TRIAL STATISTICAL ANALYSIS PLAN

c33215538-03

BI Trial No.:	1436-0001
Title:	A First-in **H**uman trial to study safety and tolerability of single rising intravitreal d**O**ses (open label, non-randomized, uncontrolled) and in addition the early biological response of multiple intravit**R**eal dosing (single-masked, ra**N**domized, sham-controlled) of **BI** 764524 in panretina**L**photocoagulation (PRP) treated pro**L**iferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI) – the **HORNBILL** Study.
Investigational Product(s):	(including Protocol Amendments No 1-5 [c29487972-06]) BI 764524
Responsible trial statistician(s):	[redacted]
Date of statistical analysis plan:	25 MAY 2023
Version:	3

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
AE	Adverse Events
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC_{0-tz}	Area under the concentration-time curve of the analyte in serum over the time interval from 0 to the last quantifiable drug concentration
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity
BCVA	Best Corrected Visual Acuity
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
BMI	Body mass index
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in serum
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation
CVC	Combined Vascular Complex
DBLM	Database Lock Meeting

Term	Definition / description
DILI	Drug induced liver injury
DLE	Dose Limiting Event
DVC	Deep Vascular Complex
ECG	Electrocardiogram
EOS	End of Study
ES	Enrolled set
FAZ	Foveal Avascular Zone
FTR	Full Thickness Retina
gCV	Geometric Coefficient of Variation
[redacted]	[redacted]
gMean	Geometric Mean
HR	Heart Rate
[redacted]	[redacted]
IPD	Important Protocol Deviation
IVT	intravitreal
[redacted]	[redacted]
LLT	Lower Level Term
IQRMP	Integrated Quality and Risk Management Plan
Max	Maximum
MedDRA	Medical Dictionary for Drug Regulatory Activities
MD	Multiple Dose
Min	Minimum
N	Number non-missing observations
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography
P10	10^{th} percentile
P90	90^{th} percentile
PK	Pharmacokinetic
PKS	PK parameter analysis set
Q1	1^{st} quartile
Q3	3^{rd} quartile
QRS	Combination of the Q, R, and S waves in electrocardiogram

Term	Definition / description
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTcB	QT interval corrected for heart rate using the method of Bazett
QTcF	QT interval corrected for heart rate using the method of Fridericia
RAGe	Report Appendix Generator system
REP	Residual Effect Period
SD	Standard Deviation
SRD	Single Rising Dose
SVC	Superficial Vascular Complex
t_{max}	Time from dosing to maximum measured concentration of the analyte in serum
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
[redacted]	[redacted]
VEGF	Vascular Endothelial Growth Factor
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 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, randomization.

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 8.1 or higher, [redacted]) or SAS Version 9.4 (or later version).

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.

For a more accurate reflection of the data, the term 'combined vascular complex' (CVC) for FAZ-related parameters has been renamed as 'full thickness retina' (FTR). For the MD part, the main assessment for FAZ parameters in FTR was changed to a manual grading of the 3mm OCTA scans i.e., the MD part endpoints related to FAZ area in FTR mentioned in the CTP are considered to be based on manually graded data for 3mm scan size. If an OCTA measurement is done for a specific scan size, this will be indicated in the endpoint label. For other OCTA endpoints where a measurement was not performed for a specific scan size, it will be deemed that the measurement was made primarily based on a 6mm scan size and if this was not possible then otherwise taken from a 3mm scan size.

Sensitivity statistical analysis of the efficacy endpoints using LOCF will not be performed as the handling of missing data is taken into account within the MMRM approach

5. ENDPOINTS(S)

The pharmacokinetic and pharmacodynamic parameters listed in Section 2.2 of the CTP for drug BI 764524 will be calculated according to relevant BI internal procedure.

5.1 PRIMARY ENDPOINT(S)

Section 2.1.2 of the CTP:
SRD part:

- *Number of patients with dose limiting events (DLEs) from drug administration till day 8 (7 days after treatment).*

For definition of DLEs, refer to Section 7.4.

MD part:

- *number of patients with drug related adverse events (AEs) from drug administration till end of study (EOS)*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

Section 2.1.3 of the CTP:
SRD part:

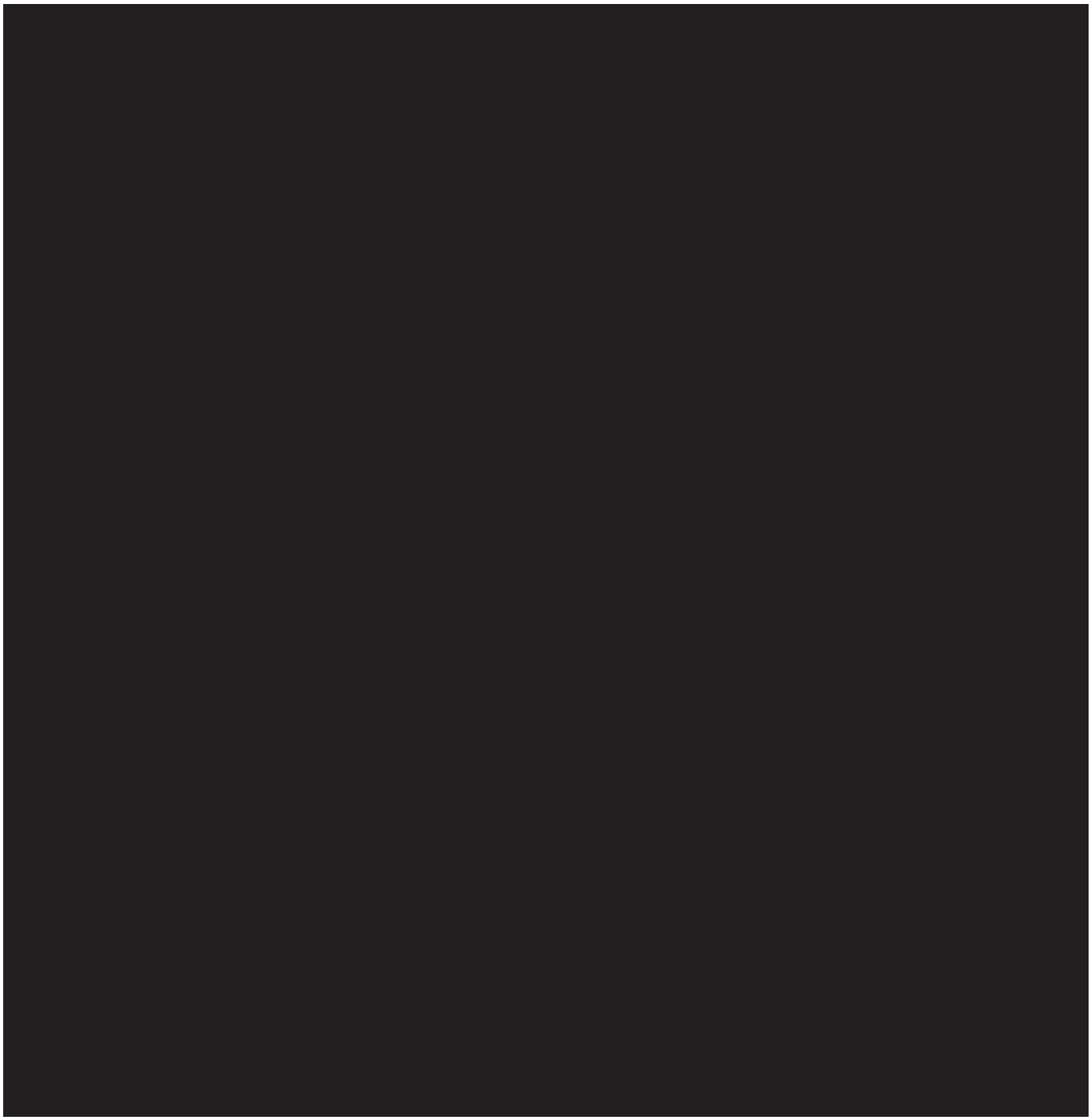
- *number of patients with drug related AEs at EOS*
- *number of patients with ocular AEs (eye disorders) at EOS*

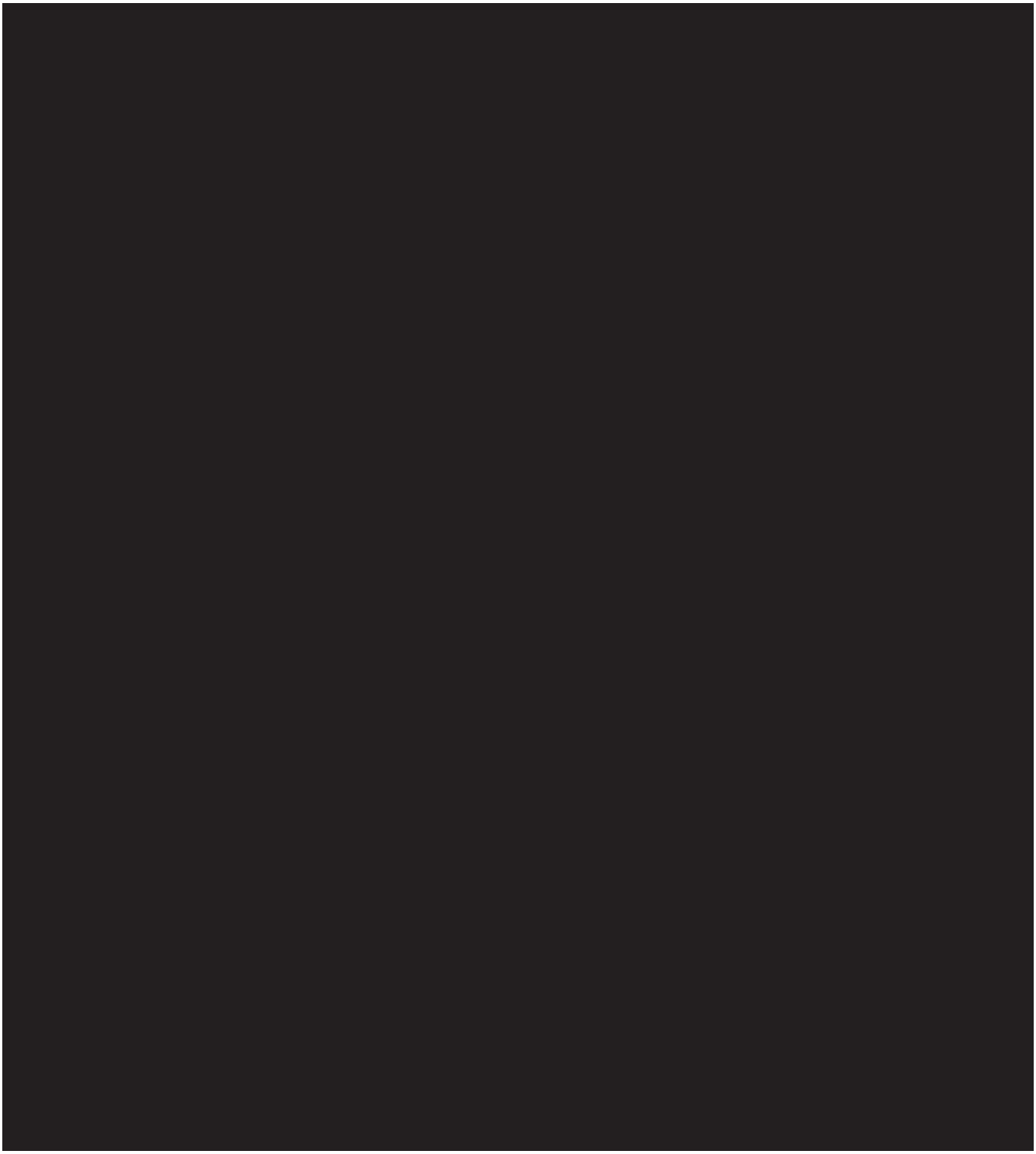
MD part:

- *change from baseline of the size of the FAZ area in optical coherence tomography angiography (OCTA) in superficial* vascular complex and full thickness retina *at Visit 5.*
- *change from baseline of the size of the FAZ area in optical coherence tomography angiography (OCTA) in superficial* vascular complex and full thickness retina *at Visit 7.*
- *change from baseline of BCVA at Visit 3*
- *change from baseline of BCVA at Visit 4*
- *change from baseline of BCVA at Visit 5*
- *change from baseline of BCVA at Visit 6*
- *change from baseline of BCVA at Visit 7*
- *change from baseline of Central retinal thickness (SD-OCT) at Visit 3*
- *change from baseline of Central retinal thickness (SD-OCT) at Visit* 4
- *change from baseline of Central retinal thickness (SD-OCT) at Visit 5*
- *change from baseline of Central retinal thickness (SD-OCT) at Visit 6*
- *change from baseline of Central retinal thickness (SD-OCT) at Visit 7*
- *number of patients with ocular AEs (eye disorders) at EOS*

Note that the above FAZ area in FTR is understood to be the FAZ area in FTR for the 3mm scan size, manually graded.

5.3 FURTHER ENDPOINT(S)

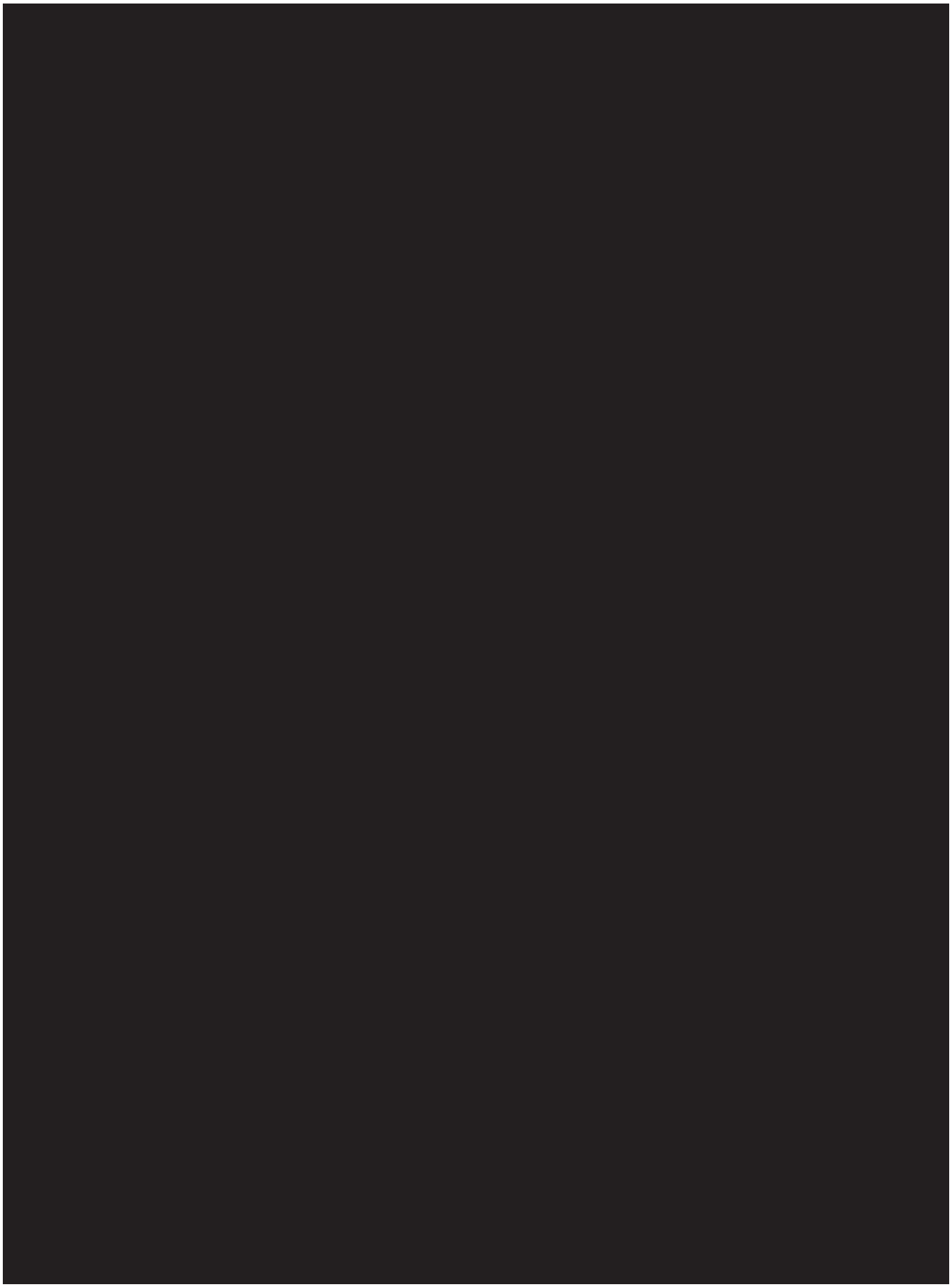




Concise summary of efficacy endpoints to be described in CTR:

SRD Part

FAZ area in superficial vascular complex
FAZ area in full thickness retina
BCVA
Central Retinal Thickness



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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

The trial will consist of an SRD part followed by an MD part. The SRD part will be conducted open-label, non-randomized, and uncontrolled, whereas the MD part will be single-masked, randomized and sham-controlled.

It was planned to assign up to 45 patients in total, up to 15 in the SRD part in (3 sequential dose groups comprising at least 3 patients each) and 30 in the MD part (20 patients on BI 764524 and 10 patients on sham injection).

With recruitment completed, the actual numbers enrolled are 12 patients in the SRD part and 32 in the MRD part (3 patients discontinued and were replaced).

For details of dosage and formulation see Tables 6.1:1 and 6.1:2 below.

Table 6.1: 1 Treatments and labels used in the analysis – SRD part

Dose group	Treatment	Description	Short label
1	D	BI 764524 [redacted] SRD	BI [redacted] SRD
2	E	BI 764524 [redacted] SRD	BI [redacted] SRD
3	F	BI 764524 [redacted] SRD	BI [redacted] SRD

Table 6.1: 2 Treatments and labels used in the analysis – MD part

Dose group	Treatment	Descriptive	Short label
1	A	BI 764524 [redacted] g	BI [redacted] MD
2	S	Sham injection	Sham MD

Section 7.3.4 of the CTP:
For BI 764524 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 following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00h (midnight) on the day of informed consent until the first administration time of BI 764524)
- **On treatment**
  - **BI treatment** (separately for each treatment, ranging from the time of first administration of BI 764524 until 0:00h (midnight) on the day after trial completion date)

The following AE displays will be provided in the report:

Section 15.3 (presented separately for SRD and MD part) 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 section 16.1.13.1.8 in addition:

- a total over all on-treatment phases ("Total")
- a total over all on-treatment phases in the SRD part ("Total - SRD part")
- a total over all on-treatment phases in the MD part ("Total - MD part")
- a total over all on-treatment phases involving BI 764524 ("BI Total")

- a total over all on-treatment phases involving BI 764524 in the SRD part ("BI Total – SRD part")
- a total over all on-treatment phases involving BI 764524 in the MD part ("BI Total – MD part")

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.

Tables of vital signs and laboratory values will present results for the above mentioned on treatment phase.

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

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

Section 7.3 of the CTP:
Important protocol deviation (IPD) categories will be suggested in the Integrated Quality and Risk Management Plan (IQRMP), 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 latest 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 Deviations (iPD)" (3).

If any iPDs are identified, they are to be summarised into categories and will be captured in an accompanying Excel spreadsheet (DV sheet), where the categories which are considered to be iPDs in this trial are defined (4). The decision on the exclusion of subjects with iPDs from population sets will be documented in the decision log.

The iPDs will be summarised and listed.

6.3 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 tables / listings and the disclosure tables for enrolment.

Section 7.3 of the CTP:
Treated set (TS)
The treated set includes all patients who were randomized and treated with at least one dose of study drug (either treatment with BI 764524 or Sham).

[redacted]

Biomarkers

Section 7.3.3.2 of the CTP:

[redacted]

Biomarker set (BMS):
Biomarker data and parameters of a patient will be included in the statistical biomarker (BM) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of biomarkers (to be decided no later than in the Report Planning Meeting) or due to non-evaluability.

Exclusion of a patient's data will be documented in the CTR.

Biomarker data and 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.

Table 6.3: 1 Subject sets analysed

Class of endpoint	ES	TS	PKS	BMS
Primary endpoints		X		
Analysis of PK endpoints			X	
Analysis of PD endpoints/biomarkers				X
[redacted]		[redacted]		
Other secondary and further endpoints		X		
Safety parameter		X		
Demographic/baseline parameter		X		
Important protocol deviations		X		
Disposition/Disclosure (enrolment)	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 7.5.

Imputation might be necessary for AE dates in the safety evaluation. Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035 (7)).

Missing time at unscheduled ocular assessment 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 data and outliers of PK data are handled according to BI standards.

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, a missing value is obtained only in case that

(i) all on-treatment values are missing and
(ii) the baseline value is less than or equal to 500 msec, or missing.

If condition (i) is fulfilled but the baseline value is greater than 500 msec, this case will be categorized as ‘no new onset’. If baseline is missing and the maximum on treatment QTc interval is greater than 450 msec (or 500 msec for QT interval, respectively), this is classified as a ‘new onset’ in the respective category. If baseline is missing and the maximum QTc interval is less than or equal to 450 msec (or 500 msec for QT interval, respectively), this will be categorized as ‘no new onset’. If baseline is missing, a QTc/QT interval > 500 msec at any time on treatment will be a notable finding.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before first administration of trial medication (= value at V2, in case no actual time is given in data).

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.

This rule will also apply to the additional endpoint, [redacted].

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

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

MD Part:
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, Table 6.7: 2, and Table 6.7: 3.

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 where the worst scenario is chosen. If there are two observations which have the same difference in days to the planned day, the later value will be selected.

For [redacted], the worst case scenario will be used (i.e. highest value will be taken) if more than one measurement is made in the same time window.

Section 5.2.5.1 of the CTP:
Central ECG lab evaluation will be performed for all ECGs indicated in the Flow Chart I and 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.*

The baseline value of an ECG variable is defined as the mean of the ECG measurements prior to drug administration.

Unscheduled measurements of laboratory 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.

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

			Time window [days]		
Visit number (CTP)	Visit label (analysis)	Planned Day	Window per CTP	Start (extended)	End (extended)
V2	**Baseline**	1	± 0	NA	1
V3	**Week 4**	29	± 3	2	43
V4	**Week 8**	57	± 3	44	71
V5	**Week 12**	85	± 7	72	99
V6	**Week 16**	113	± 7	100	134
V7	**Week 22/EoS**	155	+7	135	End of Trial visit date

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

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

			Time window [days]		
Visit number (CTP)	Visit label (analysis)	Planned Day	Window per CTP	Start (extended)	End (extended)
V2	**Baseline**	1	± 0	NA	1

			Time window [days]		
Visit number (CTP)	Visit label (analysis)	Planned Day	Window per CTP	Start (extended)	End (extended)
V3	**Week 4**	29	± 3	2	43
V4	**Week 8**	57	± 3	44	71
V5	**Week 12**	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: 3 Time window assignment physical examination measurements to visits for statistical analysis of the MD Part

			Time window [days]		
Visit number (CTP)	Visit label (analysis)	Planned Day	Window per CTP	Start (extended)	End (extended)
V1	**Baseline**	… -1	NA	NA	1
V5	**Week 12**	85	± 7	2	End of Trial visit date

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

7. PLANNED ANALYSIS

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

The prior specified in the CTP, Section 7.1 will be used in all BLRM evaluations.

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (8)) with the exception of those generated for PK-calculations (6).

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.

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

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

[redacted]

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 (%) 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.

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

[redacted]

[redacted]

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 summarized by treatment group and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Summaries will be presented for concomitant therapies ongoing at baseline and separately for those newly onset after first drug intake. Use of non-drug therapies will also be summarized.

Concomitant diseases and non-drug therapies 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 displayed as a footnote in the respective output.

The diagnoses and medications and non-drug therapies 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, efficacy and safety data 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. This is performed by a qualified physician. In the MD part the unmasked injector with no other involvement in the trial will administer the trial medication.

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 ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

SRD part:

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 grade 3+ according to the NEI Grading of vitreous haze, and anterior chamber cells of 3+ according to standardization of Uveitis Nomenclature (SUN) working group (WG) grading scheme for anterior chamber cells (see Table 5.2.1: 1 below) 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*
- [redacted]
- *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).*

Section 5.2.7.1.4 of the CTP:
All AEs meeting the criteria for a dose limiting event (DLE) as defined in Section 5.2.1 are defined as AESIs for this trial.

Descriptive statistics (number and percentage of patients with DLEs) will be provided by dose group and in total.

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

[redacted]

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

Section 7.3.2 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.

The change from baseline in FAZ area (separately for the superficial vascular complex and full thickness retina) over time 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 j^{th} visit of the i^{th} 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.

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.

5. 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.

The analysis will be performed on the TS. The above analysis is to be repeated for the below endpoints:

i. The change from baseline in Central Retinal thickness over time.
ii. The change from baseline in BCVA over time.
iii. The change from baseline in FAZ area 3mm scan size in full thickness retina over time.

The focus in the CTR will be on the manually graded 3mm scan size FAZ FTR parameters, as such the pre-existing manually corrected FAZ FTR parameters (not assessed by scan size) will be placed in Appendix 16.1.13.1 and will not be described in the CTR.

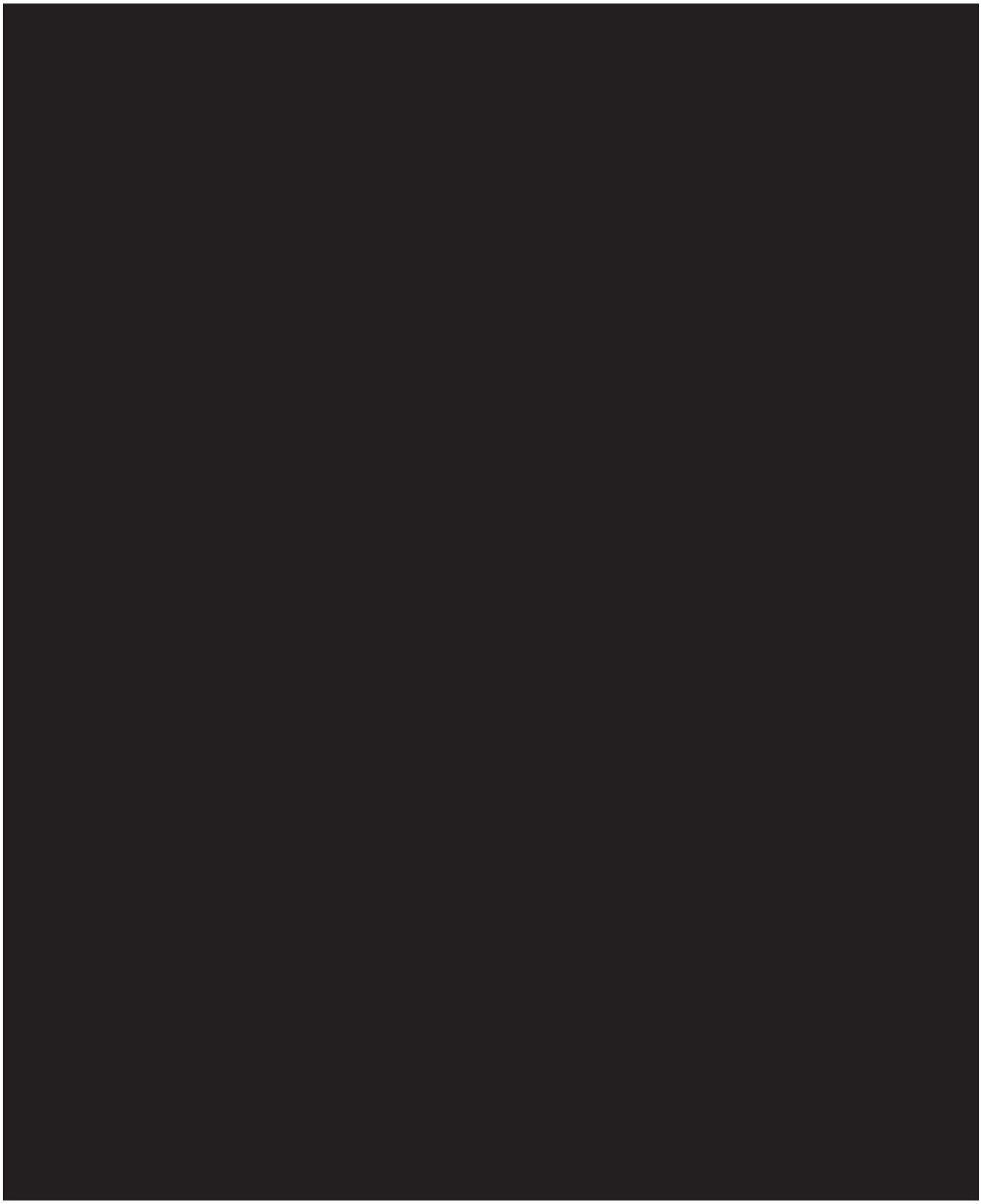
For all continuous longitudinal secondary endpoints, time profiles of mean (±SD) absolute values and mean (±SD) changes from baseline by treatment group as well as individual time profiles (absolute values and changes from baseline) per treatment group will be provided for the study eye / fellow eye in addition.

7.5.3 Interim analysis

Section 7.4 of the CTP:
For this trial, a “Fast track” analysis of the MD part is planned at Visit 6 (Week 16). After all data of the above-mentioned time point are available, a snapshot of the database will be taken.
This snapshot will be used for performing the Fast track analysis.

For the fast track analysis, the change from baseline in FAZ area 3mm scan size in full thickness retina over time will be analysed using the MMRM described in Section 7.5.2, with the restriction that only visits up to Visit 6 (Week 16) are included in the model.

[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) (14), the following information will be included in Appendix 16.1.13.1 of CTR:

- number of subjects included by country
- number of subjects 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 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] (9).

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.

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

- All AE attributes are identical (lower level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest (AESI))
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started within one hour after end of the first occurrence)

Section 5.2.7.1.4 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 transaminase) and/or ALT (alanine transaminase) ≥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 eDC. 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) as defined in Section 5.2.1 are defined as AESIs for this trial.

The analysis of adverse events will be based on the concept of treatment emergent adverse events.

Section 5.2.7.1.4 of the CTP: *For BI 764524 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.*

According to ICH E3 (11), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at the RPM/DBLM at the latest.

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

The frequency of patients with AEs will be summarized by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with other significant AEs according to ICH E3 (11), for patients with serious AEs, for patients with drug-related AEs, for patients with drug related serious adverse events for patients with AESIs, for patients with ocular AEs, and for patients with ocular AEs in the study eye.

The SOC and PTs will be sorted by frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.

In addition, frequencies of patients 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).

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 possible clinically significant will be flagged in the data listings.

To support analyses of liver related adverse drug effects, 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 adverse events 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 significant abnormal or not (at the RPM/DBLM at the latest).

Descriptive statistics of laboratory data including change from baseline will be calculated by visit based on the worst value of the patient at that visit.

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure, pulse rate and body weight).

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.

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 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.

Ophthalmologic data

[redacted] will be analysed descriptively by time point, treatment group and in total.

Shift tables from baseline in SUN grading for anterior chamber cells, in other slit lamp examinations and in Diabetic Retinopathy Severity Scale will be presented by time point, treatment group and in total.

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-KMED-TMCP-MAN-0012:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
3.	*BI-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, KMED.
4.	*BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version; KMED.
5.	*BI-KMED-COPS-OTH-0101:* "Integrated Quality and Risk Management Plan", current version; KMED.
6.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED.
7.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version; KMED.
8.	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
9.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
10.	[redacted]

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
12.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.
13.	Ring A. Statistical models for heart rate correction of the QT interval. Stat Med 2010 [R10-2920]
14.	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.
15.	*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	**10-MAY-22**	[redacted]	None	This is the final TSAP
2	**25-APR-23**		Section 2, 4, 5.2.2, 5.3, 7.5.2, 7.5.3, 7.6, 7.8.4, 9, 10.1	Updated the secondary and further endpoints and their analysis. Removed Interim analysis description; Reduction of ECG analyses descriptions, implemented protocol amendment updates, additional endpoints were added which are not available in the protocol,
3	**25-MAY-23**		Section 4, 6.7, 7.5.2, 7.5.3	BCVA analysis updated to only include all patients, Fast Track Analysis reduced to only FAZ 3mm FTR, Rule introduced to how to deal with more than one [redacted] measurement in the same time window. Time windows corrected and aligned with ADS plan.

APPROVAL / SIGNATURE PAGE

Document Number: c33215538 **Technical Version Number:3.0**

Document Name: 8-01-tsap-core

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 dosing (single-masked, raNdomized, sham-controlled) of BI 764524 in panretinaLphotocoagulation (PRP) treated proLiferative diabetic retinopathy (PDR) patients with diabetic macular ischemia

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	[redacted]	26 May 2023 16:26 CEST
Approval		26 May 2023 16:26 CEST
Author-Trial Statistician		26 May 2023 17:31 CEST
Approval-Project Statistician		26 May 2023 18:19 CEST
Approval-Clinical Trial Leader		29 May 2023 10:22 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed