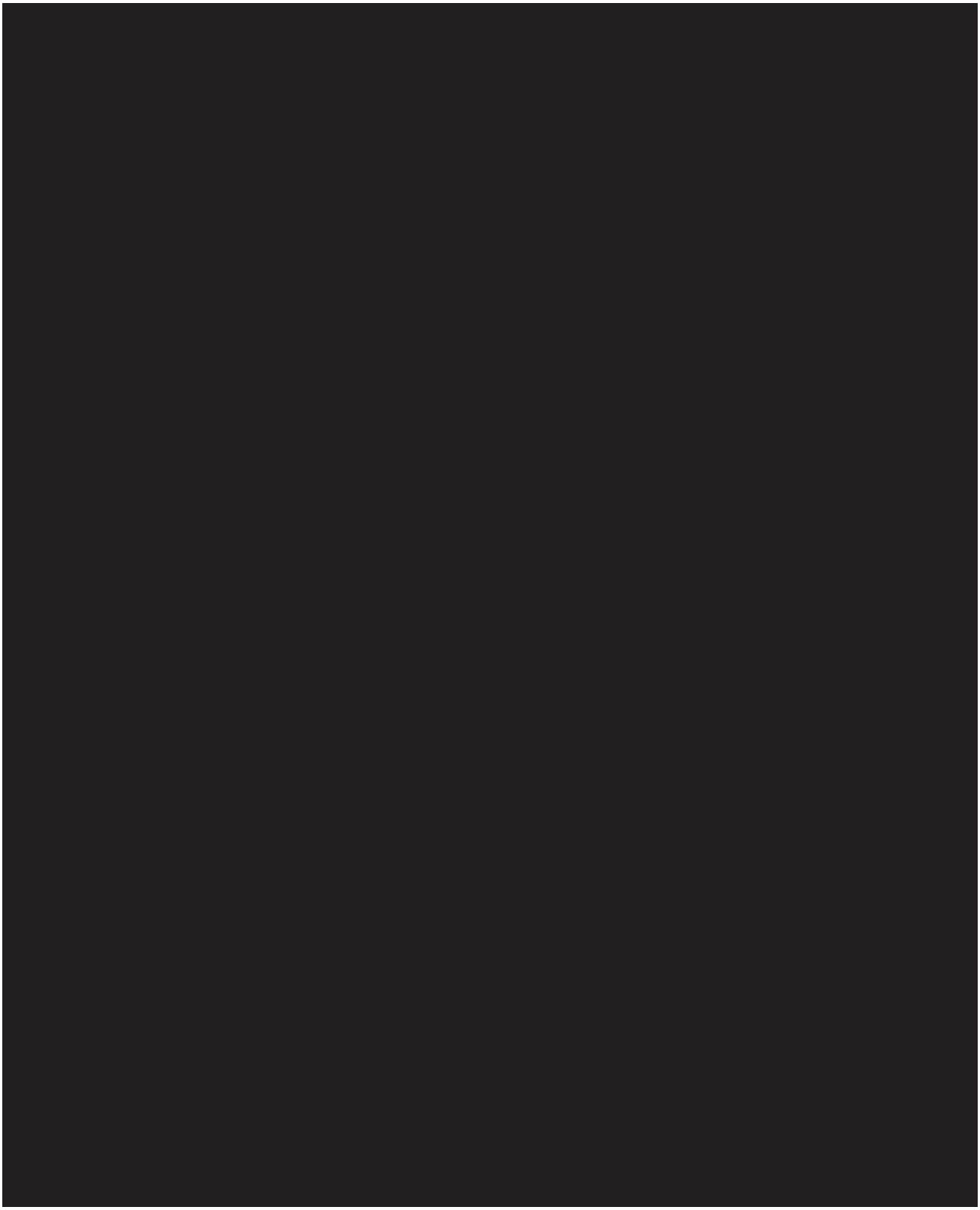
Section 2.1.3 of the CTP:
SRD part:

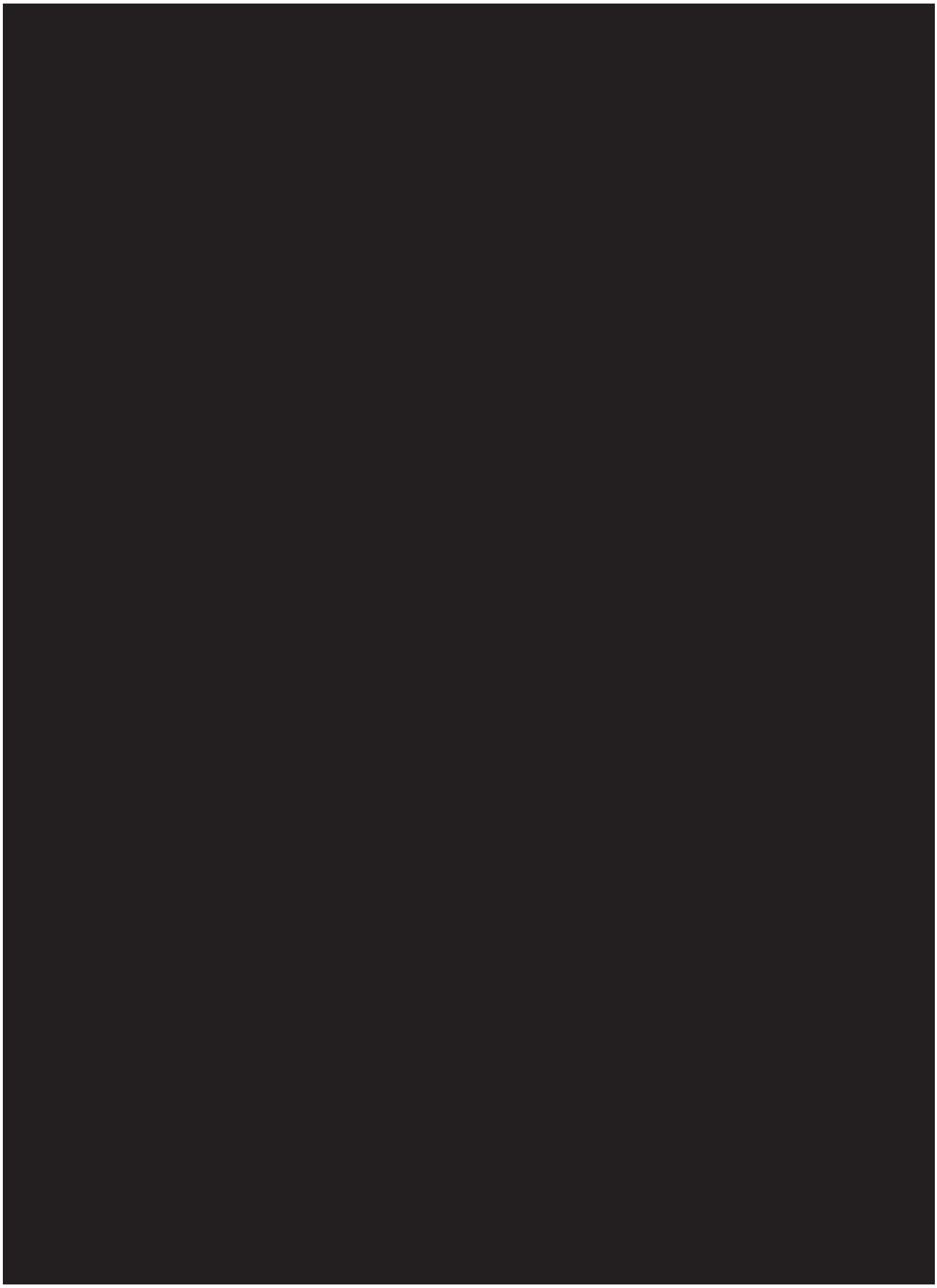
- *Number of patients with drug-related AEs from drug administration until EOT*
- *Number of patients with any ocular AEs in the study eye from drug administration until EOT*
- C_{max} *(maximum serum concentration of BI 754132 after a single intravitreal dose)*
- $AUC_{0-\infty}$ *(area under the concentration-time curve of BI 754132 in serum over the time interval from 0 extrapolated to infinity)*
- t_{max} *(time from dosing to maximum serum concentration of BI 754132)*

MD part:

- *Systemic exposure of BI 754132 after multiple IVT doses by determination of* $C_{min,1}$ *and* $C_{min,2}$ *(trough levels before second and third administrations) and* serum *concentrations 4, 8 and 14 weeks after the third administration*

The pharmacokinetic parameters listed in Section 2.1 of the CTP for drug BI 754132 will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [BI-KMED-TMCP-HTG-0025] (7). General note: PK parameters (planned as secondary or further endpoints) are determined only if sufficient data is available.





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on investigational products, assignment of treatment and selection of doses, please see CTP, Section 4.

The study will be performed as a non-randomized, open-label trial in an uncontrolled manner.

It is planned that up to 24 patients (in SRD part it is expected to enrol up to 18 patients (planned 15 plus 3 additional if DLEs occur), in MD part it is expected to enroll 6 patients) with geographic atrophy secondary to age-related macular degeneration participate in this study, according to 4 sequential groups comprising 3 patients per group and 6 at final treatment group (SRD part) and 6 in MD treatment group.

For details of dosage and formulation see Table 6.1:1 below.

Table 6.1: 1 Labels for treatments for use in the CTR

Part	Treatment group	Treatment		Short label
SRD	1	A	BI 754132, injection, 0.3 mg	BI 0.3mg
SRD	2	B	BI 754132, injection, 1 mg	BI 1mg
SRD	3	C	BI 754132, injection, 3 mg	BI 3mg
SRD	4	D	BI 754132, injection, 6 mg	BI 6mg
MD	5	E	BI 754132, injection, 6 mg, q4wk	BI 6mg q4wk

CTP Section 7.2.5:

For BI 754132, the residual effect period (REP) after IVT administration is not known. Therefore, all AEs with an onset between start of treatment and the respective EOT visit will be assigned to the on treatment period for evaluation.

The following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00h (midnight) on day of informed consent until first administration time of BI 754132)
- **On treatment**
  - **BI treatment** (separately for each treatment, ranging from the time of first administration of BI 754132 until 0:00h (midnight) on the day after trial completion date)

Please note that all AEs reported between start of trial drug administration and the last per-protocol contact will be considered on treatment (i.e. no follow-up period is considered in this trial).

The following AE displays will be provided in the report:

Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the short label of the study treatment). Screening will not be included in this analysis.

The following totals will be provided in addition in Section 15.3:

- a total over all on treatment phases included in this analysis ("**Total**") (SRD part only)

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, the screening period will be included and no totals will be provided.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated patients.

Section 7.2.1.2 of the CTP: *Important protocol deviations (iPDs) will be defined in the Integrated Quality and Risk Management (IQRM) plan. iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.*

Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting and database lock meeting (RPM/DBLM). At this meeting, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

IPDs will be identified no later than in the Report Planning Meeting. If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes (decision log) and in the iPD specification file (3). The iPD categories in the iPD specification file will be updated as needed. The decision on exclusion of subjects from analysis sets will be made after discussion of exceptional cases and implications for analyses. The iPD specification file (e.g. the DV domain specifications) will be stored within the TMF in EDMS.
The iPDs will be summarised and listed.

6.3 SUBJECT SETS ANALYSED

- Enrolled set (ENR):
  This subject set includes all patients who were enrolled in the study (i.e. signed informed consent) regardless of whether they were treated or not. The ES is used for the disposition table / listing.

- Entered set (ES):
  This subject set includes all patients who signed informed consent and were entered in the study regardless of whether they were treated or not. The ES is used in the disposition table / listing.

- Treated set (TS):
  The TS will consist of all patients who were treated with at least one dose of BI 754132. This is the full analysis set population in the sense of ICH-E9 (1). It is used for demographics, baseline characteristics, and safety analyses including ECG, as well as for the description of biomarkers.

- PK parameter analysis set (PKS):
  The PK parameter analysis set (PKS) includes all patients from the TS receiving BI 754132 who provide at least one serum sample for determination of PK parameters that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified below).
  It is used for the descriptive analyses of PK parameters.

- DLE evaluable set (SRD part only):
  The DLE evaluable set includes the patients from the TS who continued in the trial for at least 7 days after study drug administration and who attended Visits 2, 3, and 4, and the patients from the TS who were withdrawn from the trial before Visit 4 due to a DLE. It is used for the SMC outputs.

Section 7.2.1.2 of the CTP:
Serum *concentration data and parameters of a* patient *will be included in the PK analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a* patient*'s data will be documented in the CTR.*

Relevant protocol deviations may be

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

Serum *concentrations and/or* PK *parameters of a* patient *will be considered as non-evaluable, if for example there were missing samples/concentration data at important phases of PK disposition curve.*

Serum *concentration data and* PK *parameters of a* patient *which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).*

The descriptive analysis of PK concentrations will be based on the ADS ADPC as described in Section 7.

Table 6.3: 1 Subject sets analysed

Class of endpoint	ES	TS	PKS
Primary endpoints and further safety assessments (incl. ECG)		X	
Analysis of biomarker		X	
Analysis of PK endpoints (secondary and further)			X
ADA analysis		X	
Demographic/baseline parameters		X	
Important protocol deviations		X	
Disposition	X		
Exposure		X	

[redacted]

6.5 POOLING OF CENTRES

Due to the limited number of patients, all patients will be pooled without using different weights for centres.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the CTP, Section 7.3.

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035 (4)).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-MAN-0014 (5)).

Missing baseline laboratory values will be imputed by the respective values from screening.

If single cardiac cycles of an ECG (out of the generally four) are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

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

For the classification of the on treatment QTc/QT intervals into 'no new onset' / 'new onset' categories, the handling of missing value is described in Appendix Section 10.1.2.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value for laboratory data, vital signs data and ophthalmological data is defined as the last measurement before first administration of BI 754132 (= value at V2, in case no actual time is given in data).

Section 5.2.4 of the CTP: *For the endpoints, baseline is defined as the value at Visit 2; if not measured at Visit 2 then baseline is the value at Visit 1.*

The acceptable time windows for visits are given in the CTP Flow Charts.

Adherence to time windows will be checked via the consistency check listings at the RPM/DBLM.

Unscheduled measurements of laboratory data, ophthalmologic data and vital signs data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

Section 5.2.6 of the CTP: *Central ECG lab evaluation will be performed for all ECGs indicated in the* CTP *Flow Charts. For all ECGs, this will include the intervals RR, PR, QRS and QT measured semi-automatically. The screening ECGs will be checked for abnormalities.* […].

At Visit 1, single ECGs will be recorded. At Visit 2-10, triple ECGs will be recorded (three single ECGs within 180 sec).

Section 7.2.5 of the CTP: *The baseline value of an ECG variable is defined as the mean of the ECG measurements prior to drug administration* on visit 2. The screening ECGs will not be included in calculation of baseline.

7. PLANNED ANALYSIS

Results will be shown separately for SRD part and MD part (except some outputs in Appendix 16.1.13.1).

Safety analysis (refer to Section 7.8) will be performed by [redacted] and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

The prior specified in the CTP, Section 7.2.1.1 will be used in all BLRM evaluations.

Descriptive data analysis of PK parameters and concentrations will be performed by the [redacted] and will be presented in Section 15.6 and in Appendix 16.1.13.5 of the CTR.

[redacted]

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (6)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (7).

The individual values of all patients will be listed, sorted by treatment group, patient number, and visit.

The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

N	number non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For analyte concentrations and PK parameters, the following descriptive statistics will additionally be calculated:

Nobs	number of observations
CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be

calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Tabulations of frequencies for categorical data will include all possible categories available in the eCRF and will display the number of observations in a category, as well as the percentage (%) for each treatment group. Percentages will be rounded to one decimal place and will be based on all patients 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.

Exclusion of PK parameters

The ADS ADPP (PK parameters) contains column variables APEX and APEXCO indicating inclusion/exclusion (APEX) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters only if they are not flagged for exclusion, that is APEX is equal to “Included”.

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEX or ACEXCO indicating inclusion/exclusion (ACEX) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to ‘DESC STATS’, the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’, the value can be used for further analyses based on actual times. If ACEXCO is set to ‘HALF LIFE’, the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in BI-KMED-TMCP-MAN-0014 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) and BI-KMED-TMCP- MAN-0010: “Description of Analytical Transfer Files and PK/PD Data Files” (11).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.

The data will be summarised by treatment group (SRD and MD part) and in total (SRD part only).

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the latest version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be specified during RPM. The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Patients without any concomitant diagnoses or concomitant therapies should be marked with a "No" in the respective column.

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM/DBLM.

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured sample concentrations will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM/DBLM (see Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

SRD part:
Section 5.2.1 of the CTP: *A dose limiting event (DLE) is defined as the occurrence of any of the following events as ocular DLE (in the study eye):*

- *Development of sterile endophthalmitis and/or sterile inflammation of the vitreous grade 3+ according to Standardization of Uveitis Nomenclature (SUN) working group (WG) grading scheme for anterior chamber cells measured by slit lamp and a duration of 5 or more days*
- *Visual loss of more than 15 letters at any given time point due to treatment effect in the study eye confirmed on consecutive visits*
- *Persistent IOP over 30 mmHg for 3 days*
- *Signs of vascular occlusion in the retina (haemorrhage of the macula would not be included as this is a possible sign of CNV occurrence; peripheral retinal haemorrhage may be a sign of vascular occlusion)*

[…]

or as systemic DLE:

- *Drug-related AEs of moderate and severe intensity according to CTCAE (14) out of the following:*
  - *Self-reporting paraesthesia, dysgeusia, taste abnormality, taste disorder, hyposmia (15)*
  - *Diarrhea, cough (16)*

Each DLE needs to be reported as AESI.

Descriptive statistics (number and percentage of patients with ocular (in study eye) and systemic DLEs) will be provided by treatment group and in total, based on the TS.

The results of the final BLRM after completion of the SRD part will be provided based on the TS, and based on the DLE evaluable set in case the DLE evaluable set and the TS differ.

MD part:
Descriptive statistics (number and percentage of patients with drug-related AEs) will be provided, based on the TS.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

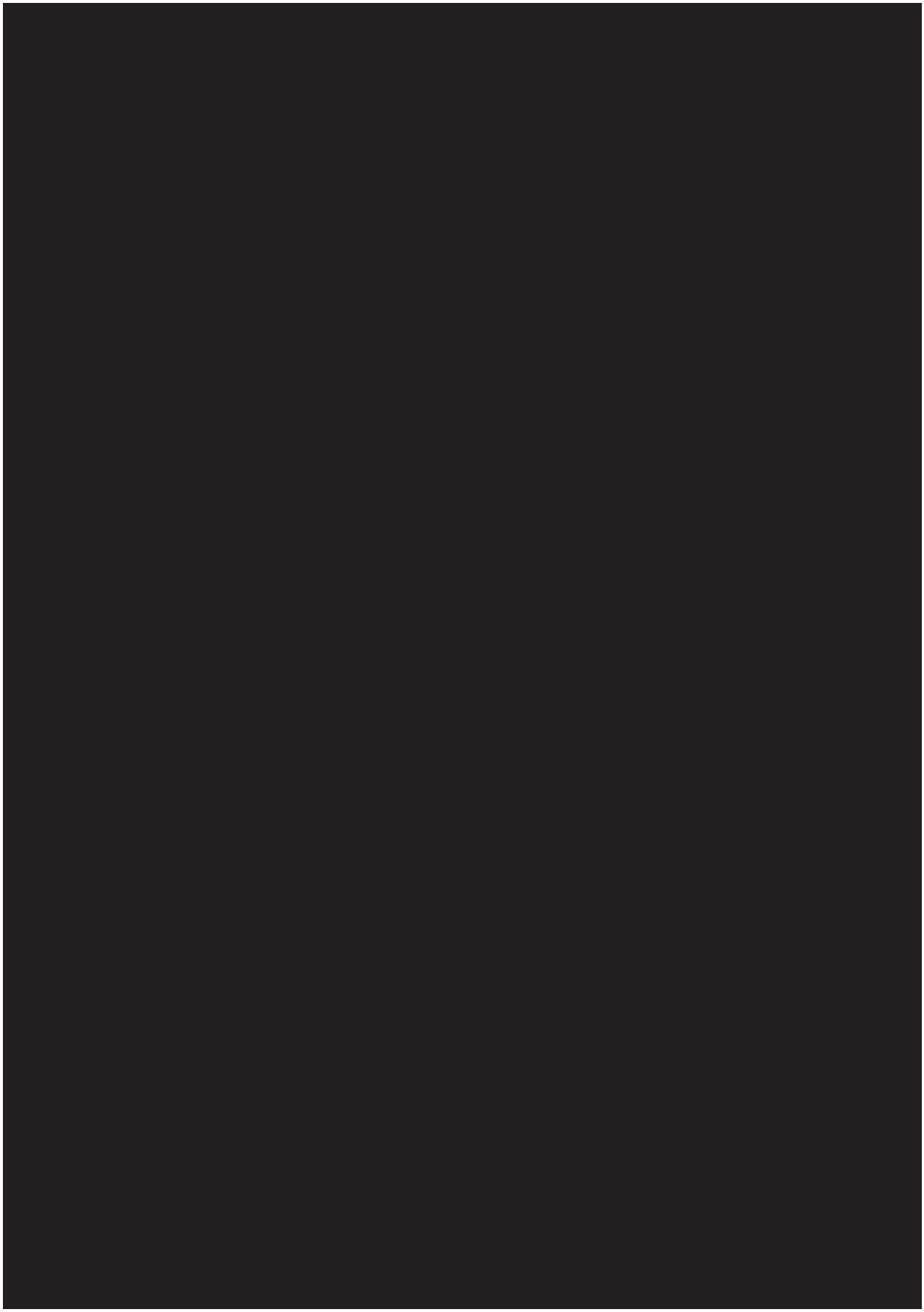
This section is not applicable as no key secondary endpoints have been specified in the protocol.

7.5.2 Secondary endpoints

All secondary safety endpoints defined in Section 5.2.2 will be analysed descriptively, based on the TS (refer to TSAP Section 7.8.1 Adverse events for details).

SRD part:
The PK endpoints C_{max}, $AUC_{0-\infty}$, and t_{max} specified in Section 5.2.2 will be analysed descriptively, based on the PKS. Dose proportionality will be explored descriptively for the PK endpoints $AUC_{0-\infty}$ and C_{max} if feasible.

MD part:
Systemic exposure of BI 754132 after multiple IVT doses by determination of $C_{min,1}$ and $C_{min,2}$ (trough levels before second and third administrations) and serum concentrations 4, 8 and 14 weeks after the third administration will be determined in the MD part along with descriptive statistics, based on the PKS.



[redacted]

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each patient.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

If not stated otherwise, the safety results will be sorted by treatment group.

The safety data for treated patients who failed to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

Per the European Union (EU) Regulation 536/2014 (Annex V, Point 4) (17), the following information will be included in Appendix 16.1.13.1 of CTR:

- number of patients included by country
- number of patients inside (member states) and outside the EU (third countries)
- frequency of serious drug-related AEs by treatment, primary system organ class and preferred term.

7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA. The version to be used will be specified in RPM and will be displayed as a footnote in the respective output.

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" [BI-KMED-BDS-HTG-0041] (8).

The standard AE analyses will be based on the number of patients with AEs (and not on the number of AEs).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to 'screening' or 'on treatment' phases as defined in Section 6.1.

According to ICH E3 (9), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event

that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of adverse events (including number of patients with any AE, DLEs, drug related AEs, ocular AEs, AESIs, serious AEs, other significant AEs and drug related serious AEs) will be presented.

The frequency of patients with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with serious AEs, for patients with drug-related AEs, for patients with drug-related serious adverse events, for patients with ocular AEs, for patients with DLEs and for patients with AESIs. In addition, the frequency of patients with AEs will be summarised by treatment, worst intensity, primary system organ class (SOC) and preferred term (PT).

The SOCs will be sorted by default alphabetically, PTs will be sorted by frequency (within SOC).

According to the clinical study protocol, adverse events of special interest (AESI) will be analysed:
Section 5.2.8.1.4 of the CTP: *The following are considered as AESIs:*

- *Hepatic injury*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
    - *an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or*
    - *aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

  These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF.
  In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

All AEs meeting the criteria for a dose limiting event (DLE) […] *are defined as AESIs for this trial.*

In addition, non-serious AEs that were reported at a frequency of > 5% (at PT level) for patients in at least one treatment group will be summarised by treatment, primary SOC and PT.

For disclosure of adverse events on EudraCT additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on EudraCT

For all ocular adverse events, ocular symptoms will be listed in addition.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [BI-KMED-BDS-HTG-0042] (10).

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as possibly clinically significant will be flagged in the data listings.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as adverse events (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.
It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM/DBLM at the latest).

Descriptive statistics of laboratory data (normalised values) including change from baseline will be calculated by time point based on the worst value of the patient at that time point (or assigned to that planned time point).

7.8.3 Vital signs

For vital signs (blood pressure, pulse rate and body weight), descriptive statistics including change from baseline will be calculated by treatment group and by planned time point based on the first value of the patient at that planned time point (or assigned to that planned time point). In the listing the difference from baseline will also be displayed.

Clinically relevant findings in vital signs will be reported as AEs.

7.8.4 ECG

Continuous safety ECG monitoring (by investigator)

Clinically relevant abnormal findings will be reported as adverse events.

No separate listing or analysis of continuous ECG monitoring will be prepared.

12-lead ECG

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

All evaluations of ECG data will be based on the TS.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. For QTcB and RR only listings will be provided. Occurrences of notable findings will be flagged.

Comments regarding the ECGs will be listed.

Categorical endpoints

For the categorical endpoints frequency tables will be provided.

Categorical endpoints will also include morphological findings that might be attributable to treatment. In particular, new onsets of findings not present at baseline will be explored. A morphological finding observed on treatment that was not reported at baseline will be categorized as a 'new onset' of this finding.

For all patients with any notable finding in ECG intervals, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the absolute values and changes from baseline over time of QTcF, QT, HR, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.

7.8.5 Others

Physical examination

Physical examination findings, including general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such.

No separate listing or analysis of physical examination findings will be prepared.

Ophthalmological data

The following endpoint will be listed and will be analysed descriptively by treatment group (SRD and MD part) and in total (SRD part only):

- The results of the IOP measurements as well as the corresponding changes from baseline for each time point and the study eye / fellow eye

All of the following endpoints will be listed only (for the study eye / fellow eye):

- The results of the SUN grading for Anterior Chamber Cells (slit lamp)

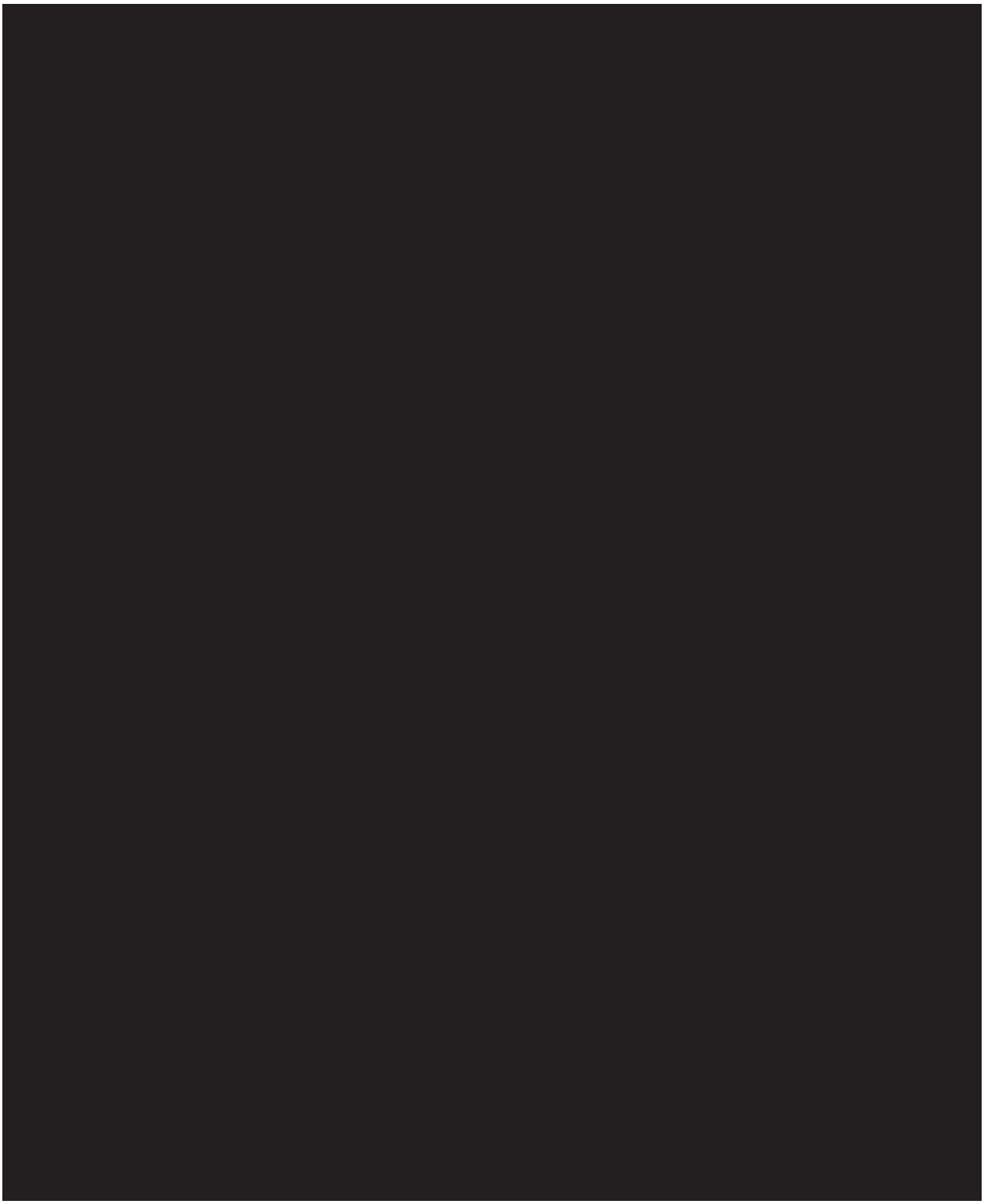
- Other results of the Slit Lamp examination / Indirect ophthalmoscopy (categories defined in eCRF) regarding eyelid, conjunctiva, cornea, anterior chamber cells, anterior chamber flare, hypopyon, iris, lens status, lens opacity, posterior capsule status, vitreous chamber cells, vitreous chamber flare, posterior vitreous detachment, optic disc, cup to disc ratio, central retina, retinal periphery, retinal tear, retinal detachment).
- Color fundus photography (evidence of GA (*present, absent, cannot determine*), GA distribution (*single lesion, multifocal, cannot determine*), GA Foveal Involvement (*minimal, moderate, complete, cannot determine*), choroidal neovascular membrane (*yes, no, cannot determine*), drusen (*present, absent, cannot determine*), reticular pseudo drusen (present, absent, cannot determine), intraretinal hemorrhage (*yes, no, cannot determine*), subretinal hemorrhage (*yes, no, cannot determine*), CFP additional findings,
  additionally for MD part: hemorrhage (*yes, no, cannot determine*), optic disc pallor (*yes, no, q, cannot determine*), cup to disc ratio (%), optic disc margin (*well defined, ill defined, cannot determine*))
- Categorical assessments from OCT (overall quality (*good, fair, poor*), volume (uL), geographic atrophy (*yes, no*), GA foveal involvement (*no GA, minimal or no, moderate, complete, cannot determine*), drusen (*yes, no*), hyper reflective drusen spots (*no drusen, yes, no*), subretinal drusen deposits (*yes, no*), choroidal neovascular membrane (*yes, no*), intraretinal fluid (*yes, no*), outer retinal tabulation (*yes, no*), ellipsoid zone disruption (*yes, no, cannot determine*), disruption compare to previsit (*no EZ disruption outside GA, progressed, regressed, no change, newly observed*), granularity (*yes, no, cannot determine*), granularity compare to previsit (*no os granularity outside GA, progressed, regressed, no change, newly observed*), correct segmentation lines (*yes, no*), segmentation lines were off level (*no off lines, mild, moderate, severe*), other findings,
  additionally for MD part: evidence of optic disc swelling (*yes, no, cannot determine*), retinal nerve fiber layer total volume, retinal nerve fiber layer superior temporal, retinal nerve fiber layer temporal, retinal nerve fiber layer inferior temporal, retinal nerve fiber layer inferior nasal, retinal nerve fiber layer nasal, retinal nerve fiber layer superior nasal,)
- Categorical and other assessments from OCT-A (presence of CNV neovascularisation (*yes, no*), location of CNV (*no CNV, involving foveal center, subfoveal but not involving foveal center, extrafoveal*), additional findings)
- Categorical assessments from FAF (definitely decreased autofluorescence AR (*present, absent*), lesion distribution (*DDAF absent, single lesion, multifocal*), foveal region involvement in DDAF (*DDAF absent, no involvement, minor, moderate, major involvement*), junctional zone pattern (*DDAF absent, focal banded, patchy, diffuse trickling, diffuse reticular, other diffuse pattern, no increased AF, CD*), background autofluorescence (*normal, homogenously increased, homogenously decreased, reticular pseudo-drusen, other*), que. decreased autofluorescence (*present, absent*), QDAF present (*QDAF absent, surrounding areas of DDAF, isolated from areas of DDAF, both, no DDAF areas*), other findings)

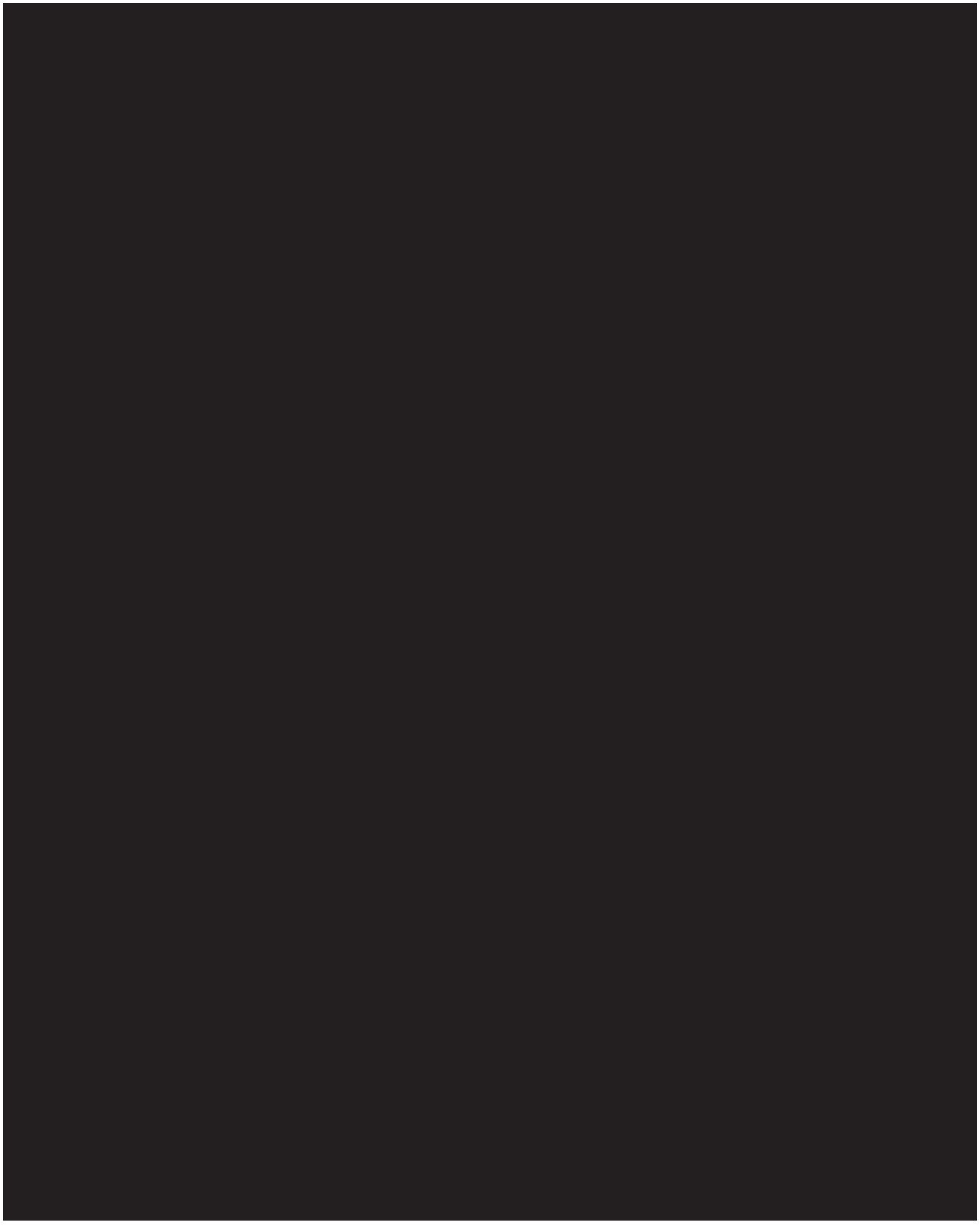
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database after completion of enrolment.

9. 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.	*BI-KMED-BDS-TEMP-0059:* "iPD specification document (sdtm-dv-domain-specification)", template, current version; KMED
4.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version; KMED.
5.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; KMED.
6.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
7.	*BI-KMED-TMCP-HTG-0025*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
8.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
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
10.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.
11.	BI-KMED-TMCP-MAN-0010: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
12.	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokin Pharmacodyn 2017 [R18-0143]
13.	Ring A. Statistical models for heart rate correction of the QT interval. Stat Med 2010 [R10-2920]
14.	U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0 (published: November 27, 2017). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf#search=%22CTCAE%22 (access date: 9 April 2017); U.S.Department of Health and Human Services, National Institutes of Health, National Cancer Institute 2017 [R18-1357]
15.	Ochs G, Penn RD, York M, Giess R, Beck M, Tonn J, et al. A phase I/II trial of recombinant methionyl human brain derived neurotrophic factor administered by intrathecal infusion to patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000. 1(3):201-206 [R19-0073]
16.	BDNF Study Group (Phase III). A controlled trial of recombinant methionyl human BDNF in ALS. Neurology 1999. 52(7):1427-1433 [R17-1162]
17.	REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, European Commission webpage.





11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**08-SEP-22**	[redacted]	None	This is the final TSAP