




Trial Statistical Analysis Plan

c09629286-02

BI Trial No.:	1320.22
Title:	A randomized, double-masked, placebo-controlled exploratory study to evaluate pharmacodynamics, safety and tolerability of orally administered BI 1026706 for 12 weeks in patients with mild visual impairment due to center-involved diabetic macular edema (DME) (Including protocol amendment 2 [c03441881-03])
Investigational Product(s):	BI 1026706
Responsible trial statistician(s):	 Tel:  Fax: 
Date of statistical analysis plan:	26 JUL 2017 SIGNED
Version:	Final
Page 1 of 24	
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1. TABLE OF CONTENTS

TITLE PAGE.....	1
1. TABLE OF CONTENTS.....	2
LIST OF TABLES	3
2. LIST OF ABBREVIATIONS.....	4
3. INTRODUCTION	6
█	█
5. ENDPOINTS.....	8
5.1 PRIMARY ENDPOINT.....	8
5.2 SECONDARY ENDPOINTS	8
█	█
6. GENERAL ANALYSIS DEFINITIONS.....	10
6.1 TREATMENTS	10
6.2 IMPORTANT PROTOCOL VIOLATIONS.....	11
6.3 PATIENT SETS ANALYSED	12
█	█
6.5 POOLING OF CENTRES.....	13
6.6 HANDLING OF MISSING DATA AND OUTLIERS	13
6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS.....	14
7. PLANNED ANALYSIS	16
7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS	16
7.2 CONCOMITANT DISEASES AND MEDICATION.....	16
7.3 TREATMENT COMPLIANCE	17
7.4 PRIMARY ENDPOINT.....	17
7.5 SECONDARY ENDPOINTS	17
7.5.1 Key secondary endpoint.....	17
7.5.2 Other secondary endpoint	18
█	█
7.7 EXTENT OF EXPOSURE	18
7.8 SAFETY ANALYSIS	19
7.8.1 Adverse events	19
7.8.2 Laboratory data.....	20
7.8.3 Vital signs	20
7.8.4 ECG	21
7.8.5 Others	21
8. REFERENCES	22
█	█
10. HISTORY TABLE	24

LIST OF TABLES

Table 6.2: 1	Important protocol violations	11
Table 6.3: 1	Patient sets analysed	13
Table 6.7:1	Time windows of treatment period visits	15
Table 10: 1	History table	24

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
██████	██
BRPM	Blinded report planning meeting
CSFT	Central Subfield Thickness
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CTX	Carboxy-Terminal Collagen Crosslinks
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
DME	Diabetic Macular Edema
EMEA	European Agency for the Evaluation of Medicinal Products
FAS	Full analysis set
HMA	Hemorrhage/ Micro-aneurysms
ICH	International Conference on Harmonisation
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for Repeated Measures
MQRM	Medical Quality Review Meeting
O*C	Oracle Clinical
██████	██
PK	Pharmacokinetics
PPS	Per protocol set
PSTAT	Project Statistician
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
SA	Statistical analysis

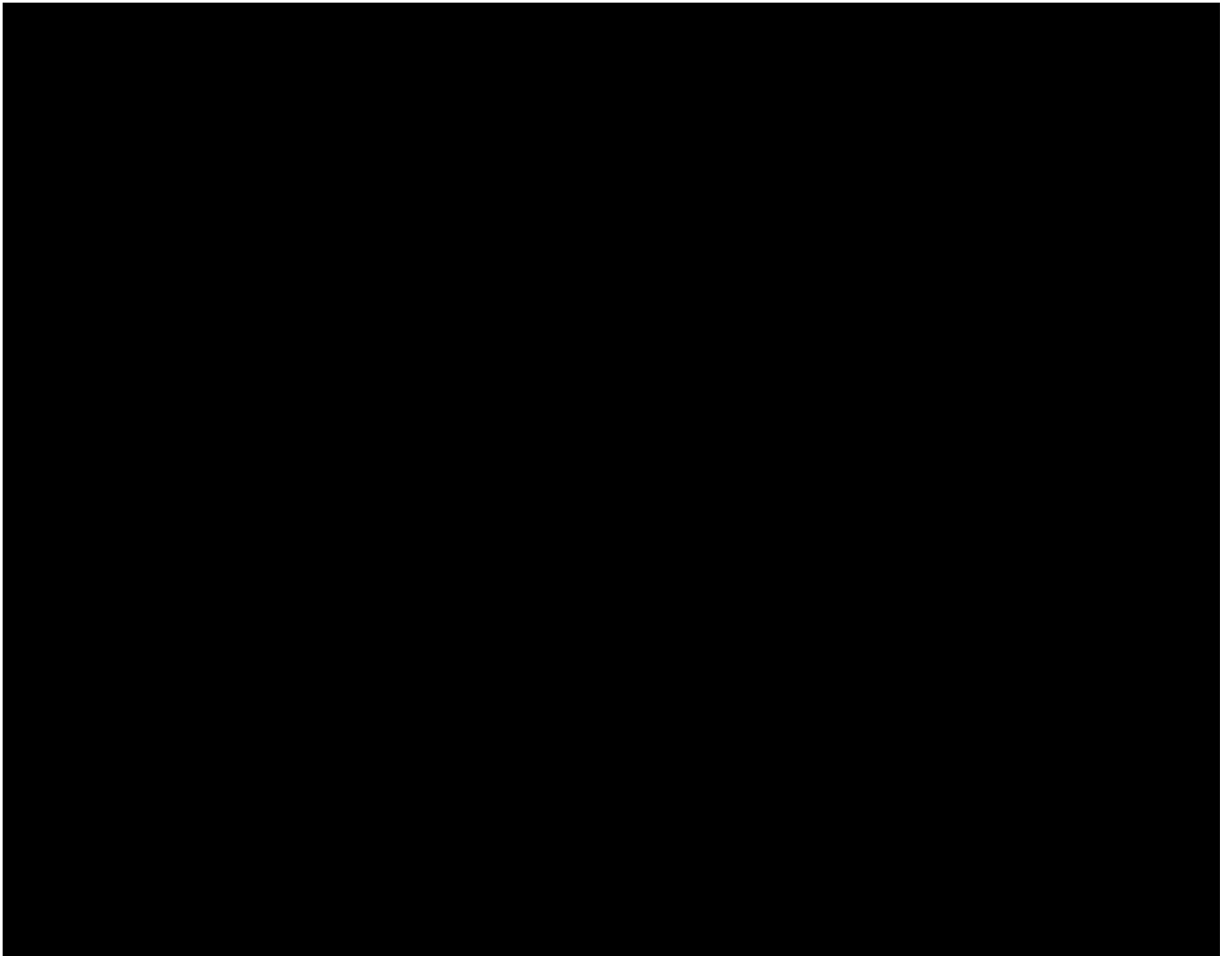
Term	Definition / description
SD	Standard deviation
SD-OCT	Spectral-Domain Optical Coherence Tomography
SMQ	Standardised MedDRA query
SOC	System organ class
TCM	Trial Clinical Monitor
TESS	Treatment emergent signs and symptoms
ToC	Table of contents
TMW	Trial Medical Writer
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per ICH E9 [3], 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.

SAS[®] Version 9.4 or newer version will be used for all analyses.



5. ENDPOINTS

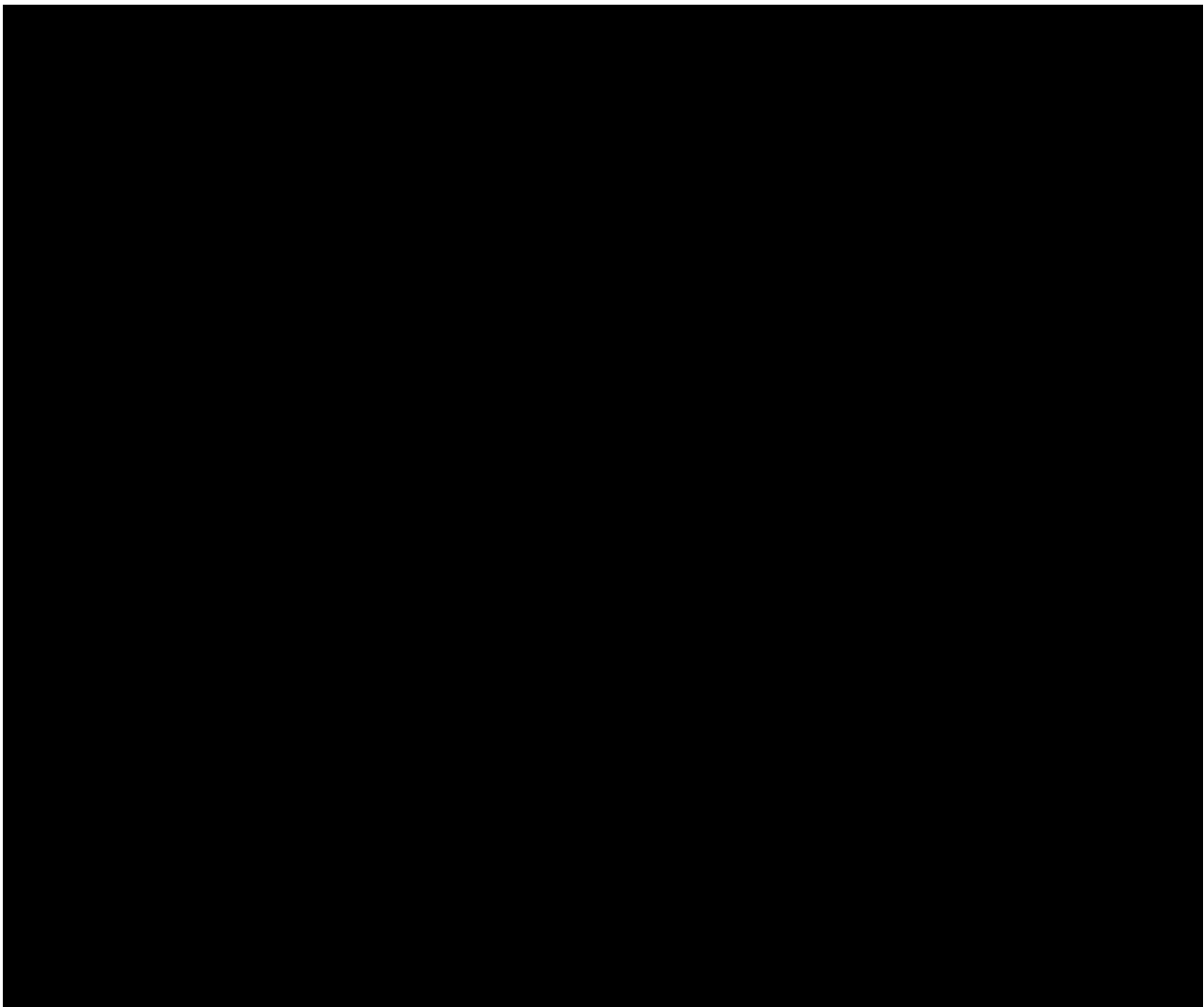
5.1 PRIMARY ENDPOINT

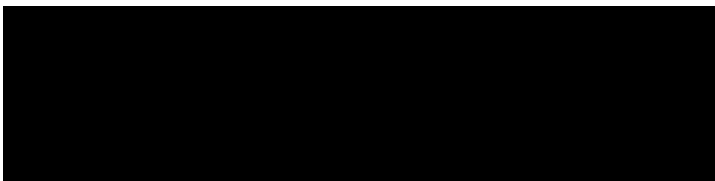
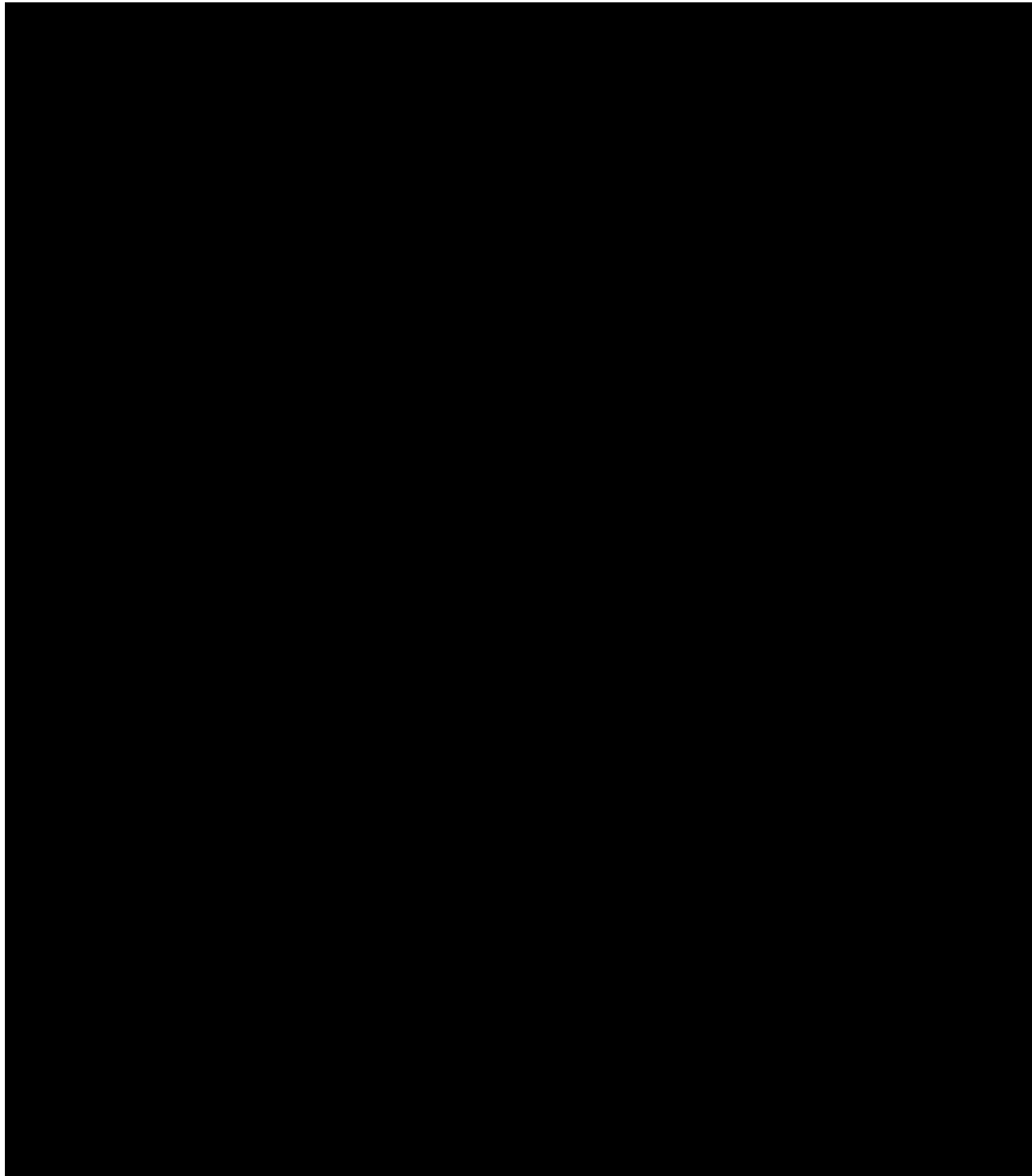
The primary endpoint will be the change from baseline in CSFT in μm at Week 12, as measured by SD-OCT. Baseline CSFT is determined at visit 2a. If not measured at Visit 2a, then baseline will be the value at Visit 1.

5.2 SECONDARY ENDPOINTS

Safety and tolerability of BI 1026706 will be assessed by the frequency of adverse events over the treatment period. The definitions of adverse events can be found in the protocol section 5.3.6.1

- Serious Adverse Events (SAEs)
- Drug related adverse events
- Adverse events of special interest (AESIs)





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For reporting purposes, all randomised patients will be classified into one of the following randomised treatment groups

Sort order	Treatment	Long label	Short label
01	C	BI 1026706 100mg film coated tablets	BI 1026706 100mg
02	D	Placebo matching BI 1026706 100mg film coated tablets	Placebo

These will be the default labels and sort order for reporting the treatment groups.

Patients will be analysed according to the treatment groups to which they were randomised. If there are cases of patients receiving incorrect treatment then an 'as treated' analysis will be performed in addition.

The following treatment periods based on actual start and stop dates of study treatment administration are defined:

Screening: day of informed consent to day prior to the start of randomised study medication

On-treatment: day of first administration of randomised study medication to the last day of study medication administration

Post-treatment: day after the last dose of randomised study medication and thereafter

For the safety analysis, post-treatment events that start up to 4 days after the last administration of trial medication will be assigned to randomised treatment. Adverse events that start on the 5th day after the last administration of trial medication will be considered post-treatment.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important PVs. The final column describes which PVs will be used to exclude patients from the different patient analysis sets.

No per protocol (PPS) analysis will be performed for this study; however patients with important protocol violations (IPVs) will be documented. The following list of potential IPVs will be used; note this is a working list and may not be finalised until the final Blinded report planning meeting (BRPM) prior to database lock.

Table 6.2: 1 Important protocol violations

Category / Code	Description	Requirements	Excluded from
A	Entrance criteria not met		
A1.1	Inclusion criteria 1, 2, or 7 not met	Inclusion criteria 1, 2, or 7 not met as specified in the protocol.	None
A1.2	Trial diagnosis not met	Inclusion criteria 3, 4, 5, or 6 not met as specified in the protocol.	None
A2	Exclusion criteria present	Exclusion criteria as specified in the protocol present. Applies for criteria 1, 2, 5, 7, 9 – 23, 25-29	None
B	Informed consent		
B1	Informed consent not available/not done	Informed consent date missing; no signature on ICF	All
B2	Informed consent too late	Informed consent date was after Visit 1 date	None
C	Trial medication and randomization		
C1	Incorrect trial medication taken	Medication kit assigned not matching treatment patient was randomised to and/or not matching IVRS assignment	None

Table 6.2: 1 (continued) Important protocol violations

Category / Code	Description	Example/Comment	Excluded from
C2	Randomisation order not followed	Patient received trial medication from medication kit assigned to another patient	None
C3.1	Wrong dosage schedule	Capsules (BI 1026706 or matching placebo) taken once daily instead of bid and/or incorrect daily dose taken (more or less than two capsules)	None
C3.2	Treatment non-compliance	Overall compliance <80% or >120%. Final decision to be made at BRPM.	None
C4	Medication code broken inappropriately	Medication code broken inappropriately - reason for medication code break <reason> (Manual PV)	None
D	Concomitant medication		
D2	Prohibited medication taken concomitantly with study drug after randomization until End-of-Treatment visit is completed	<ul style="list-style-type: none"> • Systemic anti-VEGF or pro-VEGF treatment • Use of systemic steroids >10mg prednisone equivalent/day • Current or planned during the study period, use of medications known to be toxic to the retina, lens or optic nerve • plans to initiate intensive insulin treatment within the study period (Manual PV) • Potent and moderate CYP3A4 inhibitors • Potent and moderate CYP3A4 inducers • Potent and moderate P-gp inhibitors • Potent and moderate P-gp inducers • Sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, P-gp and Breast Cancer Resistance Protei (BCRP) substrates with a narrow therapeutic window 	None
E	Other		
E1	Study eye not determined	If the study eye is not indicated in the eCRF	None
E2	Missing data	No post-baseline assessment of CSFT	None
E3	Incorrect timing	Assessment of primary endpoint CSFT not within the time window	None

6.3 PATIENT SETS ANALYSED

The statistical analysis will be based on the following populations:

Treated Set (TS)

The TS will consist of all patients who were treated with at least one dose of study drug (BI 1026706 or placebo).

Full Analysis Set (FAS)

The FAS will consist of all patients who were randomised, treated with at least one dose of BI 1026706/placebo and provided baseline and at least one post-randomization CSFT measurement.

Pharmacokinetic Analysis Set (PKS)

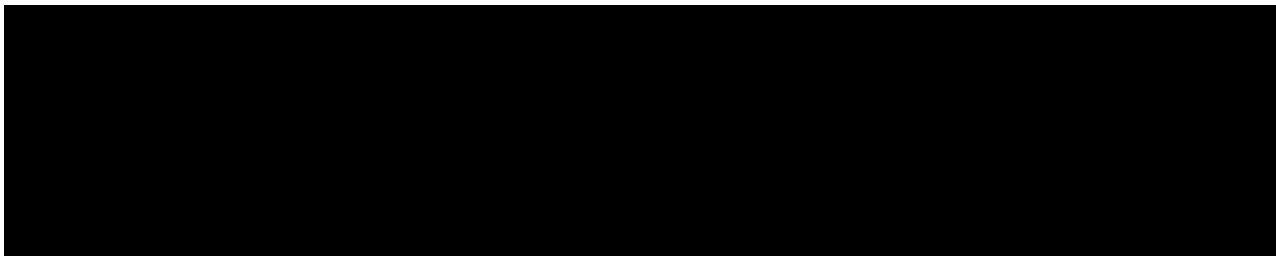
The PKS will consist of all patients in the TS for whom at least one evaluable BI 1026706 plasma concentration is available.

Table 6.3: 1 Patient sets analysed

Class of endpoint	TS	Patient set	
		FAS	PKS
Primary endpoints		primary analysis	
Further endpoints		X	
Safety endpoints	X		
Pharmacokinetic endpoints			X
Demographic/baseline endpoints	X	(X)	

(X) An additional FAS presentation of the demographic/baseline endpoints may be provided in the EoT section, if patient numbers for FAS and treated set are clearly different (i.e., a non-negligible number of treated patients does not have post randomization data for the primary endpoint).

Note that the number of patients with available data for an endpoint may differ. For details, see section “Handling of missing data”.



6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

For the primary analysis of the primary endpoint, if a patient misses a visit, the missing data will not be imputed and only on-treatment data will be included. The mixed effect model will handle missing data based on a likelihood method based on the “missing at random”

assumption. Every randomised patient with at least baseline and one on-treatment measurement will be included in the analysis.

To evaluate the impact of any missing data to the analyses of primary endpoint, multiple imputation will be used to handle missing data as a sensitivity analysis. All variables included in the analysis model will be included in the imputation model. In addition, after exploring the missing data mechanism and observed measurements on the blinded data, additional variables may be identified and added to the imputation model.

If the data is monotone missing, a regression model will be used for imputation including baseline CSFT and primary endpoint at Visits 3, 4, 5 by treatment, and stratification factor previous DME treatment.

In the case of non-monotone missing, a Markov chain Monte Carlo (MCMC) step will be used to create monotone missing data in multiple datasets. The regression method will then be used to complete the imputation in each dataset. For each imputed complete dataset, the primary MMRM model described in [Section 7.4](#) will be used for the analyses. The results will be pooled following the standard multiple imputation procedure.

Missing or incomplete AE dates will be imputed according to BI standards (“Handling of missing and incomplete AE dates”) [8]. Missing data and outliers of PK data are handled according to [6].

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study day will be calculated relative to the date and time of the first dose of double-masked randomised treatment. The day prior to the start of double-masked randomised treatment will be ‘Day -1’ and the start of double-masked randomised treatment will be ‘Day 1’; therefore ‘Day 0’ will not exist.

For efficacy analyses, baseline is defined as the latest measurement on or before the date of the first randomised treatment administration at Visit 2a. Therefore baseline values are measured at Visit 2a for [REDACTED] and endpoints assessed by SD-OCT (i.e., CSFT, [REDACTED] If Visit 2a measurement is missing, then Visit 1 will be used as baseline. [REDACTED]

[REDACTED] Visit 1 measurement will be used as baseline as per Flow Chart.

Planned time windows are defined in the CTP. For analyses purposes, data from Ophthalmological exams will be allocated to visits by means of windows with the limit between adjacent windows half-way between the planned dates for the visits; the middle day is counted to the window of the later visit. For example, Visit 2a is planned on Day 1 and Visit 2b is planned on Day 8. Therefore, the window of Visit 2a reaches until Day 3, the windows of Visit 2b starts on Day 4. If there are multiple measurement values within one window, 3 cases have to be distinguished:

The following time windows are planned:

- Pre-treatment, the latest measurement is to be selected as baseline as described above;

- After study treatment start, the value closest to the nominal day will be selected for assessment endpoints at a particular visit and for by-visit displays. All values will be stored in analysis datasets;
- For post-treatment, the lastest value in the respective window will be used .

Table 6.7:1 Time windows of treatment period visits

Window No.	Window label	Nominal visit	Nominal day	
-4	Screening	VISIT 1	-28	
0	Baseline	VISIT 2a	1	
1	Week 1	VISIT 2b	8	
4	Week 4	VISIT 3	29	
8	Week 8	VISIT 4	57	
12	Week 12	VISIT 5/EOT ¹	85	
16	Week 16	VISIT 6/EOS	113	

1. Patients may stop study medication prematurely at any visit before Week 12, the nominal day and interval will remain missing in analysis datasets..

These windows will also be used for safety laboratory assessments. If there are multiple measurements within one window, the last value will be used as confirmation.

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

For time to event analysis tables, the median and quartiles will be provided.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

All calculated statistics will be presented to one more decimal place than the original measurement accuracy of the variable being summarised.

All p-values will be displayed to four decimal places (or “<0.0001” if appropriate).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

The following variables will be displayed in the demographics table: gender, race, age, height, weight, smoking and alcohol status.

Baseline disease status will be summarised descriptively, including the best corrected visual acuity score, intraocular pressure measurement, and the results of the slit lamp examination.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded using the current version of MedDRA coding system. Medications will be coded using the WHO 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. Subjects without any concomitant diagnosis or therapy should be marked with a “No” in the respective column. Historical anti-DME therapy will be summarised separately according to the ATC4 grouping.

Study eye will be listed.

In addition, any further anti-DME therapy initiated during the course of the trial will be summarised in a separate table along with a summary of reasons for initiating standard of care.

7.3 TREATMENT COMPLIANCE

The percentage of medication taken of study drug as reported on the compliance eCRFs will be summarized descriptively by visit and treatment group. Additionally, summary statistics of overall compliance will be presented by treatment group. Cumulative compliance per patient will be calculated based on weighted average of available on-treatment by visit data, weighted by number of days between visits (e.g., for patient who had 80% compliance at Visit 3 (Week 4, Day 29), 100% compliance at Visit 4 (Week 8, Day 57), 100% compliance at Visit 5 (Week 12, Day 85), the overall compliance would $(29*0.8 + 28*1 + 28*1)/85 = 93.2\%$.

7.4 PRIMARY ENDPOINT

The primary analysis of the primary endpoint, change from baseline in CSFT at 12 weeks, will be performed on the FAS. Therefore, all randomised patients who were treated with at least one dose of BI 1026706/placebo, had a baseline and at least one on-treatment CSFT measurement will be included.

Comparisons between treatment groups for the primary endpoint will be based on a mixed effect repeated measures model (MMRM). This model will include treatment, previous DME treatment, week and treatment by week interaction as fixed categorical effects. Also, baseline CSFT and baseline CSFT by week interaction as continuous fixed effects. An unstructured covariance matrix will be used to model the within-patient variation. The SAS procedure MIXED will be used involving the REML and the Kenward-Roger approximation for the denominator degrees of freedom. This approach is described in Kenward and Roger (R10-4391). Adjusted mean values as well as treatment contrasts will be presented together with the 95% CIs and p-values.

The statistical model will be:

$$\begin{aligned} \text{CSFT change from baseline} = & \text{overall mean} + \text{continuous baseline CSFT} + \\ & \text{previous DME treatment} + \text{treatment} + \text{week} + \\ & \text{baseline CSFT by week interaction} + \\ & \text{treatment by week interaction} + \text{random error} \end{aligned}$$

Baseline CSFT will be defined as the last available CSFT measurement obtained before randomisation.

Data obtained after the start of rescue medication will not be used in the primary analysis of the primary endpoint. Waterfall plots of CSFT change from baseline will be presented. A sensitivity analysis using multiple imputation methods is described in [Section 6.6](#).

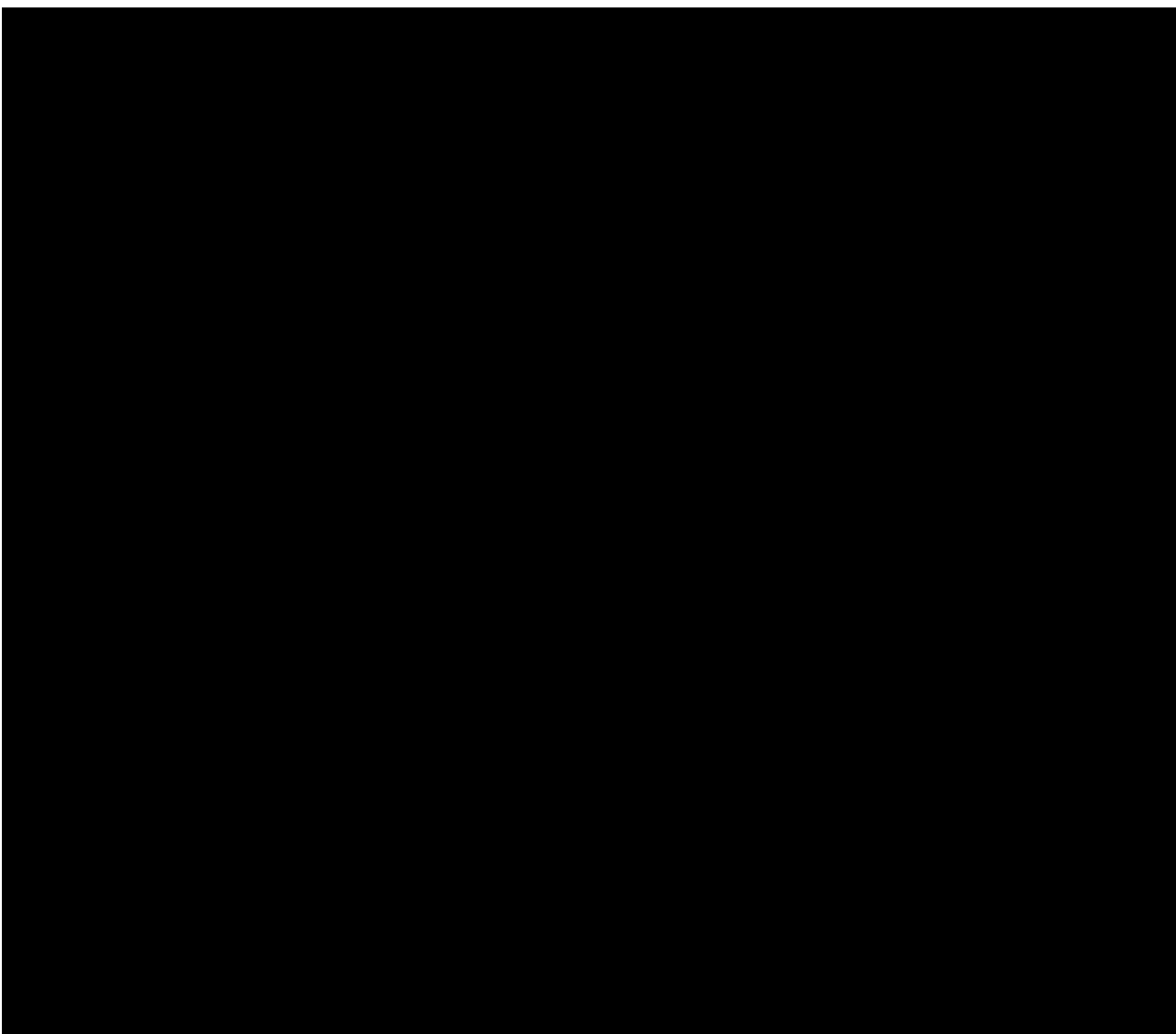
7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Other secondary endpoint

Secondary endpoints are safety endpoints. The analyses of safety endpoints are described in [Section 7.8](#).



7.7 EXTENT OF EXPOSURE

Duration of treatment exposure (days) across the randomised treatment period will be calculated for each patient. The total exposure will also be summed over all patients within each treatment group and transformed into patient years. A standard descriptive summary of these data will be provided for the treated set of patients. In addition, the number and percentage of patients in the treatment exposure categories 0-6 weeks, >6 to 12 weeks will be summarised.

Kaplan-Meier curves by treatment group showing the number of patients at risk (exposed) during the randomised treatment period will be produced.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set and performed in accordance with BI standards. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

The format of the listings and tables will follow the BI guideline ‘Reporting of clinical trials and project summaries’ [1, 9]

The individual values of all subjects will be listed, sorted by treatment, subject number and visit. The listings will be contained in Appendix 16.2.

7.8.1 Adverse events

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

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

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to the guideline ‘Handling and summarization of adverse event data for clinical trial reports and integrated summaries’ [8, 10].

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till last drug intake + 4 days will be assigned to the randomised treatment. All adverse events occurring before first drug intake will be assigned to ‘screening’ and all adverse events occurring after the residual effect period will be assigned to ‘post-treatment’ (for selected tables in 16.1.9.2 and listings only). For details on the treatment definition, see [Section 6.1](#).

According to ICH E3 [4], 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 a Medical Quality Review Meeting.

Adverse events of special interest (AESIs)

The following are considered to be AESIs:

- Hepatic injury defined by the following alterations of hepatic laboratory parameters:
 - Elevation of AST and/or ALT ≥ 3 fold upper limit of normal (ULN) combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample, and/or
 - Marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN.

Depending on the number of AESIs, either a summary table by MedDRA preferred term or a listing will be produced.

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with other significant adverse events according to ICH E3 [4], for patients with adverse events of special interest and for patients with serious adverse events.

The system organ classes will be sorted alphabetically; preferred terms will be sorted by frequency (within system organ class).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards “Handling, Display and Analysis of Laboratory Data” [11]. The following analyses will be presented for all applicable laboratory parameters:

- Descriptive statistics;
- Frequency of patients with possible clinically significant abnormalities.

Baseline is defined by the last available measurement before study drug administration. In case of repeated measurements performed for the same visit the last observation will be used for tabulation.

7.8.3 Vital signs

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

7.8.4 ECG

Clinically relevant ECG findings on-treatment will be reported and summarized as adverse events.

7.8.5 Others

For the clinical trials disclosure process (e.g. clinicaltrial.gov) special safety displays may be necessary, e.g. the number of non-serious Adverse Events. All required displays / ADS for the clinical trials disclosure process will be included in the technical TSAP, section Display Plan or ADS Plan as applicable.

8. REFERENCES

1	<i>001-MCG-159_RD-03</i> : “Standard table shells for inferential and descriptive End-of-Text tables (EoT-Catalogue)”, current version; IDEA for CON.
2	<i>001-MCG-410</i> : "Structure, Derivation, and Documentation of Analysis Data Sets", current version; IDEA for CON.
3	<i>CPMP/ICH/363/96</i> : "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
4	<i>CPMP/ICH/137/95</i> : “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
5	<i>001-MCP-090</i> : "BI Style Guide", current version; IDEA for CON.
6	<i>001-MCS 36-472</i> : "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
7	<i>001-MCS-50-413</i> : "Handling of Protocol Violations in Clinical Trials and Projects", current version; group: Study Conduct; IDEA for CON.
8	<i>001-MCG-156_RD-01</i> : "Handling of missing and incomplete AE dates", current version; IDEA for CON.
9	<i>001-MCG-159</i> : "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
10	<i>001-MCG-156</i> : "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
11	<i>001-MCG-157</i> : "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	15-AUG-16	[REDACTED]	None	This is the initial TSAP with the necessary information for trial conduct.
Final	25-JUL-17	[REDACTED]	Section 4, [REDACTED] 6.6, [REDACTED] 6.7, 7.3, [REDACTED] 7.7, 7.8.2.	<p>TSAP Template 001-MCS-40-415_RD-02 (1.0) applied; Section 4, CSET response added; [REDACTED]</p> <p>Section 7.1 and 7.2. Section 6.6, sensitivity analysis described; handling of missing or incomplete AE dates updated; Section 6.7, analyses time windows defined; Section 7.3, treatment compliance defined;</p> <p>[REDACTED]</p> <p>Section 7.7, Kaplan-Meier analyses removed; Section 7.8.2, Analyses of clinical laboratory data specified.</p>