TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c31147466-02**
BI Trial No.:	**1336-0007**
Title:	Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with wAMD (open label, non-randomized, uncontrolled). (Including Protocol Amendments No.1-7 [c17360540-08])
Investigational Product:	BI 836880
Responsible trial statisticians:	[redacted] Email: [redacted]
Date of statistical analysis plan:	02 FEB 2024
Version:	2.0

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body mass index
CSFT	Central Subfield Thickness
CV	Arithmetic Coefficient of Variation
DBLM	Database Lock Meeting
DLE	Dose Limiting Event
ES	Enrolled Set
EOT	End of Trial
FAS	Full Analysis Set
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
IOP	Intraocular Pressure
iPD	Important Protocol Deviation
IQRMP	Integrated Quality and Risk Management Plan
IRF	Intra-retinal Fluid
IVT	Intravitreal
LLT	Lower Level Term
Max	Maximum
Min	Minimum
MRD	Multiple Rising Dose
N	Number of non-missing observations
OCT	Optical Coherence Tomography
P10	10^{th} percentile
P90	90^{th} percentile
PED	Pigment Epithelial Detachment
Q1	1^{st} quartile

Term	Definition / description
Q3	3rd quartile
q4w	Once in 4-weekly interval
RAGe	Report Appendix Generator system
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SHRM	Subretinal Hyper-Reflective Material
SMC	Safety Monitoring Committee
SoC	Standard of Care
SOC	System Organ Class
SRD	Single Rising Dose
SRF	Sub-Retinal Fluid
SUN	Standardization of Uveitis Nomenclature
TS	Treated Set
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 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 WinNonlinTM software (version 8.1.1 or higher, [redacted]) or SAS Version 9.4 (or later version).

The statistical analyses will be performed within the validated working environment CARE, including SASTM (current Version 9.4, by [redacted] and a number of SASTM-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 CTP will be performed and are described in more detail in this TSAP.

The baseline definition of CTP was clarified in TSAP:
In CTP Section 5.1 it is '*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*'. If an actual time is given in the data, it will be checked whether the measurement at visit 2 was done before or after trial drug administration. If it is done after administration, the measurement will not be used as a baseline measurement. The baseline definition was updated to 'The baseline value is defined as the last measurement before first administration of BI 836880 (= value at V2, in case no actual time is given in data)'.

The definition of responder in further endpoints was clarified in TSAP. In CTP section 2.2.2, one of the further endpoints in MRD part is "Responder (yes/no) defined as absence of intra-retinal or sub-retinal fluid (IRF/SRF) or resolution of SHRM/PED in the study eye at Week 16 (Visit 6, cohort 3 only)". This definition is modified as: "Responder (yes/no) defined as resolution of IRF and SRF or resolution of SHRM/PED in the study eye at Week 16 (Visit 6, cohort 3 only)". To avoid redundancy, endpoint "Absence (yes/no) of intra-retinal or sub-retinal fluid (IRF, SRF) in the study eye at Week 16 (Visit 6, cohort 3 only)" and "Resolution (yes/no) of subretinal hyper-reflective material/retinal pigment epithelial detachment (SHRM/PED) in the study eye at Week 16 (Visit 6, cohort 3 only)" could be removed.

5. ENDPOINTS

The pharmacokinetic and pharmacodynamic parameters listed in Section 2.2 of the CTP for drug BI 836880 will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' [001-MCS-36-472] (4).

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

SRD part:

- *Number of patients with ocular dose limiting events (DLEs) from drug administration until end of trial (EOT).*

For definition of DLEs, refer to Section 7.4.

MRD 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.

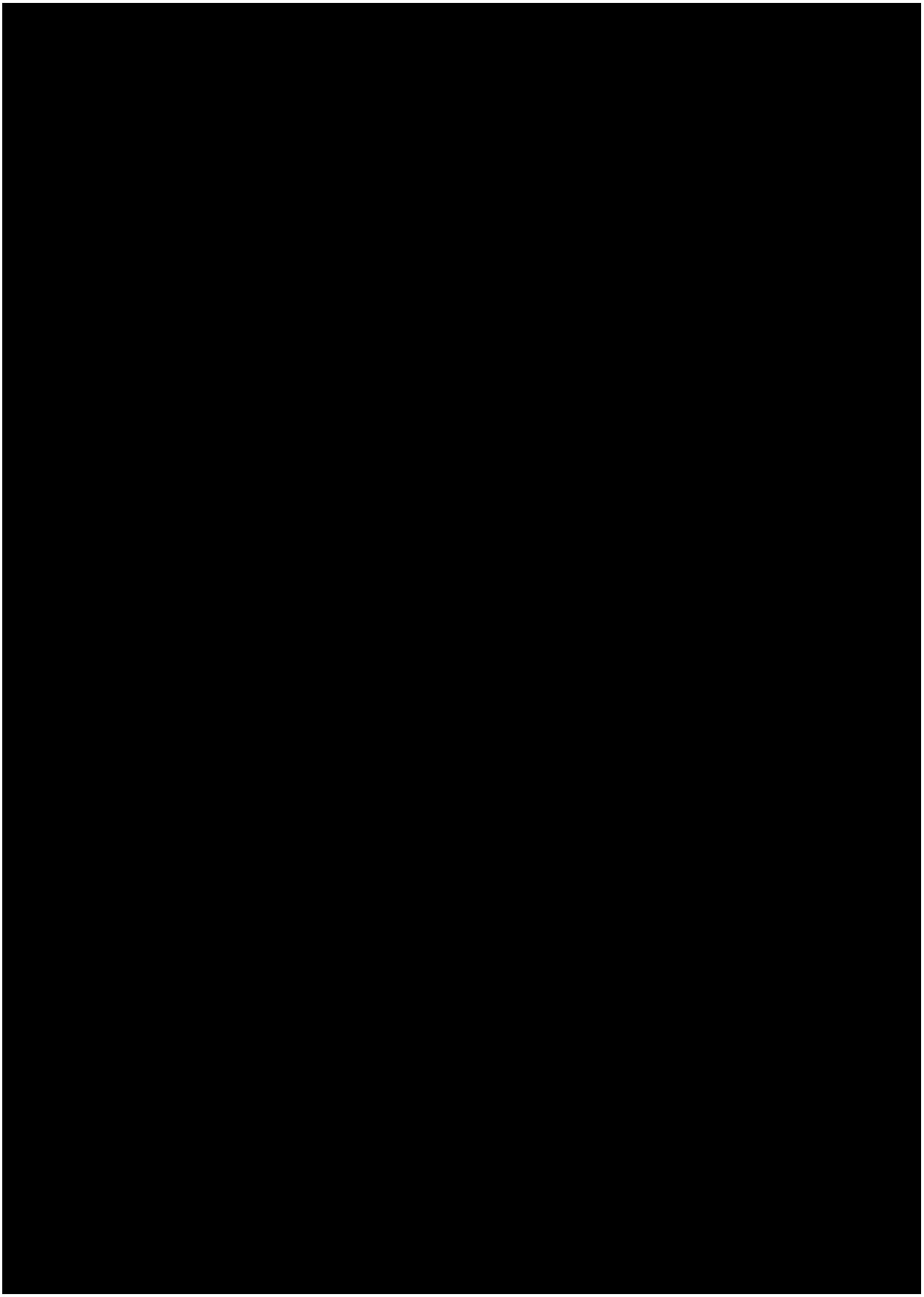
5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:
SRD part:

- *Number of patients with drug related AEs*
- *Number of patients with any ocular AEs in the study eye*

MRD part:

- *Percent change from baseline in Central Subfield Thickness (CSFT) in the study eye at Week 12 (Visit 5), for each dose*
- *Change from baseline in BCVA in the study eye at week 12 (Visit 5)*
- *Time to recurrence after the last treatment*
- *Number of patients with any ocular AEs in the study eye*



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

The trial will consist of an SRD part followed by an MRD part. Both parts will be conducted open-label, non-randomized, and uncontrolled.

It was planned to assign up to 42 patients in total, up to 15 in the SRD part (5 sequential dose groups comprising 3 patients each) and 27 in the MRD part (11 patients in dose group 1 (first cohort) and 16 patients in dose group 2 (4 patients from cohort 2 and 12 patients from cohort 3)).

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		Short Label
1	A	BI 836880, 80 mg/mL solution, 0.06 mg, ivt	BI 0.06mg
2	B	BI 836880, 80 mg/mL solution, 0.18 mg, ivt	BI 0.18mg
3	C	BI 836880, 80 mg/mL solution, 0.5 mg, ivt	BI 0.5mg
4	D	BI 836880, 80 mg/mL solution, 1.0 mg, ivt	BI 1mg
5	E	BI 836880, 80 mg/mL solution, 2.0 mg, ivt	BI 2mg

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

Dose group	Treatment		Short Label*
1	F	BI 836880 Concentrate for Solution for Injection 80 mg/mL, diluted with Diluent to 20 mg/mL solution, 1.0 mg, ivt	BI 1mg q4w – cohort 1
2	G	BI 836880 Concentrate for Solution for Injection 80 mg/mL, diluted with Diluent to 40 mg/mL solution, 2.0 mg, ivt	BI 1mg q4w – cohort 2
3	H	BI 836880 solution for injection 40 mg/mL, 2.0 mg, ivt	BI 1mg q4w – cohort 3

* cohort 1: resistant patients, cohort 2: naïve patients, cohort 3; frequently treated patients

Cohorts 2 and 3 are displayed separately although belonging to the same dose group.

Section 7.3.4 of the CTP:

For BI 836880, 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.

Thus, no follow-up period is considered in this trial. 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 836880)
- **On treatment**
    - **BI treatment** (separately for each treatment, ranging from the time of first administration of BI 836880 until 0:00h (midnight) on the day after trial completion date) – labelled with the short labels defined in tables above

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 - the actual treatment is equal to the study treatment). Screening will not be included in this analysis. In Section 15.3, a total overall, on treatment phases included in this analysis ("**Total**") will be provided in addition.

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

Important PDs will be reviewed at Medical Quality Review Meetings (MQRM) and/or TOM conducted periodically during the trial. 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)" (**10**).

Section 7.3 of the CTP: *Important protocol deviations (iPDs) will be defined in the Integrated Quality and Risk Management (IQRM) plan.*
Categories which are considered to be iPDs in this trial were defined in the integrated quality and risk management plan (IQRMP) prior to trial initiation. The iPD list was transferred into the iPD specification file (due to changes in the SOP). Within this transfer some minor adaptations were made to comply with new naming conventions and categorizations.

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 summarized into categories and will be captured in the decision log (16) and/or via iPD specification file (sdtm-dv-domain-specification) (12). Both documents will be stored within the TMF in EDMS.
The iPDs will be summarised and listed.

Table 6.2: 1 Important Protocol Deviations

Category / Code		**Description**	**Comment**	**Excluded from**
A		**Eligibility Criteria**		
	A1	**Eligibility Criteria**	Critical inclusion/exclusion criteria violated	No analysis sets
	A2	**Eligibility Criteria**	Withdrawal criteria as defined in the protocol met, but subject was not withdrawn	No analysis sets
B		**Informed Consent**		
	B1	**Informed Consent**	Required Informed Consent not available/not done	All analysis sets
	B2	**Informed Consent**	Informed consent given late	No analysis sets
C		**Trial Medication and Randomization**		
	C1	**Trial Medication and Randomization**	Incorrect dose injected	ERS
	C2	**Trial Medication and Randomization**	Treatment out of protocol defined window	ERS
D		**Concomitant Medication**		
	D1	**Concomitant Medication**	Improper medication washout	ERS
	D2	**Concomitant Medication**	Prohibited medication use	ERS
E		**Critical Study Procedure/Assessment**		
	E2	**Critical Study Procedure/Assessment**	OCT assessment out of window	ERS
F		**Safety Procedures/SAE Reporting**		

Category / Code		Description	Comment	Excluded from
	F1	**Safety Procedures/SAE Reporting**	Critical safety procedure not followed	No analysis sets
G		**Privacy/Data Protection**		
	G1	**Privacy/Data Protection**	Privacy and/or data protection violated	No analysis sets
Q		**Non-important COVID-19 Related**		
	Q1	**Non-important COVID-19 Related**	Missed examination	No analysis sets
	Q2	**Non-important COVID-19 Related**	Missed visit	No analysis sets
	Q3	**Non-important COVID-19 Related**	Drug shipment	No analysis sets

6.3 INTERCURRENT EVENTS

This section is not applicable.

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)
The TS will consist of all patients who were treated with at least one dose of BI 836880.

Full Analysis Set (FAS; only MRD part)
The FAS will consist of all patients who were treated with at least one dose of BI 836880 and have baseline and on-treatment CSFT measurements for the study eye in the time interval from drug administration to week 12. It will be used for the analysis of CSFT (change and percent change) only.

Evaluable Responders' Set (ERS, MRD cohort 3 only):
The ERS will consist of all patients who completed three doses of BI 836880 and have SD-OCT measurements at Week 16 (Visit 6) and haven't received SoC or any prohibited medication through week 16.

Patients with iPDs related to efficacy assessments that are expected to majorly affect the validity of assessment of efficacy at week 16 will be excluded from ERS. These include for

e.g., lack of compliance (including missed treatments, treatment misallocation and treatment/OCT assessment outside window), missing data, SoC or any prohibited medication, improper assessment at reading center and deviation from inclusion/exclusion criteria.

Any dropouts or withdrawals prior to completion of three doses of BI 836880 will be considered as a criterion of exclusion from ERS. In addition, any dropouts or withdrawals after completion of three doses of BI 836880 will also be excluded from ERS, unless SD-OCT measurements are available for that patient at Week 16.

Pharmacokinetic parameter analysis set (PKS):
This set includes all subjects in the treated set (TS)

- who received at least one dose of the test product BI 836880 and
- who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment.

Descriptive and model-based analyses of PK parameters will be based on the PKS.

Table 6.4: 1 Subject sets analyzed

Class of endpoint	ES	TS	FAS	ERS	PKS
Primary endpoints		X			
Analysis of CSFT (percent) change from baseline – MRD part only			X		
Other secondary and further endpoints		X			
Responder analysis				X	
Safety parameter		X			
Demographic/baseline parameter		X			
Important protocol deviations		X			
Disposition/Disclosure (enrolment)	X				
PK, ADA and PD analysis					X

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in CTP, Section 7.5.

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) (3).

Missing data and outliers of PK data are handled according to BI standards.
PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

Section 7.5 of the CTP: *Missing baseline laboratory values will be imputed by the respective values from the screening visit.*

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before first administration of BI 836880 (= 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.*

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

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

To utilize all available data, including values collected between protocol-specified visit windows and unscheduled visits, time intervals will be defined for analysis of efficacy data. If multiple values are recorded within a visit interval, the value collected closest to the planned visit date will be included in analyses of efficacy endpoints (CSFT, BCVA, and responder analysis) and IOP.

Unscheduled measurements of laboratory 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.

Table 6.7: 1 Visit intervals for efficacy endpoints (CSFT, BCVA, responder analysis) and IOP

		Interval Definition		
Visit	**Planned day**	**From (day)**	**To (day)**	**Visit description**
1	-28 to -3	NA	-1	Screening
2	1	1	1	Baseline
3	29	2	43	Week 4
4	57	44	71	Week 8
5	85	72	99	Week 12
6	113	100	127	Week 16
7	141	128	155	Week 20
8	169	156	Last assessment date	Week 24

7. PLANNED ANALYSIS

If not stated otherwise, the SRD part and the MRD part will be analyzed separately. The MRD part consists of three cohorts which will be shown in one table, except for the tables based on ERS which is defined for Cohort 3 only.

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 7.1 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 of the CTR and Appendix 16.1.13.5.

Descriptive data analysis of biomarker/PD parameters and concentrations will be performed by the [redacted] and will be presented in Section 15.7 of the CTR and Appendix 16.1.13.6.

Descriptive data analysis of ADA results will be performed by the [redacted] and will be presented in Section 15.8 of the CTR and Appendix 16.1.13.7.

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045) (6) except for those generated for PK-calculations following BI standards for PK/PD analysis (5).

The individual values of all patients will be listed, sorted by dose group, cohort (MRD part only), 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 as well as for all PK parameter, 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

Section 7.3.5 of the CTP:
The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic 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 CRF and will display the number of observations in a category, as well as the percentage (%) for each dose 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 missing values.

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

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 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, consequently, any calculation that relies on λz) only; the value is included for all other analyses.

Further details are given in 001-MCS-36-472 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) and 001-MCS-36-472_RD-03 “Description of Analytical Transfer Files and PK/PD Data Files” (9).

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 dose group/cohort and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Previous and concomitant therapies will be presented per dose group/cohort without consideration of time intervals and treatment periods. In addition, the rescue medication will be presented separately for MRD part.

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. Exposure table/listing would quantify whether administration per dose was as per the protocol or not, to indicate any potential compliance issues. Any deviations from complete intake will be addressed in the MQRM/ RPM/DBLM and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

Section 5.2.1 of the CTP:
For the SRD part and MRD cohort 1:

A DLE is defined as the occurrence of any of the following events in the study eye:

- *Development of sterile endophthalmitis and/or sterile inflammation of the vitreous grade 4+ according to standardization of Uveitis Nomenclature (SUN) working group (WG) grading scheme for anterior chamber cells* (see CTP) *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).*

[…]
DLE criteria are not applicable to MRD cohorts 2 and 3. Should an event involving intraocular inflammation/signs of vascular occlusion, decreases in visual acuity, and/or intraocular pressure occur, the event should only be reported as an AESI as described in CTP *Section 5.2.8.1, and not as a DLE.*

Section 7.3.1 of the CTP:
SRD part:

The primary safety endpoint "Number of patients with ocular DLEs from drug administration till EOT" will be analysed descriptively, based on the TS.

[…]

MRD part:
The primary safety endpoint "Number of patients with drug related AEs from drug administration till EOT" will be analysed descriptively, based on the TS.

Descriptive statistics will be provided by dose group/cohort and in total (more details regarding the analysis of AEs are described in Section 7.8.1).

[redacted]

7.4.4 Supplementary analysis

No supplementary analysis is planned.

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 7.3.2 of the CTP:
In principle, all secondary endpoints specified in Section 5.2.2 *will be analyzed descriptively, based on the TS. The analysis of percent change from baseline in CSFT in the study eye at week 12 (Visit 5) will be done by dose, based on the FAS.*

Descriptive statistics for absolute values as well as changes from baseline (percent changes and changes in CSFT and changes in BCVA (study eye)) will be provided by dose group/cohort and in total. Time profiles of mean (±SD) absolute values and mean (±SD) changes from baseline by cohort as well as individual time profiles (absolute values and changes from baseline) per treatment group/cohort will be provided. For percent changes of CSFT, median and minimum/maximum values will be shown instead.
For those endpoints related to adverse events refer to Section 7.8.1.

Section 5.2.2 of the CTP:
Time to recurrence will be assessed in the MRD part, based on the TS, from last trial drug administration to occurrence of any of the following in the study eye, leading to the use of wAMD rescue medication as decided by the investigator:

- *Increase in CSFT ≥ 75 µm with a decrease in BCVA of ≥ 5 letters compared to Visit 5,*

OR

- *Decrease in BCVA of > 5 letters compared to baseline (Visit 2), due to worsening wAMD activity,*

OR

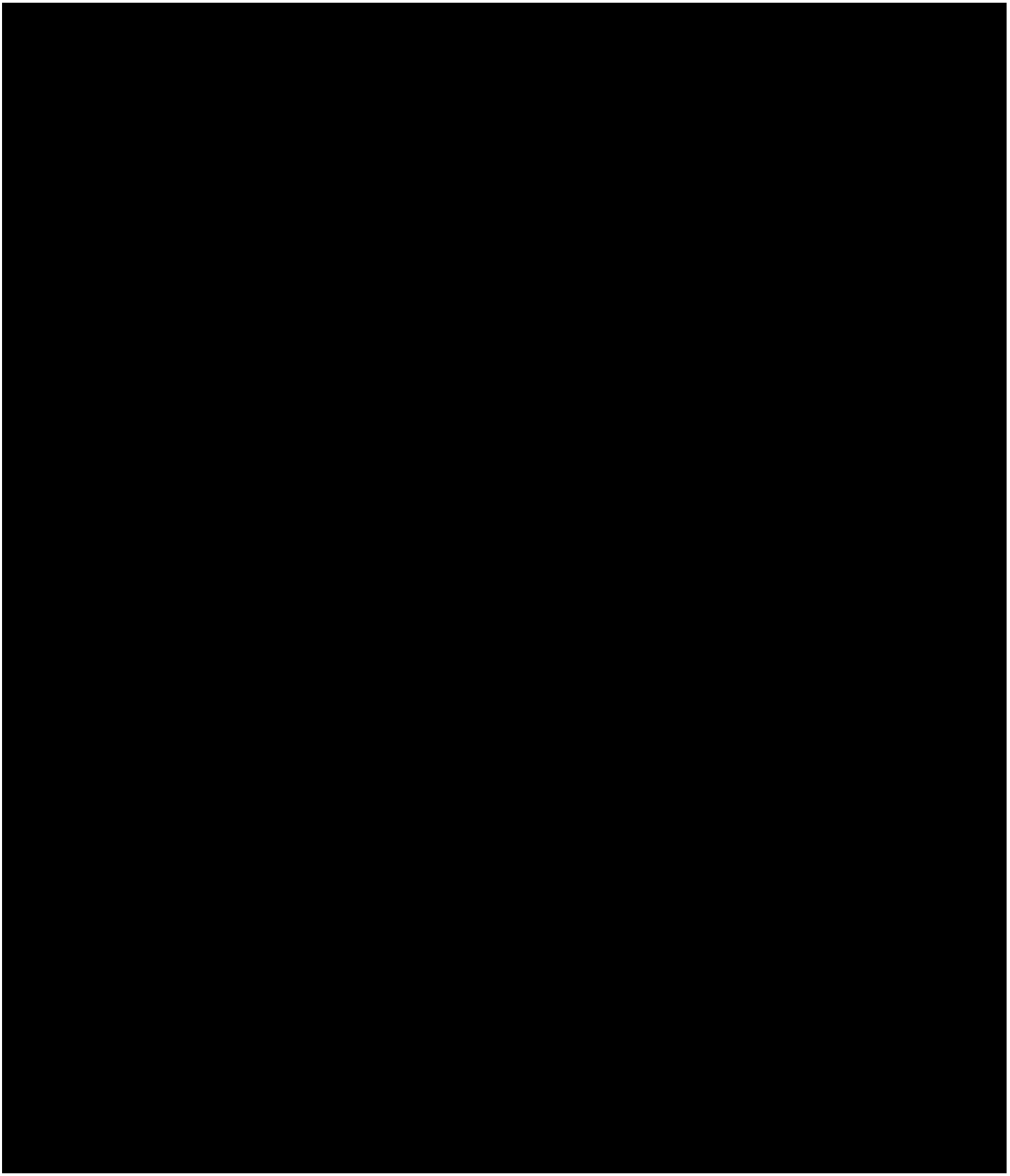
- *Decrease in BCVA of ≥ 10 letters compared to the best prior BCVA, due to worsening wAMD activity*

From above criteria, if Visit 5 BCVA/CSFT assessment data is missing, BCVA/CSFT values available earlier than Visit 5 will be used. The last trial drug administration is strictly referring to the third injection, if a patient doesn't complete three injections, the patient will not be evaluated for time to recurrence endpoint and will be censored as per Table 7.5.2:1. The details of censoring rules are listed in the table below. Kaplan-Meier curves will be estimated by cohort.

Table 7.5.2: 1 Censoring Rules for time to recurrence

No.	Scenario	Relative Day of Event or Censoring	Outcome
1	A patient meets more than one recurrence rule	Earliest day of recurrence	Event (Recurrence)
2	A patient completed the treatment and follow-up without recurrence	Last day of follow-up	Censored
3.	SAE after completion of three injection	Day of SAE	Censored
4.	Treatment discontinuation (not completing all three injections)	Time to censoring value is assigned to 1 (day 1 = the first day after last injection)	Censored

[redacted]



[redacted]

7.6.2 Pharmacokinetic/Pharmacodynamic endpoints

Descriptive statistics of plasma concentrations, ADA, PK and PD endpoints will be done by [redacted] and will be presented in Section 15.6,15.7 and 15.8 of the CTR.

The analysis of PK & PD parameters as well as the tables and graphs for the pharmacokinetic non-compartmental analyses will follow specific definitions of this TSAP or, otherwise, the BI standard procedure "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" [001-MCS-36-472] (4).

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 dose group/cohort.

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.

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] (7) and [BI-KMED-BDS-HTG-0066] (2).

All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between start of treatment and the EOT visit will be assigned to the respective treatment. All AEs occurring before first drug intake will be assigned to 'screening'. For details on the treatment definition, see Section 6.1.

Section 5.2.8.1.4 of the CTP:
All AEs meeting the criteria for a dose limiting event as defined in Section 7.4.1 *are defined as AESIs for SRD and MRD cohort 1.*

For MRD cohorts 2 and 3, the AESIs are defined as following:

***Ocular related events** (applicable to MRD cohorts 2 & 3)*

- *Intraocular inflammation events*
  - *Anterior chamber cells of grade 1+ according to the Standardization of Uveitis Nomenclature (SUN) working group (WG) grading scheme (see* CTP *Table 5.2.1: 1)*

- *Sterile inflammation of the vitreous of 1+ according to the NEI Grading of vitreous haze (see* CTP *Table 5.2.8.1.4: 1)*

- *Signs of vascular occlusion and inflammation (vasculitis) in the retina, including peripheral retinal hemorrhages in the area supplied by the occluded vessel (hemorrhage of the macula would not be included as this is a sign of wAMD disease)*
- *Visual acuity decrease of more than 15 letters from the previous visit*
- *Persistent IOP over 30 mmHg for 3 days after study treatment is administered, despite rescue treatment*

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- *an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin≥2-fold ULN measured in the same blood draw sample, and/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 system.
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 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.

According to ICH E3 (15), in addition to Deaths and serious adverse events, AEs classified as 'other significant' 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 (including number of patients with any AE, DLEs (applicable for SRD part and MRD part cohort 1 only), drug related AEs, procedure 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 group/cohort, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with ocular AEs, for patients with DLEs, 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 drug-related AESIs and for patients with study procedure related AEs. In addition, the frequency of patients with AEs will be summarized by worst intensity, treatment group/cohort, SOC and PT.

The system organ classes will be sorted alphabetically, PTs will be sorted by frequency (within SOC).

In addition, frequencies of patients with non-serious AEs that have an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT (both trial parts combined).

For disclosure of adverse events on EudraCT the following three entries will be created, combined for both trial parts:

- 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] (8).

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 (Or assigned to that visit / planned time point).

Additionally, 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. Dose groups will be compared descriptively with regards to distribution parameters as well as with regards to frequency and percentage of patients with abnormal values or possibly clinically relevant abnormal values.

Clinically relevant findings in laboratory data will be reported as adverse events if judged clinically relevant by the investigator and will be analyzed 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).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure, pulse rate). In the vital signs listing, the difference from baseline will also be displayed.

For post-dose measurements of vital signs, descriptive statistics will be calculated by planned time point based on the first value of the subject at that planned time point (or assigned to that planned time point). For baseline value, the last measurement before drug administration will be used.

Body weight will be listed only.

Clinically relevant findings in vital signs as judged by the investigator will be reported as AEs.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' or as AEs (if they occurred during treatment) and will be analyzed as such.

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.

7.9 OTHER ANALYSIS

Ophthalmological data

All the following endpoints will be listed and will be analyzed descriptively by dose group/cohort and in total.

- The results of the IOP measurements as well as the corresponding changes from baseline at each time point for the study eye and the fellow eye (time profiles will be provided as well)
- The results of the BCVA measurements as well as the corresponding changes from baseline at each time point for the study eye and the fellow eye (time profiles will be provided as well)
- The results of the SUN grading for Anterior Chamber Cells (slit lamp) will be analyzed descriptively at each time point by number and percentages for the study eye and the fellow eye. (If no entries unequal 0/not evaluable are available, a listing will be sufficient.)

The following parameters will be listed only:

- Other results of the Slit Lamp examination (categories defined in CRF: 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, retinal tear, retinal detachment).
- Color fundus photography (gradeability (yes/no), overall quality (good, fair, poor), vitreous haze, additional CFP findings)
- Categorical assessments from OCT (gradeability (yes/no), scans to be analysed (25 line scan, 49 line scan, both), overall quality (good, fair, poor), CNV presence (present, absent), if present only: type of CNV, CNV involvement of the foveal center, IRF within the central 6mm of the macula (present, absent), , GA presence (*present, absent*), drusen (*present, absent*), PED (*present, absent*), of present only: type of PED, outer retinal tabulation (*present, absent*),correction of segmentation lines (*yes, no*), if yes only: level of segmentation, additional findings
- Categorical and other assessments from OCT-A (gradability (*yes/no*), type of device used, overall quality (*good, fair, poor*), vessel flow density (Deep Capillary Plexus (% of area): foveal, parafoveal-superior, parafoveal-nasal, parafoveal-inferior, parafoveal-

temporal, perifoveal-superior, perifoveal-nasal, perifoveal-inferior, perifoveal-temporal, presence of CNV (*present, absent*), if present only: location of CNV (*DCP, outer retina, choroid, DCP+outer retina, outer retina+choroid, DCP+outer retina+choroid*), additional findings)

7.9.1 Biomarker analyses

Not applicable.

7.9.2 PK / PD analyses

Covered in Section 7.6.2.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Not applicable due to open label handling of the trial as described in CTP section 4.1.6.1.

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-BDS-HTG-0066:* "Analysis and Presentation of AE data from clinical trials", current version, KMED.
3.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version; KMED.
4.	001-MCS-36-472*:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", 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-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
8.	*BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; KMED.
9.	*BI-KMED-TMCP-MAN-0010:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
10.	*001-MCS-40-413:* Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.
11.	*BI-KMED-BDS-QRC-0065:* "Transition Plan for Implementing Protocol Deviation Process for Clinical Trials", template, current version, KMED.
12.	*BI-KMED-BDS-TMP-0059:* "iPD specification document (sdtm-dv-domain-specification)", template, current version, KMED.
13.	*BI-KMED-BDS-TMP-0083:* "iPD for Reconciliation", template, current version, KMED.
14.	*001-MCS-40-135_RD-01:* "Integrated Quality and Risk Management Plan", current version, Group "Clinical Operations", IDEA for CON.
15.	*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.
16.	*001-MCS-50-415_RD-03:* "Clinical Trial Analysis Decision Log (template) Decision Log", current version, Group "Biostatistics & Data Sciences", IDEA for CON.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	07-DEC-2023	[redacted]	None	This is the final TSAP. 12JAN2024: Correction of version date in history table
2.0	02-FEB-2024	[redacted]	None	1. Changes requested by publishing check: a. Update the document number from "c31147466-01" to "c31147466-02". b. Correct the table number on page 23 to "Table 7.5.2:1". c. Remove extra space between table number and title for Table 7.5.2:1 and 6.7:1. 2. Change in History table.