Boehringer Ingelheim

TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	c36993496-02
BI Trial No.:	1451-0001
Title:	A First in Human trial to study safety and tolerability of single rising intravitreal doses (oPen label, non-randomized, uncontrolled) and in Addition the early biological Response of mulTiple intravitreal doses (double-masked, RandomIzed, sham-controlleD) of BI 765128 in panretinal photocoaGulation (PRP) treated diabetic rEtinopathy (DR) patients with diabetic macular ischemia (DMI) – the PARTRIDGE study (Revised Protocol including Amendments 1-4 [c34591878-06])
Investigational Product:	BI 765128
Responsible trial statistician:	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ Phone: ▮▮▮▮▮▮ Fax: ▮▮▮▮▮▮
Date of statistical analysis plan:	07 SEP 2023
Version:	2.0
	Page 1 of 41

1.   TABLE OF CONTENTS

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LIST OF TABLES

Boehringer Ingelheim   **Page 5 of 41**
TRIAL STATISTICAL ANALYSIS PLAN
1451-0001   c36993496-02

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ADA	Anti-drug antibody
ADS	Analysis data set
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AU	Arbitrary units
AUC	Area under the curve
██████	████████████████████████████████
████	████████████████████████████████
██████	████████████████████
BCVA	Best corrected visual acuity
BLRM	Bayesian logistic regression model
BMI	Body mass index
BMS	Biomarker analysis set
CARE	Clinical data Analysis and Reporting Environment
CFB	Change from baseline
CI	Confidence interval
████	██████████████████████
████	██████████
████	██████████
c-NRP-1	Neurolipin 1
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting

Term	Definition / description
DLE	Dose limiting event
DRIL	Disorganisation of retinal inner layer
DRSS	Diabetic retinopathy severity scale
ECGPCS	ECG Pharmacokinetic Concentration Set
EDMS	Electronic documentation management system
EOS	End of Study
ES	Enrolled set
ETDRS	Early treatment diabetic retinopathy study
FAZ	Foveal avascular zone
gCV	Geometric coefficient of variation
gMean	Geometric mean
███	████████████
IOP	Intra-ocular pressure
IVT	Intravitreal
█	████████████
LLBCVA	Low luminance best corrected visual acuity
LOCF	Last observation carried forward
Max	Maximum
MD	Multiple dosing
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
Min	Minimum
N	Number of non-missing observations
NEI	National Eye Institute
Nobs	Number of observations
OCTA	Optical coherent tomography angiography
P10	10th percentile
P90	90th percentile
███	████████████
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile

Term	Definition / description
RAGe	Report Appendix Generator system
REP	Residual effect period
RPM	Report planning meeting
SCR	Screening
SD	Standard deviation
(SD-)OCT	(Spectral domain) optical coherence tomography
SOC	System organ class
SRD	Single rising dose
SUN	Standardization of Uveitis Nomenclature
██	███████
██	███████████████████
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VFD	Vessel flow density
██	████████████████████████
WHO-DD	World Health Organization Drug Dictionary

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).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by ███████████████████████████, 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 as compared to the CTP will be done in the analysis:

An additional subject analysis set was defined: The enrolled set (ES) will be used for presentation of disposition.

The acceptable time windows for deviations from the scheduled time will be extended as compared to the clinical trial protocol (for further details, please see Section 6.7).

In the model-based analysis of secondary endpoints, a mixed model for repeated measures (MMRM) will be used instead of a generalized mixed linear model (see Section 7.5.2).

Sensitivity statistical analysis of the efficacy endpoints using last-observation-carried-forward (LOCF) will not be performed as the handling of missing data is taken into account within the MMRM approach.

5.   ENDPOINTS

5.1   PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

Part A:
- *Number of subjects with ocular dose limiting events (DLEs) from drug administration until day 8 (7 days after treatment)*

Part B:
- *Number of subjects with drug related AEs from drug administration until EOS* (end of study)

Dose limiting events were defined in the CTP as the following ocular events:

Section 5.2.1 of the CTP:

A DLE is defined as the occurrence of any of the following events in the study eye within the evaluation period (7 days after drug administration):

- *Development of sterile endophthalmitis and/or sterile inflammation of the vitreous of grade 3+ according to the NEI* (National Eye Institute) *Grading of vitreous haze, and anterior chamber cells of 3+ according to the Standardization of Uveitis Nomenclature (SUN) working group grading scheme (see* CTP *Table 5.2.1: 1) and a duration of 5 or more days between day 1 and day 8*

- *Visual loss of more than 15 letters at any given time-point*

- *Persistent IOP over 30 mmHg for 3 days*

- *Signs of vascular occlusion in a 1st (the main branch) or 2nd degree (the vessel after the first bifurcation of the main branch) retinal vessel, including peripheral retinal hemorrhages in the area supplied by the occluded vessel (hemorrhage of the macula would not be included as this is a symptom of the disease)*

Boehringer Ingelheim   **Page 11 of 41**
TRIAL STATISTICAL ANALYSIS PLAN
1451-0001   c36993496-02

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:

Part A:
- *Number of subjects with drug related AEs at EOS*
- *Number of subjects with any ocular AEs (eye disorders) at EOS*

Part B:
- *Change from baseline of the size of the FAZ* (Foveal Avascular Zone) *in optical coherence tomography angiography (OCTA) at visit 5*
- *Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 6*
- *Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 7*
- *Change from baseline of BCVA* (Best Corrected Visual Acuity) *at Visit 7*
- *Number of subjects with any ocular AEs (eye disorders) from drug administration until EOS*

5.4   OTHER VARIABLES

Section 5.2.2 of the CTP:
A complete physical examination will be performed at the time points specified in the CTP Flow Charts. *It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities.*

Measurement of height and body weight will be performed at the time points specified in the CTP *flowchart.*

Age [years] will be determined as the difference between year of informed consent and year of birth.

BMI will be calculated as weight [kg] / (0.01 * height [cm])^2.

6.   GENERAL ANALYSIS DEFINITIONS

6.1   TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups and selection of doses, please see CTP, Sections 3 and 4.

This phase I/IIa trial in patients with diabetic macular ischemia consists of 2 parts, a single-rising dose (SRD) part and a multiple dose (MD) part:

The single-rising dose part (Part A) of the trial with 3 dose groups is designed as non-randomized, open-label and uncontrolled. Each dose group consists of at least 3 evaluable patients, the highest dose groups consists of 6 patients.

The multiple dose part (Part B) is designed as double-masked, randomized and sham-controlled. Thirty patients will be recruited, in a 2:1 ratio of active treatment versus sham. Patients receive three administrations of trial medication ▮▮▮▮▮▮▮.

For both parts, one eye will be selected, according to inclusion /exclusion criteria, as the study eye to be treated.

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

Table 6.1: 1   Treatments and labels used in the analysis

Treatment	Short label
▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮	

Section 7.3.5 of the CTP:

For BI 765128, the residual effect period (REP) after IVT administration is not known. Therefore, all AEs with an onset between start of treatment and the respective EOS visit will be assigned to the on treatment period for evaluation. The safety analysis will be performed by planned dose group.

The following study phases will be defined for the analysis of adverse events (AEs):

- **Screening** (ranging from 0:00h on day of informed consent until first administration of study medication (BI/Sham))

- **On treatment** (ranging from the first time of administration of BI or Sham until 0:00h on the day after trial termination date)

Section 7.3.5 of the CTP:
Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

The following AE displays will be provided in the report:

In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays, the on treatment phase will be analysed (labelled with the short label of the study treatment). The screening phase will not be included in this analysis.
In Appendix 16.1.13.1.8, parts will be combined and not displayed separately.

The following totals will be provided in addition for Section 15.3.

- a total over all on treatment phases **("Total")**

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, the screening period will additionally 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 subjects enrolled (i.e. signed informed consent available) who did not fail during screening. 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 (RPM)/ database lock meeting (DBLM). At this meeting, it will be decided whether a discrepant data point can be used or whether it must be corrected in the clinical database. 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).

Important protocol deviation (iPD) categories are pre-specified in the iPD specification file (DV domain). IPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

If any iPDs are identified, they are to be summarised into categories and will be captured in the iPD specification file (DV domain) and in the decision log. Both documents will be stored within the TMF in EDMS.

The iPDs will be summarized and listed in the CTR.

6.3   INTERCURRENT EVENTS

For the following intercurrent events in the MD part, the hypothetical strategy as defined in ICH E9(R1) (13) will be applied for all ophthalmological efficacy endpoints (see Table 5.3: 1), i.e. data obtained after the intercurrent event will be censored and not included in the statistical analyses:

- Treatment discontinuation
- Administration of any anti-VEGF treatment in study eye or any intravitreal/intraocular steroid treatment other than the randomised treatment, if administration occurred during the trial

Censoring will be applied to all efficacy endpoints of the study eye. The start date of censoring is 28 days after treatment discontinuation or 1 day after start of a relevant concomitant medication (see definition above) in the study eye, whatever occurs first.

6.4   SUBJECT SETS ANALYSED

Enrolled set (ES)
This subject set includes all patients who were enrolled in the study regardless of whether they were treated or not. The ES is used for the disposition table / listing and the disclosure tables for enrolment.

Section 7.3 of the CTP:

Treated set (TS)
For part A the treated set includes all subjects who were treated with at least one dose of study drug.
For part B the treated set includes all subjects who were randomized and treated with at least one dose of study drug (either treatment with BI 765128 or Sham).

Analyses regarding safety and efficacy will be performed on the TS. For ophthalmological efficacy analysis, intercurrent events have to be taken into account respectively (see Section 6.3). For FAZ area, a supplementary analysis including all available data irrespective of intercurrent events (i.e. following the treatment policy approach as defined in ICH E9(R1)) will be performed in addition. The analysis population for the outputs of this analysis will be labelled "TS (supplementary analysis including data after intercurrent events)".

Section 7.3 of the CTP:

Table 6.4: 1   Subject sets analysed

Class of endpoint	ES	TS	PKS
Analysis of ophthalmological endpoints		X	
Analysis of safety endpoints (incl. ECG)		X	
██████████████			█
██████████		█	
Disposition / Disclosure of enrolment	X		
Demographic/baseline parameter		X	
Important protocol deviations		X	
Exposure		X	

██████████████████

6.6   HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the CTP, Section 7.4.

Section 7.4 of the CTP:

Safety

Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all AEs, with particular emphasis on potential DLEs.

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████████████████████████

Efficacy

All data will be analyzed and presented without any form of imputation.

Missing time at unscheduled ocular assessments performed on the day of administration are regarded as on treatment. The missing time will be imputed and set to 23:59 at the day of administration.

Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035) (3).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-HTG-0025 (4) and BI-KMED-TMCP-MAN-0014 (5).

ECG analysis

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 values is described in Additional Section 10.1.2.

6.7   BASELINE, TIME WINDOWS AND CALCULATED VISITS

Section 5.1 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.
Baseline is defined as the last measurement before first administration of trial medication.

Section 6.1 of the CTP:
The acceptable time windows for visits are given in the CTP *Flow Charts. For planned individual serum concentration sampling times, refer to* CTP *appendix 10.1.*

Analysis of AE data, potentially clinically significant abnormal laboratory values, concomitant medication or non-drug therapies, as well as use of rescue therapy will not be based on visits. Therefore, no assignment to time windows will be necessary for such data.

All other safety and efficacy measurements will be assigned to visits based on extended time windows around the planned visit dates, defined relative to the day of first trial treatment (which is scheduled for Visit 2). These extended time windows are defined in Table 6.7: 1 to Table 6.7: 5.

Only one observation per time window will be selected for statistical analysis at a particular visit – the value which is closest to the protocol planned visit day will be selected, except for safety lab and ▮▮▮ where the worst scenario is chosen (i.e. for IOP the highest value will be taken). If there are two observations which have the same difference in days to the planned day, the later value will be selected. If there is more than one IOP measurement being the worst value within a time window, the value collected closer to the planned day will be selected.

Table 6.7: 1   Time window assignment of efficacy, safety lab, ▉, vital signs and weight measurements to visits for statistical analysis of the SRD Part

Visit (CTP)	Week	Visit label (analysis)	Planned Day	Time window [days]		
				Window per CTP	Start (extended)	End (extended)
V2	Baseline	**Baseline**	1	± 0	NA	1
V3*		**Day 4 (FU)**	4	± 1	2	6
V4*	Week 1	**Day 8 (FU)**	8	± 2	7	11
V5	Week 2	**Day 15 (FU)**	15	± 2	12	22
V6	Week 4	**Day 29 (FU)**	29	± 3	23	43
V7	Week 8	**Day 57 (FU)**	57	± 7	44	78
V8	Week 14/EOS	**Day 99 (EOS)**	99	± 7	79	End of Trial visit date

* Safety lab is not scheduled for Day 4. Consequently, the time window for Day 8 is [2, 11], the other time windows remain the same.

Table 6.7: 2   Time window assignment of 12 lead ECG measurements to visits for statistical analysis of the SRD Part

Visit (CTP)	Week	Visit label (analysis)	Planned Day	Time window [days]		
				Window per CTP	Start (extended)	End (extended)
V2	Baseline	**Baseline**	1	± 0	NA	1
V3		**Day 4 (FU)**	4	± 1	2	16
V6	Week 4	**Day 29 (FU)**	29	± 3	17	43
V7	Week 8	**Day 57 (FU)**	57	± 7	44	78
V8	Week 14/EOS	**Day 99 (EOS)**	99	± 7	79	End of Trial visit date

Days are counted relative to the day of first treatment, which is defined as Day 1.

Table 6.7: 3   Time window assignment of efficacy, safety lab, ▉ and vital signs measurements to visits for statistical analysis of the MD Part

Visit (CTP)	Week	Visit label (analysis)	Planned Day	Time window [days]		
				Window per CTP	Start (extended)	End (extended)
V2	Baseline	**Baseline**	1	± 0	NA	1
V3	Week 4	**Day 29**	29	± 3	2	43
V4	Week 8	**Day 57**	57	± 3	44	71

Visit (CTP)	Week	Visit label (analysis)	Planned Day	Time window [days]		
				Window per CTP	Start (extended)	End (extended)
V5	Week 12	**Day 85 (FU)**	85	± 7	72	99
V6	Week 16	**Day 113 (FU)**	113	± 7	100	127
V7	Week 20/EOS	**Day 141 (EOS)**	141	± 7	128	End of Trial visit date

Table 6.7: 4   Time window assignment of 12 lead ECG measurements to visits for statistical analysis of the MD Part

Visit (CTP)	Week	Visit label (analysis)	Planned Day	Time window [days]		
				Window per CTP	Start (extended)	End (extended)
V2	Baseline	**Baseline**	1	± 0	NA	1
V3	Week 4	**Day 29**	29	± 3	2	43
V4	Week 8	**Day 57**	57	± 3	44	71
V5	Week 12	**Day 85 (FU)**	85	± 7	72	End of Trial visit date

Days are counted relative to the day of first treatment, which is defined as Day 1.

Table 6.7: 5   Time window assignment of physical examination measurements (weight) to visits for statistical analysis of the MD Part

Visit (CTP)	Week	Visit label (analysis)	Planned Day	Time window [days]		
				Window per CTP	Start (extended)	End (extended)
V2	Baseline	**Baseline**	-28 to -3	NA	NA	1
V5	Week 12	**Day 85 (FU)**	85	± 7	2	End of Trial visit date

Days are counted relative to the day of first treatment, which is defined as Day 1.

Section 5.2.5.1 of the CTP:
Central ECG lab evaluation will be performed for all ECGs indicated in the CTP *Flow Chart I and* CTP *Flow Chart II. 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 all time points mentioned in the CTP Flow Charts, single ECGs will be recorded shortly before the PK sampling at the respective time points, and will be transferred to the central ECG lab.

Boehringer Ingelheim   **Page 25 of 41**
TRIAL STATISTICAL ANALYSIS PLAN
1451-0001   c36993496-02

7. PLANNED ANALYSIS

If not stated otherwise, all outputs will be displayed separately by study part.

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

Efficacy analysis of ophthalmological endpoints will be performed by the ████████ ████████████████████████████ and will be presented in Section 15.2 of the CTR and in Appendices 16.1.13.1.7 and 16.2.6.

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No inferential statistical interim analysis was planned. A Bayesian logistic regression model (BLRM) analysis was performed after each dose group of trial part A to guide dose escalation in this study. The prior specified in the CTP Section 7.1 was used in all BLRM evaluations.

The data of the last screening attempt of re-screened patients will be considered. In case the last screening attempt of re-screened patients is missing this value will be imputed with the previous screening value.

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 subjects will be listed, sorted by treatment group, subject 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:

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

Units of variables should be given in the titles or column/row descriptors in brackets (e.g. (mg)).

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 and in total.

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 coding system of the Medical Dictionary for
Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health
Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a
footnote in the respective output. If a concomitant medication has multiple Anatomical
Therapeutic Chemical (ATC) codes, it is presented with all ATC codes.

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

An additional table/listing will be provided for previous ophthalmic interventional therapies.
Separate tables will be provided for concomitant medication before start of treatment and
with new onset after start of treatment.

The relevance of the concomitant therapies to the evaluation of PK and efficacy endpoints
will be decided no later than at the RPM.

7.3   TREATMENT COMPLIANCE

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication
in the trial centre under supervision of the investigating physician or a designee. The
measured serum concentrations and urinary excretion of trial medication 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 (cf. TSAP Section 6.2) and described in the CTR.

7.4   PRIMARY OBJECTIVE ANALYSIS

7.4.1   Main analysis

SRD part:
The primary endpoint 'number of subjects with DLEs from drug administration till day 7' will be analysed descriptively (see Section 7.8 for details).

MD part:
Refer to TSAP Section 7.8 for a description of the analysis of the primary endpoint (treatment-emergent drug-related AEs).

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

Section 7.3.3 of the CTP:

The secondary endpoints (refer to Section 5.2.2) will be summarized by means of descriptive statistics (at least n, mean, standard deviation, median, minimum and maximum) for continuous variables or frequency tables for categorical variables. (…)

Analyses regarding safety and efficacy will be performed on the TS.

Model-based analyses will be performed for all ophthalmological efficacy endpoints of the MD part that were defined as secondary endpoints, i.e. FAZ area and BCVA. These analyses will only be done for the study eye and not for the fellow eye.

The change from baseline in the respective secondary endpoint will be analysed via a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM).

The model will include the fixed, categorical effects of treatment at each visit and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

The statistical model will be as follows

$$y_{jjk} = \beta_j\, S_i + \tau_{jk} + e_{ij}$$

$$e_{ij} \sim N_Z\, (\mathbf{0}, \boldsymbol{\Sigma}).$$

y_{ijk} = response variable (as change from baseline) for subject i at visit j receiving treatment k,

S_i = the baseline measurement of subject i, i=1,2,…

β_j = coefficient of baseline effect at visit j

τ_{jk} = the effect of treatment k at visit j, j=1,…,Z and k = 1, ..,Y ,

e_{ij} = the random error associated with the jth visit of the ith subject. Errors are independent between subjects.

$\boldsymbol{\Sigma}$ = an unstructured covariance matrix

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Least-squares means per treatment and for the treatment difference will be provided by time point, and in addition corresponding two-sided 95% confidence intervals and p-values will be presented.

The following SAS code can be used to fit the model:

```
PROC MIXED DATA=indata CL METHOD=REML;
CLASS subject treat visit;
MODEL endpoint = baseline treat visit treat*visit baseline*visit/ DDFM=KR
CL
ALPHA=0.1;
REPEATED visit / SUBJECT=subject TYPE=UN;
LSMEANS treat*visit/ DIFF CL ALPHA=0.1 SLICE=visit;
RUN;
```

In the event of non-convergence, the following methods will be attempted (in order) to overcome it:

1. Add the 'singular=1e-10' option in the model statement – This raises the threshold at which columns are declared linearly dependent (from typically 1e-12).

2. Set 'maxiter=100' in the Proc Mixed statement – This increases the number of convergence iterations used from a default of 50.

3. Set 'scoring=4' to specify use of the Fisher scoring algorithm in the first 4 iterations.

4. Include the statement 'performance nothread' – this removes multi-threading from the calculations.

Should none of the previous methods work, the covariance matrix will be changed from unstructured to Toeplitz with heterogeneous variances (TOEPH). Should this also not converge, a standard Toeplitz matrix (TOEP) will be fitted. Finally, if convergence still does not occur, then an order-1 autoregressive matrix (AR(1)) will be fitted.

Furthermore, for the ophthalmological secondary endpoints, time profiles of mean (±SD) changes from baseline by treatment group as well as individual time profiles (absolute values and changes from baseline) per treatment group will be provided for the study eye / fellow eye. For the secondary endpoint FAZ area, these figures will be presented for absolute and percent changes whereas plots of the other secondary endpoint BCVA will only comprise absolute changes.

7.5.3 Interim analysis

Section 7.3.7 of the CTP:

In addition, a fast track analysis of Part B *will be performed after the final subject of Part B has attended Visit 6 (i.e. approximately 8 weeks after receiving the final dose).*

For the fast track analysis, the analyses on FAZ area (3mm) will be presented.
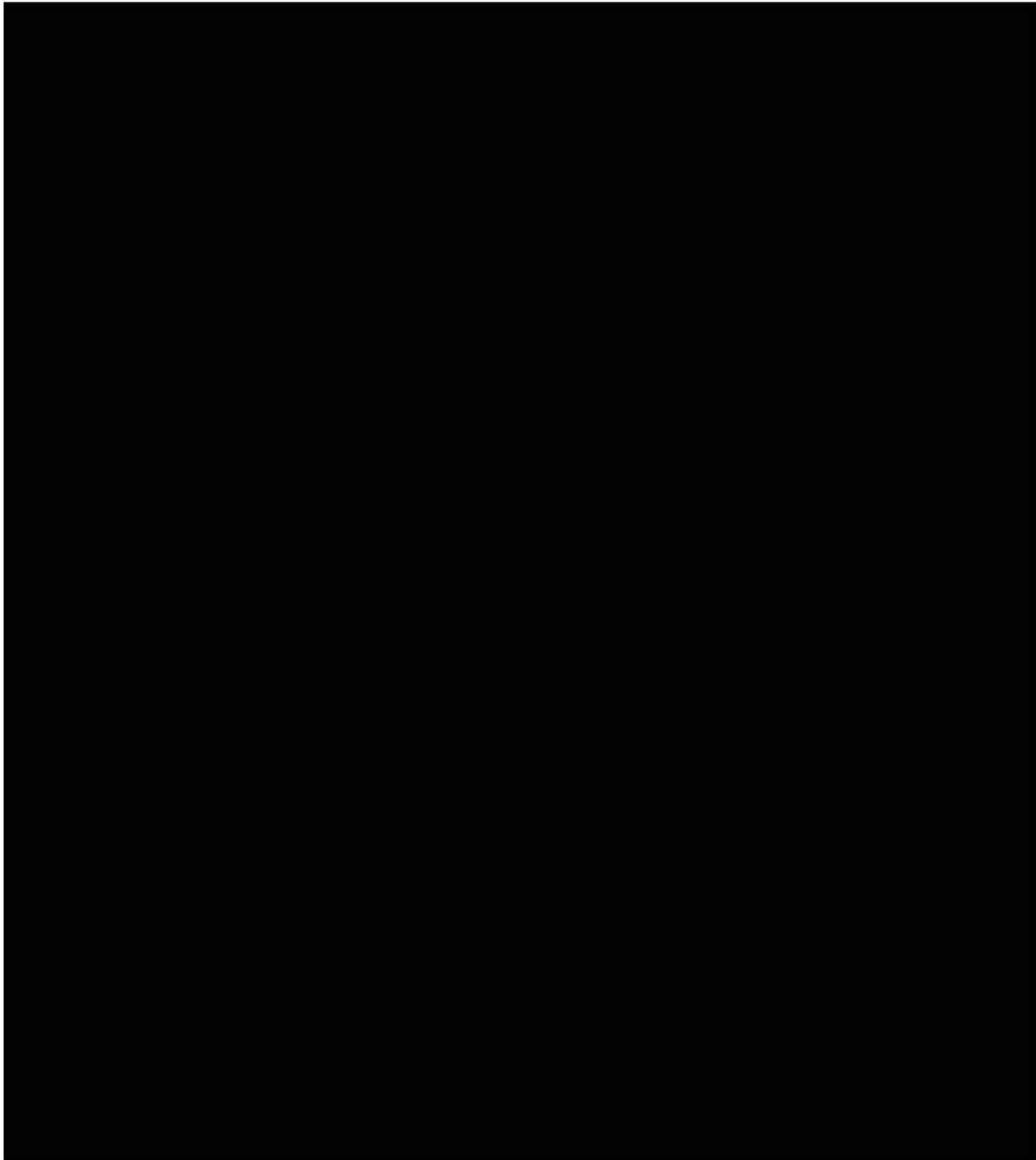
7.7 EXTENT OF EXPOSURE

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

7.8　　　SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The safety data for treated subjects 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.

7.8.1　　　Adverse Events

AEs will usually be coded with the most recent version of MedDRA. The version to be used will be specified in RPM. The coding version number will be displayed as a footnote in the respective outputs.

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. BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" [BI-KMED-BDS-HTG-0041] (9) and [BI-KMED-BDS-HTG-0066] (10) will be applied.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to 'screening' and 'on treatment' phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

According to the clinical study protocol, adverse events of special interest (AESI) will be analysed:

Section 5.2.7.1.4 of the CTP:
The following are considered as AESIs:

- *DLE*
  All AEs meeting the criteria for a dose limiting event (DLE) as defined in CTP *Section 5.2.1 are defined as AESIs for this trial.*

- *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 draw sample, or*
  - *aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.*

According to ICH E3 (11), 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 AEs will be presented. The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with

- serious AEs,
- drug-related AEs,
- drug-related serious AEs,
- ocular AEs,
- ocular AEs in the study eye,
- DLEs during study,
- DLEs during primary DLE evaluation period of 7 days (for SRD part only),
- AESIs,
- drug-related AESIs,
- other significant AEs,
- procedure related AEs.

In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, primary system organ class (SOC) and preferred term (PT).

The SOC and PTs will be sorted by frequency (within SOC).

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment 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] (12).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

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. A frequency table including the number of subjects with possibly clinically significant abnormal laboratory values by treatment group and in total will be provided by laboratory parameter. The analysis of possibly clinically significant abnormal values will be based on converted/standardised values.

A frequency table including subjects with elevated liver enzymes (potential DILI cases) will be provided in addition to support analyses of liver related adverse drug effects. In this analysis, the frequency of patients with AST and/or ALT ≥ 3xULN combined with a total bilirubin ≥ 2xULN, and the frequency of patients with AST and/or ALT ≥ 10xULN, will be displayed. 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 or 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).

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.
It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

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

7.8.3   Vital signs

For vital signs (blood pressure and pulse rate), descriptive statistics including change from baseline will be calculated by treatment group. In the listings the difference from baseline will also be displayed.

Body weight will be analysed analogously to blood pressure and pulse rate.

Clinically relevant findings 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.

7.9   OTHER ANALYSIS

Physical examination

Physical examination findings 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.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database after completion of enrolment, i.e. the randomization has been completed.

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.	*BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, Group "Clinical Operations", KMED
3.	*BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version, Group "Biostatistics & Data Sciences", KMED.
4.	*BI-KMED-TMCP-HTG-0025*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
5.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
6.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version, Group "Biostatistics & Data Sciences", KMED.
7.	*BI-KMED-TMCP-OTH-0003*: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
8.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
9.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version, Group "Biostatistics & Data Sciences", KMED.
10.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of AE data from clinical trials", current version, Group "Biostatistics & Data Sciences", KMED.
11.	*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.
12.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version, Group "Biostatistics & Data Sciences", KMED.
13.	*CHMP/ICH/436221/2017:* " ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials", current version.

Date: 07 SEP 2023, Version 2.0

11.   HISTORY TABLE

Table 11: 1   History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**30-AUG-23**	████████	None	This is the final TSAP.
2.0	**07-SEP-23**		6.3, 7	Extension of the definition of "intercurrent events" in section 6.3, two minor wording changes at p.25 in section 7.