# TRIAL STATISTICAL ANALYSIS PLAN c30324615-01

| | |
|---|---|
| **BI Trial No.:** | 1386-0012 |
| **Title:** | A randomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of orally administered BI 1467335 for 12 weeks with 12 week follow up period in patients with non-proliferative diabetic retinopathy without center-involved diabetic macular edema<br><br>Including Protocol Amendment 1 [c14141887-02], Amendment 2 [c14141887-03], Amendment 3 [c14141887-04], and Amendment 4 [c14141887-05] |
| **Investigational Product(s):** | BI 1467335 |
| **Responsible trial statistician(s):** | [redacted]<br>Email: [redacted] |
| **Date of statistical analysis plan:** | 29 JUN 2020 SIGNED |
| **Version:** | 1 |

# 1. TABLE OF CONTENTS

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# 2. LIST OF ABBREVIATIONS

| Term | Definition / description |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| AOC3 | Amine oxidase copper-containing 3 |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical classification |
| BCVA | Best corrected visual acuity |
| BI | Boehringer Ingelheim |
| BP | Blood pressure |
| BRPM | Blinded report planning meeting |
| CARE | Clinical data Analysis and Reporting Environment |
| CI-DME | Center-involved diabetic macular edema |
| [redacted] | [redacted] |
| CT | Concomitant therapy |
| CTC | Common Terminology Criteria |
| CTMS | Clinical Trial Management System |
| CTP | Clinical trial protocol |
| CTR | Clinical trial report |
| DBLM | Database lock meeting |
| DBP | Diastolic blood pressure |
| DR | Diabetic retinopathy |
| DRSS | Diabetic Retinopathy Severity Score |
| ECG | Electrocardiogram |
| ECGS | ECG analysis set |
| EOT | End of treatment |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| EudraCT | European clinical trials database |
| [redacted] | [redacted] |

| Term | Definition / description |
|---|---|
| FAS | Full analysis set |
| FP | Fundus photography |
| HR | Heart rate in beats per minute |
| ICH | International Conference on Harmonization |
| iPD | Important protocol deviation |
| LLT | Lower level term |
| MedDRA | Medical Dictionary for Regulatory Affairs |
| Max | Maximum |
| Min | Minimum |
| MMRM | Mixed effects model for repeated measures |
| MQRM | Medical quality review meeting |
| [redacted] | [redacted] |
| NPDR | Non-proliferative diabetic retinopathy |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| OD | Oculus dexter; right eye |
| OS | Oculus sinister; left eye |
| OU | Oculus uterque, both eyes |
| PD | Protocol deviation |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| PPS | Per-protocol set |
| PR interval | ECG interval from onset of P wave to the beginning of QRS |
| PT | Preferred term |
| Q1 | Lower Quartile |
| Q3 | Upper Quartile |
| QRS complex | ECG term; combination of Q, R and S waves |
| QT interval | ECG interval from beginning of QRS complex to the end of the T wave |
| QTcB [msec] | QT interval, heart rate corrected per Bazetts formula |
| QTcF [msec] | QT interval, heart rate corrected per Fridericias formula |
| RAGe | Report Appendix Generator system |

| Term | Definition / description |
|---|---|
| [redacted] | [redacted] |
| REP | Residual effect period |
| RPM | Report Planning Meeting; formerly known as BRPM |
| RR interval | ECG interval from peak of an R wave to the peak of the subsequent R wave |
| RS | Randomized set |
| SAE | Serious adverse event |
| SBP | Systolic blood pressure |
| SD | Standard deviation |
| SMQ | Standardized MedDRA query |
| SOC | System organ class |
| SS | Screened set |
| TMW | Trial medical writer |
| TS | Treated set |
| TSAP | Trial statistical analysis plan |
| ULN | Upper limit of normal |

# 3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing this 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 will be stored in a trial database within the Medidata RAVE (BRAVE) system.

The statistical analyses will be performed within the validated working environment CARE (Clinical data Analysis and Reporting Environment), including $SAS_{TM}$ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of $SAS_{TM}$-based tools (e.g., macros or the analyses of adverse event (AE) data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the clinical trial report (CTR) appendices).

[redacted]

[redacted]

# 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

**Secondary endpoint: 2-step improvement from baseline in DRSS**

Version 1.0 of the CTP stated that a logistic regression model adjusted for treatment and baseline visual acuity will be used to analyze the secondary endpoint of the proportion of patients with at least a 2-step improvement from baseline in DRSS at week 12. However, in this Phase IIa study of 100 patients, a 2-step improvement from baseline in DRSS is likely to be observed in no more than 3 patients. Given the limited amount of data expected to be available for this endpoint, these data will be summarized as the frequency and percentage of patients with improvement from baseline of 2 steps or more. Logistic regression analyses may be performed as exploratory analyses if a sufficient number of events are observed.

The description of this secondary endpoint analysis was clarified in version 2.0 of the CTP dated 18JAN2018.

**Definition of Full Analysis Set (FAS)**

The FAS definition will be generalized to include all subjects in the treated set who have a baseline and at least one post-baseline measurement for either DRSS or BCVA. Individual analyses will include only subjects with baseline and post-baseline measurements for the specific endpoint being analyzed.

[redacted]

[redacted]

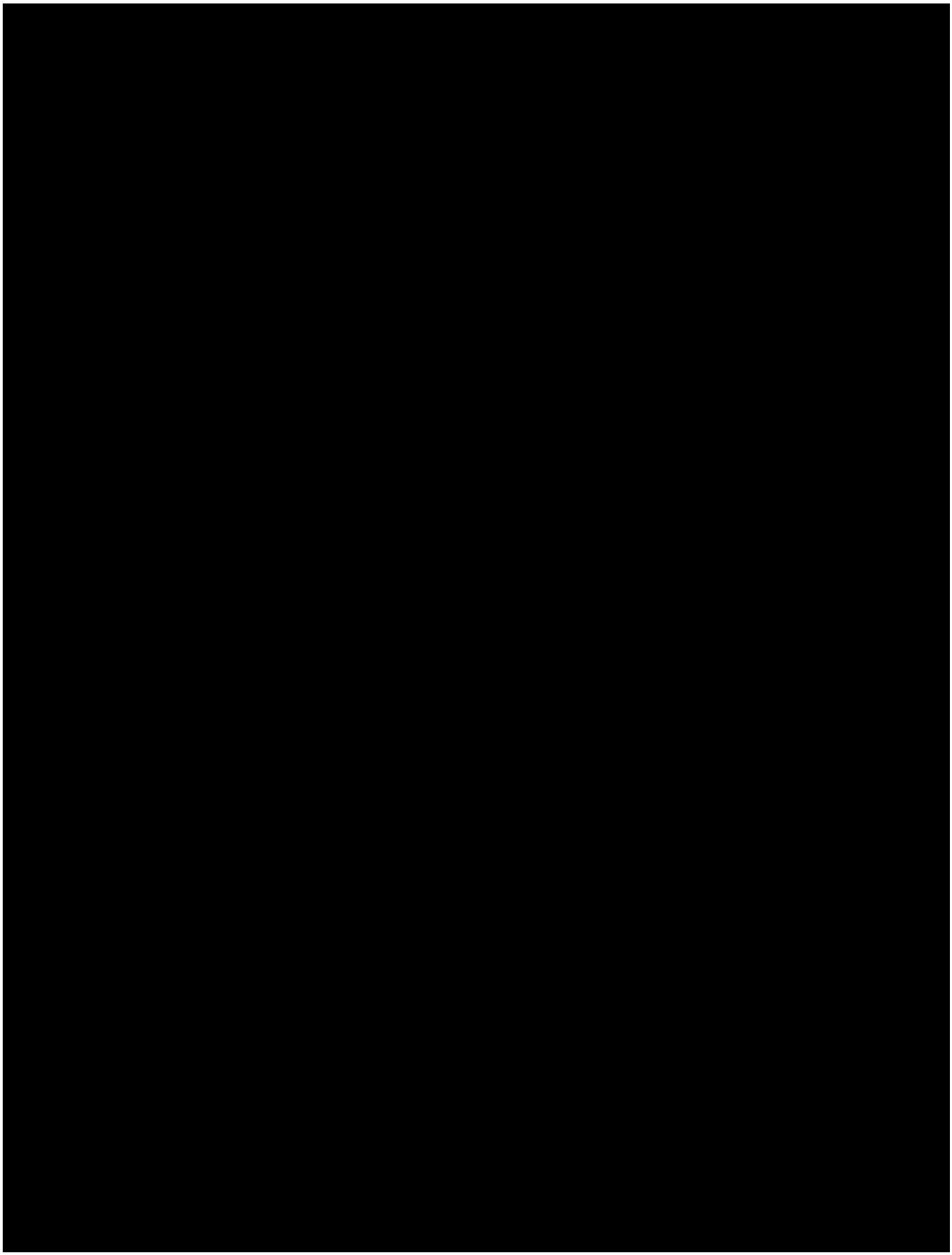
**Protocol deviations**

Per “Identify and manage important protocol deviations”(001-MCS-40-413, current version (4)), the term important protocol deviations will be used for trial reporting instead of important protocol violations.

[redacted]

[redacted]

[redacted]



[redacted]

**Assessment of COVID-19 Impact**

Site disruption due to the COVID-19 pandemic in 2020 had the potential to impact trial visits for several patients prior to database lock. To assess the impact of the pandemic on this trial, several additional data summaries are planned. The proportion of patients completing treatment prior to 01MAR2020, the proportion of patients completing the trial (Week 24 or early discontinuation) before 01MAR2020, adverse events reported before and after

01MAR2020 and type of study visit completed (phone or in clinic) will be reported for relevant visits in the CTR.

# 5. ENDPOINT(S)

## 5.1 PRIMARY ENDPOINT(S)

The primary endpoint of this trial is a safety endpoint. Per CTP Section 2.1.2, the primary endpoint is:

*Ocular safety of BI 1467335 as assessed by the proportion of patients with any ocular adverse events (according to Common Terminology Criteria for Adverse Events (CTCAE)) over the on-treatment period (over 24 weeks).*

## 5.2 SECONDARY ENDPOINT(S)

### 5.2.1 Key secondary endpoint(s)

This section is not applicable as there are no key secondary endpoints in this trial.

### 5.2.2 Secondary endpoint(s)

As defined in CTP Section 2.1.3, the secondary endpoints of this trial are:

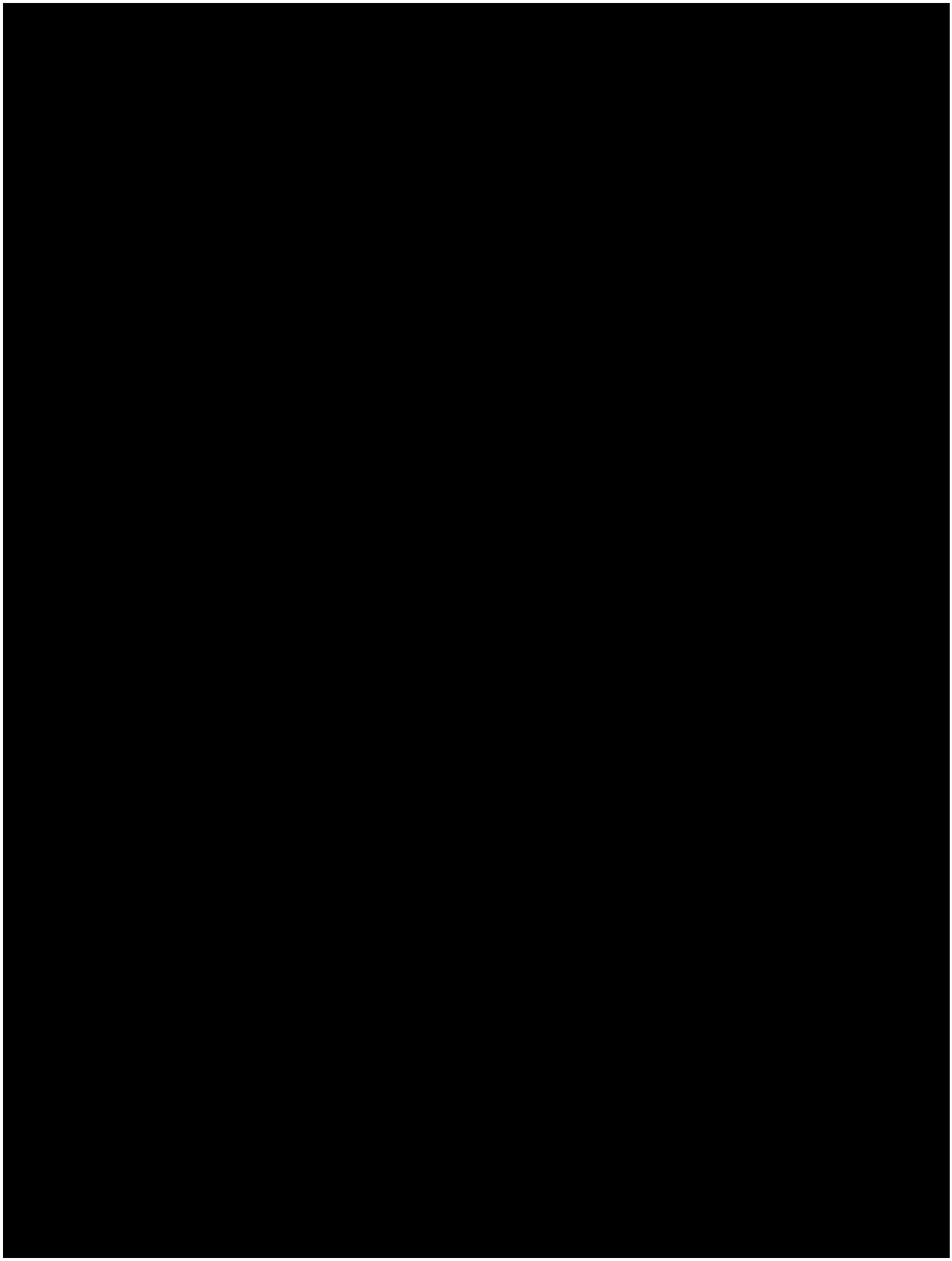
- *Improvement of at least 2 steps on the DRSS in the study eye at week 12 compared to baseline.*
- *Adverse events other than ocular adverse events over the on-treatment period (over 24 weeks), according to CTCAE.*

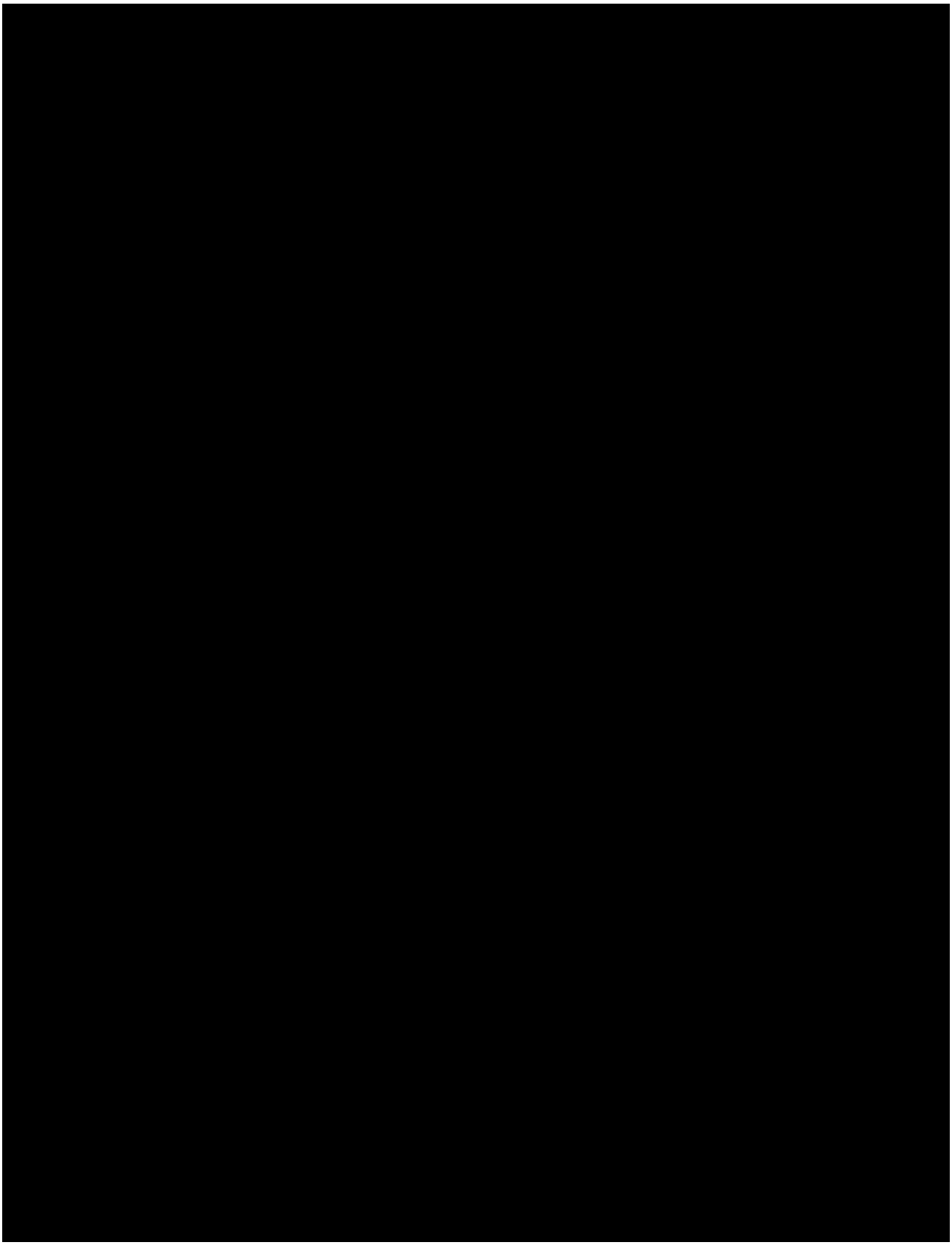
DRSS levels for an individual eye are defined in Table 5.2.2: 1.

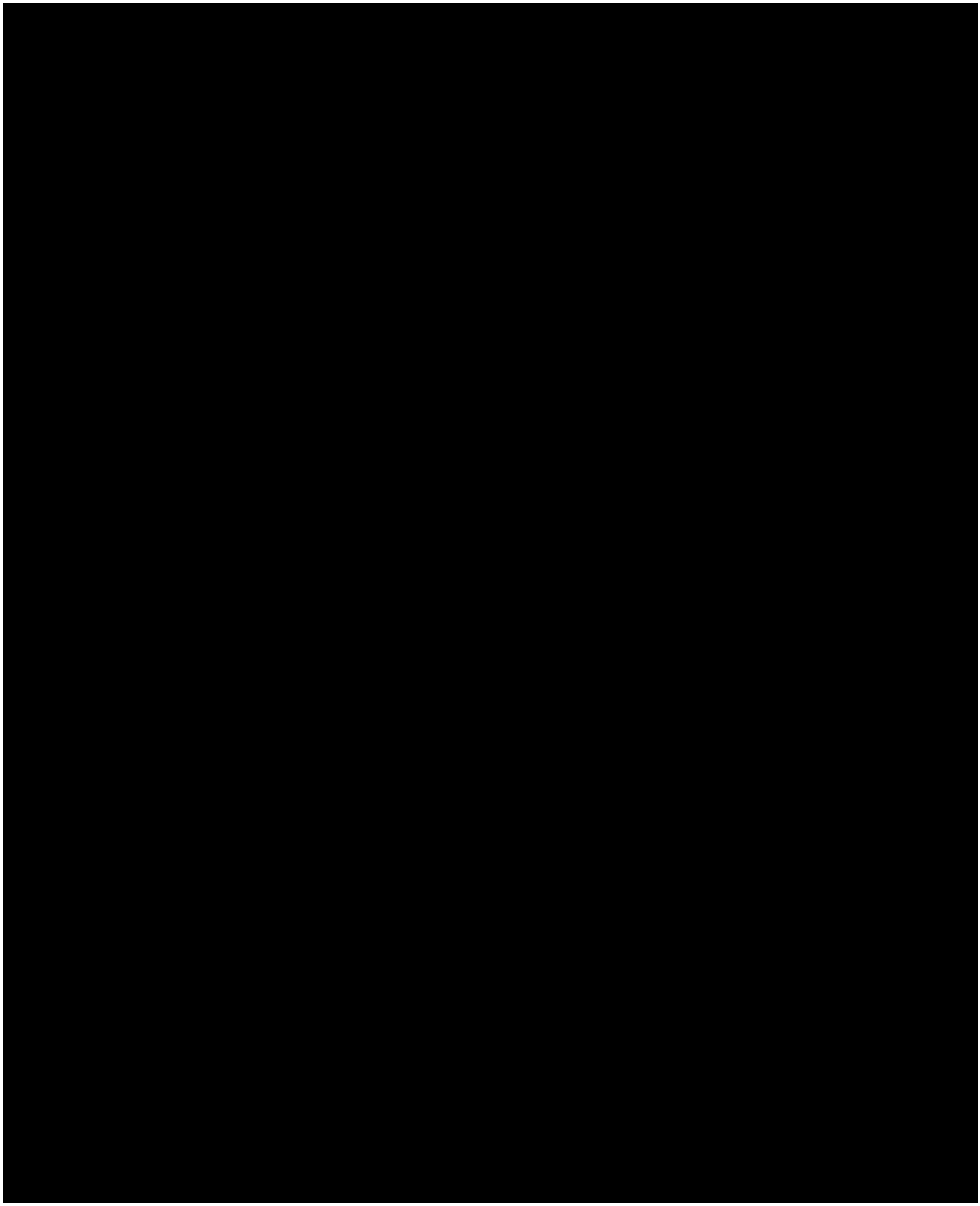
Table 5.2.2: 1 Diabetic Retinopathy Severity Score (DRSS) levels – individual eye

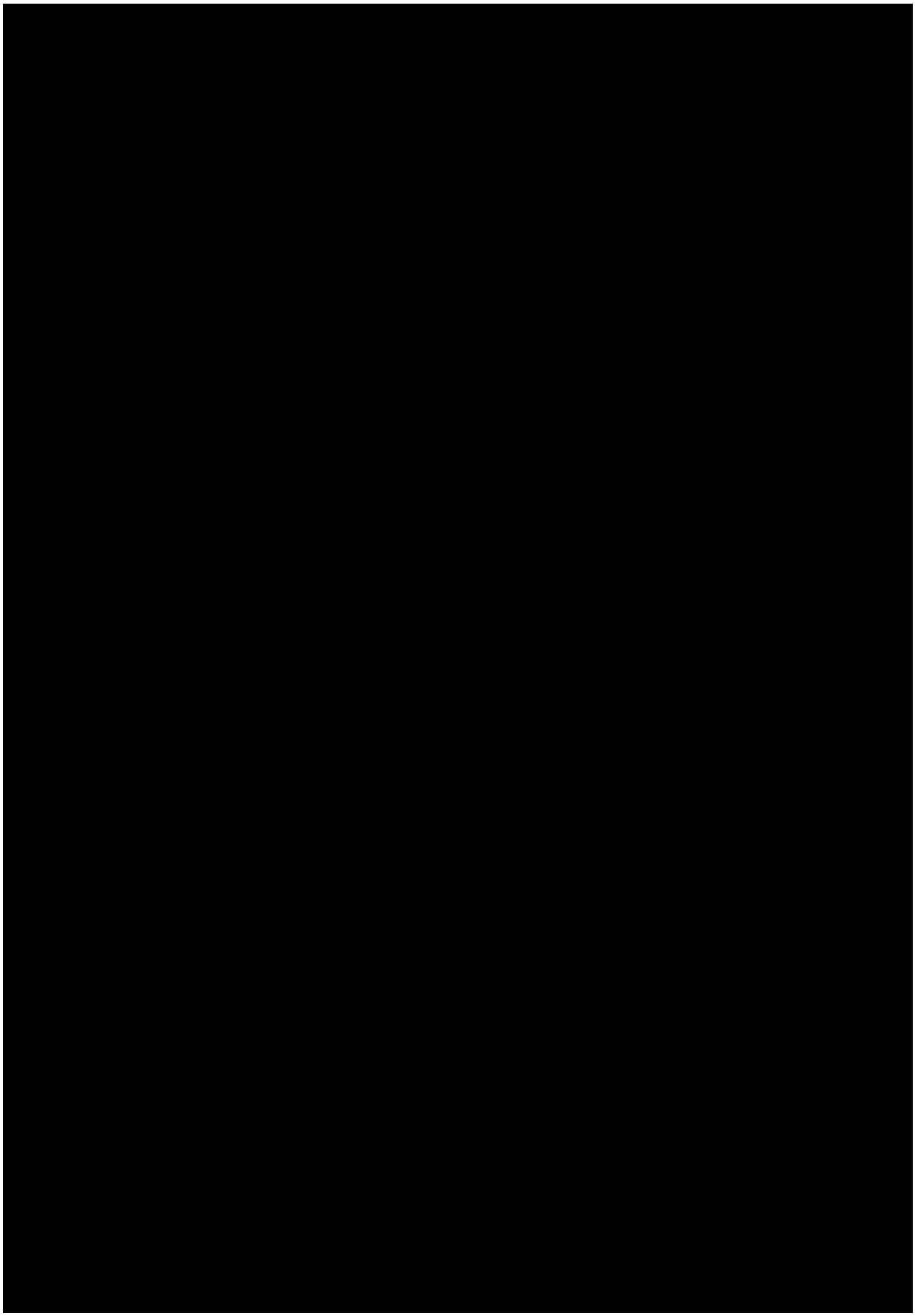
| Step | DRSS | DRSS Severity |
|---|---|---|
| 1 | 10 | DR Absent |
| 2 | 15 | DR Questionable |
| 3 | 20 | Microaneurysm only |
| 4 | 35 | Mild NPDR |
| 5 | 43 | Moderate NPDR |
| 6 | 47 | Moderately Severe NPDR |
| 7 | 53 | Severe NPDR |
| 8 | 60 | PDR |

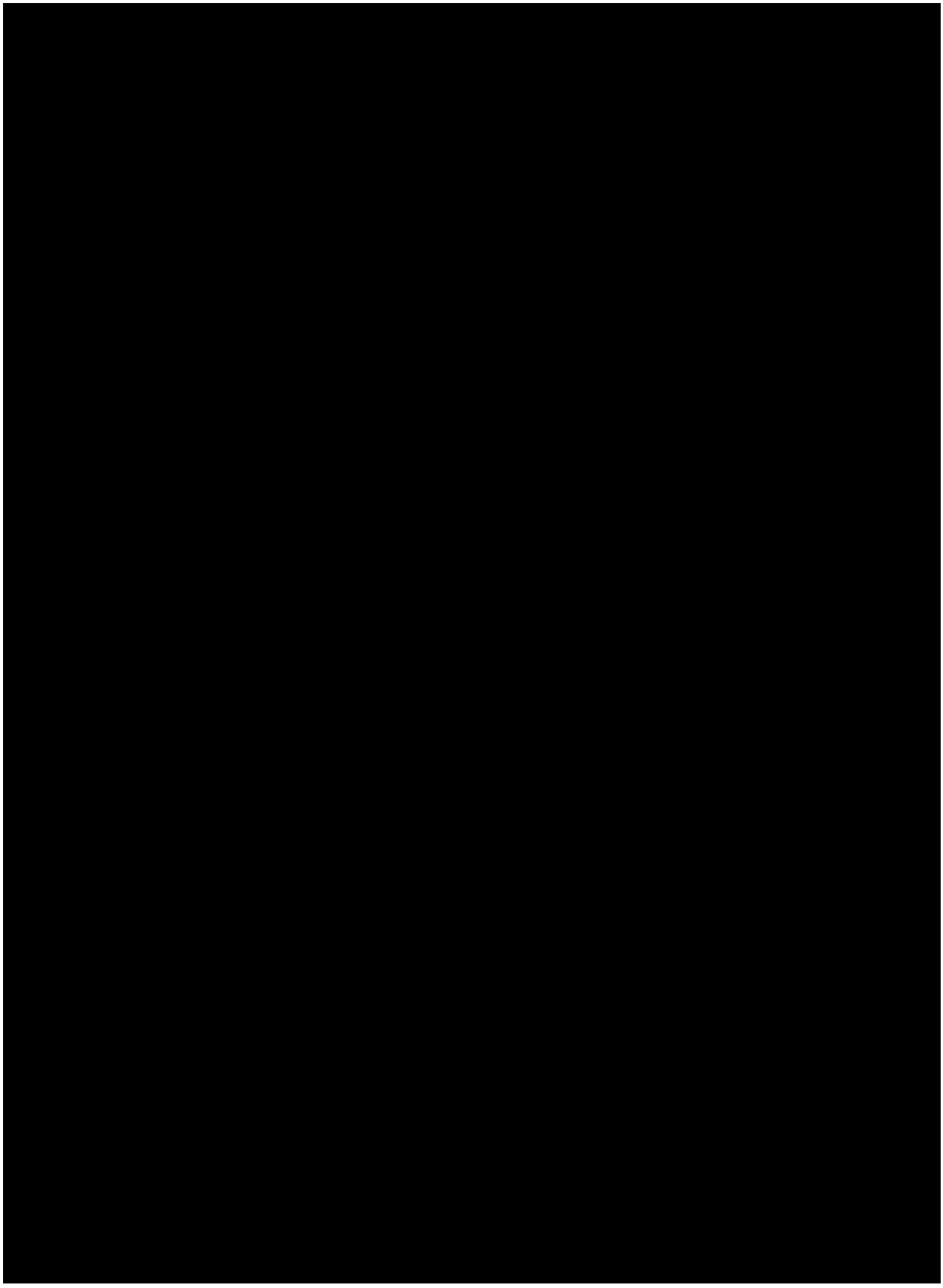
1 Higher DRSS and step values indicate more severe diabetic retinopathy.











# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENT(S)

Treatments used in this trial are described in Table 6.1:1. For basic information on treatments to be administered in this trial and the assignment of treatment arm, see CTP Section 4.

Table 6.1: 1 Treatment descriptions

| Long Name | Short Name |
|---|---|
| Placebo | Placebo |
| BI 1467335 10 mg QD | 10 mg QD |

The trial periods defined in Table 6.1:2 will be used for analysis of trial data.

Table 6.1: 2 Trial periods

| Trial Period | Start time | Stop time |
|---|---|---|
| Screening | Date of informed consent | Date of first treatment administration (Visit 2a) – 1 day |
| On-treatment (treatment period + residual effect period) | Date of first treatment administration (Visit 2a) | Date of individual patient's end of trial participation |

For this trial, the residual effect period (REP), as defined in the CTP Section 5.2.6.2, is considered the entire period from the date of last administration of trial medication until the individual patient's end of trial date. The statistical analysis and reporting of treatment-emergent adverse events will include all adverse events occurring or worsening during the on-treatment period which includes residual effect period (REP).

## 6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way.

A list of important PDs (iPD) for this trial is given Table 6.2: 1. Important PDs will be reviewed at Medical Quality Review Meetings (MQRM) conducted periodically during the trial. Other iPDs identified during MQRMs, Blinded Report Planning Meetings (BRPM), or during review of BI CTMS issues reports may supplement this list. The decision to exclude

subjects with certain iPDs from analyses will be finalized at the last BRPM prior to database lock.

Table 6.2: 1 Important protocol violations

| Category / Code | | Description | Comment | Excluded from |
|---|---|---|---|---|
| **A** | | **Entrance criteria not met** | | |
| | **A1** | **Inclusion criteria not met** | | |
| | A1.1 | Age at enrollment <18 years | Inclusion criterion 1 not met or age <18 years on demographics eCRF | None |
| | A1.2 | Female patient of childbearing potential not using required contraception | Inclusion criterion 2 not met | None |
| | A1.3 | No diagnosis of Type 1 or Type 2 diabetes | Inclusion criterion 3 not met | PPS |
| | A1.4 | HbA1c > 12% at screening | Inclusion criterion 4 not met | None |
| | A1.5 | Diagnosis of NPDR without CI-DME at screening not met | Inclusion criterion 5 not met | PPS |
| | A1.6 | BCVA ETDRS letter score < 70 letters in each eye at screening | Inclusion criterion 6 not met | PPS |
| | A1.7 | Inadequate retinal examination parameters | Inclusion criterion 7 not met | PPS |
| | **A2** | **Exclusion criteria met** | | |
| | A2.1 | Additional eye disease in the study eye that may compromise visual acuity | Exclusion criterion 1 met | PPS |
| | A2.2 | Active CI-DME and OCT central subfield thickness > 300 µm in study eye | Exclusion criterion 2 met | PPS |
| | A2.3 | Anterior segment and vitreous abnormalities in the study eye | Exclusion criterion 3 met | PPS |
| | A2.4 | Evidence of neovascularization in the study eye | Exclusion criterion 4 met | PPS |
| | A2.5 | Prior pan-retinal photocoagulation in the study eye | Exclusion criterion 5 met | PPS |
| | A2.6 | History of DME or DR treatment: macular laser within 3 months prior to screening, intraocular injections within 6 months prior to screening, or >4 prior injections in study eye | Exclusion criterion 6 met | PPS |
| | A2.7 | Treatment with MAO inhibitors or drugs with potential side effects due to MAO inhibition | Exclusion criterion 7 met | None |
| | A2.8 | Current or planned use of restricted medications | Exclusion criteria 8 or 9 met | PPS |
| | A2.9 | Glomerular filtration rate (eGFR) < 60 mL/min/1.73m$^2$ at screening or expected during trial | Exclusion criterion 10 met | None |
| | A2.10 | ALT or AST > 2x ULN or total bilirubin > 1.5x ULN | Exclusion criterion 11 met | None |
| | A2.11 | Excluded medical condition | Exclusion criteria 12, 13, 14, 15, 16 or 23 met | None |
| | A2.12 | Significant substance abuse | Exclusion criterion 17 met | None |

Table 6.2: 1 Important protocol violations (cont.)

| Category / Code | | Description | Comment | Excluded from |
|---|---|---|---|---|
| | A2.13 | Hypersensitivity to trial drug or allergy to fluorescein dye | Exclusion criterion 18 met | PPS |
| | A2.14 | Major surgery performed within 12 weeks prior to randomization or planned during trial | Exclusion criterion 19 met | None |
| | A2.15 | Current enrollment in, or < 30 days or 5 times half-life of the investigational drug since participating in, another investigational drug trial | Exclusion criterion 20 met | PPS |
| | A2.16 | Previous randomization in this trial | Exclusion criterion 21 met | PPS |
| | A2.17 | Women who are pregnant, nursing, or who plan to become pregnant during the trial | Exclusion criterion 22 met | None |
| **B** | | **Informed consent** | | |
| | B1 | Informed consent not available/not done | Inclusion criterion 8 not met; informed consent date or signature missing | All |
| | B2 | Informed consent given late | Study informed consent date after date of any study-related procedure; biobanking informed consent date after sample collection date; or re-consent given late. | None |
| **C** | | **Trial medication and randomisation** | | |
| | **C1** | **Incorrect trial medication taken** | | |
| | C1.1 | No study medication taken | Patient randomized but no evidence of study medication taken | TS, FAS, PKS, PPS |
| | C1.2 | Incorrect trial medication taken | Incorrect medication taken for >20% of treatment duration or > 20% of last dose interval before primary endpoint assessment as identified after database lock by comparison of assigned drug kit number from IRT with drug kit number recorded in eCRF. [manual review] | PPS |
| | **C3** | **Non-compliance** | | |
| | C3.1 | Non-compliance with trial medication | Mean overall treatment compliance across treatment duration for an individual <80% or >120%. | PPS |
| | **C4** | **Medication code broken** | | |
| | C4.1 | Medication code broken at site without just cause | Medication code broken for reasons other than those documented in CTP Section 4.1.5.2. [manual review] | None |

Table 6.2: 1 Important protocol violations (cont.)

| Category / Code | | Description | Comment | Excluded from |
|---|---|---|---|---|
| **D** | | **Concomitant medication** | | |
| | D2 | Use of prohibited concomitant medication | Reported use of prohibited concomitant medications, defined in CTP Section 4.2.2.1[manual review] | PPS |
| **F** | | **Trial specific** | | |
| | F1.1 | Study eye incorrectly selected. | Ophthalmologic data and/or issues report indicates study eye incorrectly selected. Incorrect study eye based on DRSS and BCVA will be flagged via SAS code. Manual review is needed to confirm protocol violations. | None |
| | F1.2 | Study eye incorrectly selected – Confirmed | Incorrect selection of study eye identified in F1.1 and confirmed by manual review. | PPS |
| | F2 | Imaging performed by non-certified personnel. | Manual review of issues report identified non-certified personnel performing imaging. | PPS |
| | F3 | Imaging performed using non-certified equipment. | Manual review of issues report noted use of non-certified imaging equipment. | PPS |
| | F4 | BCVA/CS performed by non-certified personnel. | Manual review of issues report identified non-certified personnel performing BCVA/CS assessment. | PPS |
| | F5 | BCVA/CS performed using non-certified equipment. | Manual review of issues report noted use of non-certified BVCA/CS equipment. | PPS |

Note: Missing visits, evaluations, and tests will be considered missing data, not protocol deviations.

## 6.3 PATIENT SETS ANALYSED

The following patient analysis sets are defined for this trial:

- Screened set (SS): includes all patients who sign informed consent
- Randomized set (RS): includes all patients who sign informed consent, are screened for the trial and are randomized to trial medication, regardless of whether any trial medication is administered.
- Treated set (TS): includes all patients who sign informed consent, are dispensed trial medication and are documented to have taken at least one dose of trial medication (BI 1467335 or placebo). Safety analyses, including the analyses of the primary endpoint of ocular adverse events and secondary endpoint of non-ocular adverse events, and summaries of demographics and baseline characteristics will be based on the TS.
- Full analysis set (FAS): includes all patients in the TS with non-missing baseline and at least one non-missing on-treatment measurement for DRSS or BVCA. Patients in

FAS are analyzed according to the intent-to-treat principle, i.e. patients in FAS are analyzed according to the trial medication assigned at randomization.

- Per protocol set (PPS): includes all patients from the FAS who do not have an iPD resulting in exclusion from the PPS.
- [redacted]
- ECG analysis set (ECGS): includes all subjects in TS who have at least one baseline and one post-baseline measurement for at least one ECG interval endpoint.

Analyses relevant to each patient set are shown in Table 6.3: 1.

Table 6.3: 1 Patient sets analyzed

| | Patient set | | | | | | |
|---|---|---|---|---|---|---|---|
| Class of endpoint | SS | RS | TS | FAS | PPS | [redacted] | ECGS |
| Primary and secondary safety endpoints | | | X | | | | |
| Secondary ophthalmologic endpoint | | | | X | X | | |
| Further ophthalmic endpoints | | | | X | | | |
| Safety endpoints | | | X | | | | |
| [redacted] | | | | | | [redacted] | |
| ECG endpoints | | | | | | | X |
| Demographic/baseline endpoints | | | X | | | | |
| Important protocol deviations | | X | | | | | |
| Disposition | X | | | | | | |

[redacted]

## 6.5 POOLING OF CENTRES

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

## 6.6 HANDLING OF MISSING DATA AND OUTLIERS

Techniques for handling missing data are described in Section 7.5 of the CTP. Missing and incomplete adverse event dates will be handled according to BI standards (5). The handling of missing PK data and values reported as NOS, NOR, NOA or BLQ are described in Section 10.1 of the CTP.

For efficacy analyses, missing data will not be imputed. Mixed effect models will handle missing data based on a likelihood methods under the "missing at random" assumption. No imputations of missing AEs, laboratory data or vital signs data are planned. For binary efficacy endpoints, patients with missing data in the study eye at the time point of interest will be considered non-responders, i.e. failure to achieve the defined endpoint.

For ECG data, if single cardiac cycles of an ECG (out of three) are missing, the arithmetic mean for this single ECG will be calculated with the reduced number (1 or 2) of cycles.

For the classification of the on-treatment QTc/QT intervals into 'no new onset' / 'new onset' categories, a missing value is obtained only in the 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.

For patients on active drug, missing plasma concentration values with 'BLQ' in the comment field will be replaced by ½ LLOQ.

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study day will be calculated relative to the date of the first dose of the randomized treatment. The day prior to the date of the first administration of randomized treatment will be Day -1 and the date of the first administration of randomized treatment will be Day 1. Day 0 will not exist.

Unless otherwise specified, baseline is defined as the last measurement collected on or prior to the date and time of first treatment administration. If no measurements are collected for a particular variable on or before the date of first treatment administration, no baseline value will be derived for that particular variable. Per the CTP, for the ophthalmic endpoints, baseline is defined as the value at Visit 2a; if not measured at Visit 2a then baseline is the value at Visit 1.

To utilize all available data, including values collected between protocol-specified visit windows, the time intervals and descriptions shown in Table 6.7: 1 will be used in the analysis of safety and efficacy data with the following exceptions. Adverse events and concomitant medications are also collected during phone visits 2b (Study Day 8 ± 1) and 4b (Study Day 83 ± 1). Sites in Spain have additional mandatory visits 3c and 4c during which AEs, concomitant medications, vital signs and laboratory data are collected. Separate interval mapping will be defined in Table 6.7: 2 and Table 6.7: 3, respectively, to accommodate these exceptions.

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 and vital signs data. For all other safety data, the worst of multiple values within an analysis window will be selected for analysis (see guidance for Handling, Display and Analysis of Laboratory Data (6)). Only one observation per time window will be selected for analysis at an on-treatment visit.

Table 6.7: 1 Visit intervals for efficacy endpoints

| | | Interval Definition | | |
|---|---|---|---|---|
| **Visit** | **Planned day** | **From (day)** | **To (day)** | **Visit description** |
| 1 | -28 to -3 | NA | -1 | Screening |
| 2 | 1 | 1 | 1[b] | Baseline[c] |
| 3 | 29 | 2 | 43 | Week 4 |
| 4a | 57 | 44 | 71 | Week 8 |
| EOT | 85 | 72 | Date of drug intake at EoT visit + 14 | Week 12 |
| FU1 | EOT +28 | Date of drug intake at EOT visit + 15 | Date of drug intake in EOT visit +34 | Follow-up 1 |
| FU2 | EOT +56 | Date of drug intake in EOT visit +35 | Date of drug intake in EOT visit +62 | Follow-up 2 |
| FU3 | EOT + 84 | Date of drug intake in EOT visit +63 | Last assessment date | Follow-up 3 |

[redacted]

b Day 1 is defined as the date of first treatment administration

c Baseline data must be collected before time of study drug administration during Visit 2.

Table 6.7: 2 Visit intervals for ECG, vital signs, and laboratory data

| | | Interval Definition | | |
|---|---|---|---|---|
| **Visit** | **Planned day** | **From (day)** | **To (day)** | **Visit description** |
| 1 | -28 to -3 | NA | -1 | Screening[a] |
| 2a | 1 | 1[b] (pre-dose) | 1 | Baseline[a,c] |
| 2a | 1 | 1 (post-dose) | 14 | Week 1[d] |
| 3 | 29 | 15 | 43 | Week 4 |
| 4a | 57 | 44 | 71 | Week 8 |
| EOT | 85 | 72 | Date of drug intake in EOT visit +1 | Week 12 |
| FU1 | EOT +28 | Date of drug intake in EOT visit +2 | Date of drug intake in EOT visit +34 | Follow-up 1[e] |
| FU2 | EOT +56 | Date of drug intake in EOT visit +35 | Date of drug intake in EOT visit +62 | Follow-up 2 |
| FU3 | EOT + 84 | Date of drug intake in EOT visit +63 | Last assessment date | Follow-up 3 |

a Baseline ECG data are collected at screening visit.

b Day 1 is defined as the date of first treatment administration.

c Baseline data must be collected before time of study drug administration during Visit 2.

d Only measurements collected after drug administration at Visit 2a are considered Week 1 values.

e In case of premature treatment discontinuation FU starts at +1 day after last drug admin for these values.

Table 6.7: 3 Visit intervals for vital signs and laboratory data for patients from sites in Spain only

| | | Interval Definition | | |
|---|---|---|---|---|
| **Visit** | **Planned day** | **From (day)** | **To (day)** | **Visit description** |
| 1 | -28- -3 | NA | -1 | Screening |
| 2a | 1 | 1[a] | 1 | Baseline[b] |
| 2b | 8 | 1[c] | 11 | Week 1 (Day 8) |
| 2c | 15 | 12 | 22 | Week 2 (Day 15) |
| 3 | 29 | 23 | 40 | Week 4 (Day 29) |
| 3c | 50 | 41 | 53 | Week 6 (Day 50) |
| 4a | 57 | 54 | 70 | Week 8 (Day 57) |
| 4b | 83 | 71 | 84 | Week 11 (Day 83) |
| EOT | 85 | 85 | Date of drug intake in EOT visit +1 | Week 12 (Day 85) |
| FU1 | | Date of drug intake in EOT visit +2 | Date of drug intake in EOT visit +34 | Follow-up 1[d] |
| FU2 | | Date of drug intake in EOT visit +35 | Date of drug intake in EOT visit +62 | Follow-up 2 |
| FU3 | | Date of drug intake in EOT visit +63 | Last assessment date | Follow-up 3 |

a Day 1 is defined as the date of first treatment administration

b Baseline data must be collected before time of study drug administration during Visit 2.

c Measurements collected after drug administration at Visit 2a or at Visit 2b are considered Week 1 values.

d In case of premature treatment discontinuation FU starts at +1 day after last drug admin for these values.

There will be a centralized evaluation of 12-lead ECG recordings at the time points specified in Table 6.7: 2. Three triplicate ECGs will be recorded as baseline prior to the first drug administration. The baseline value of an ECG variable is defined as the mean of these baseline ECG measurements.

# 7. PLANNED ANALYSIS

Unless otherwise specified in this TSAP or related documents, the format for displaying analysis results will follow BI guidelines and standards.

The following descriptive statistics will be displayed in summary tables of continuous variables:

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

For tables that are provided for continuous endpoints with some extreme data values, summary statistics such as median, quartiles and percentiles may be preferred to mean, standard deviation, minimum and maximum values.

Summaries of categorical data will include tabulations of the number of observations and the percentages of the respective treatment arm for all possible categories. Percentages will be rounded to one decimal place, unless the denominator is less than 100 in all treatment columns, in which case integer values will be displayed. A separate category for missing values will be displayed only if values of a particular variable are missing for at least one subject.

Individual values of data collected from all patients will be listed by treatment group, center, patient number and visit. These source data listings will be provided in Appendix 16.2 of the CTR.

## 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics are planned for this section of the report. Demographics and baseline characteristics will be summarized for the TS. Data will be presented for each treatment arm and for all treated patients combined.

The summary of demographic data will include age at time of informed consent, race, ethnicity and sex.

Baseline clinical characteristics summarized will include baseline disease characteristics, including DRSS level, BCVA score, and OCT central subfield thickness (CSFT), and substance use at screening.

In addition, data related to diabetic retinopathy history will be summarized separately. The following variables will be summarized:

- Duration of diabetic retinopathy calculated as the difference between the reported onset date and the patient's date of randomization;
- N (%) of patients reporting a history of Type I diabetes mellitus;
- Duration of diabetes mellitus Type I calculated as the difference between the reported onset date and the patient's date of randomization;
- N (%) of patients reporting a history of Type II diabetes mellitus;
- Duration of diabetes mellitus Type II calculated as the difference between the reported onset date and the patient's date of randomization;
- N (%) of patients reporting a history of arterial hypertension, myocardial infarction, transient ischemic attacks, stroke and diabetic nephropathy.

## 7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics will be provided for this section of the report based on the treated set.

Concomitant drug therapies (CT) and ophthalmic interventional drug therapies are coded according to WHO DD and will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorize CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classifications alternatives. As appropriate, patients receiving CTs with more than one possible ATC level-three category will be counted more than once; a footnote will clarify this possible double counting in tables. If a level three ATC category is not available, a lower level category may be reported. Separate summaries will be presented for concomitant drug therapies ongoing at baseline and concomitant drug therapies with start dates after date of first dose of study drug. Ophthalmic interventional drug therapies and general concomitant drug therapies will be summarized separately.

Concomitant non-drug therapies will be coded using the current version of MedDRA at the time of database lock. Ophthalmic non-drug therapies will be presented by reported term. Separate summaries will be presented for concomitant non-drug therapies ongoing at baseline and concomitant non-drug therapies with start dates after date of first dose of study drug. Ophthalmic non-drug therapies and general non-drug therapies will be summarized separately.

Concomitant medical conditions are coded similarly to AEs based on the most current MedDRA version at the time of database lock. A summary of concomitant conditions will be provided by treatment group, system organ class (SOC) and preferred term (PT).

The coding version number will be displayed as a footnote in respective outputs.

## 7.3 TREATMENT COMPLIANCE

Overall compliance will be calculated as the weighted average of the non-missing compliance values reported on the eCRF for each 28-day interval during the on-treatment period (Visits 3, 4 and EOT). The weighted average will be calculated as the sum of the reported compliance values multiplied by their respective interval durations in days, divided by 100. In the calculation of overall compliance, missing compliance values for a visit interval with confirmed drug administration records will be imputed as 100%. Compliance will be summarized by visit interval and overall.

The number and percentage of patients with non-missing overall treatment compliance of <80%, 80%-120%, and >120% and descriptive summaries of overall compliance will be reported.

## 7.4 PRIMARY ENDPOINT(S)

No primary efficacy endpoint is defined for this trial.

Analysis of the primary safety endpoint, i.e. proportion of patients with ocular adverse events over the on-treatment period, is provided in Section 7.8.

## 7.5 SECONDARY ENDPOINT(S)

Analyses of the secondary safety endpoint, i.e. proportion of patients with adverse events other than ocular adverse events over the on-treatment period, are described in Section 7.8.

### 7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoints are defined for this trial.

### 7.5.2 Secondary endpoint(s)

The frequency and percentage of patients in the FAS with at least 2 steps improvement from baseline on the DRSS, as defined in Table 5.2.2: 1, in the study eye at week 12 will be summarized by treatment. Baseline DRSS is the value recorded at Visit 2a. If DRSS is not

measured at Visit 2a, baseline DRSS is the value recorded at Visit 1. The frequency of patients reporting improvement in DRSS of at least 2 steps is expected to be low. The risk difference and corresponding 95% confidence intervals calculated using the method of Chan and Zhang (7) will be reported.

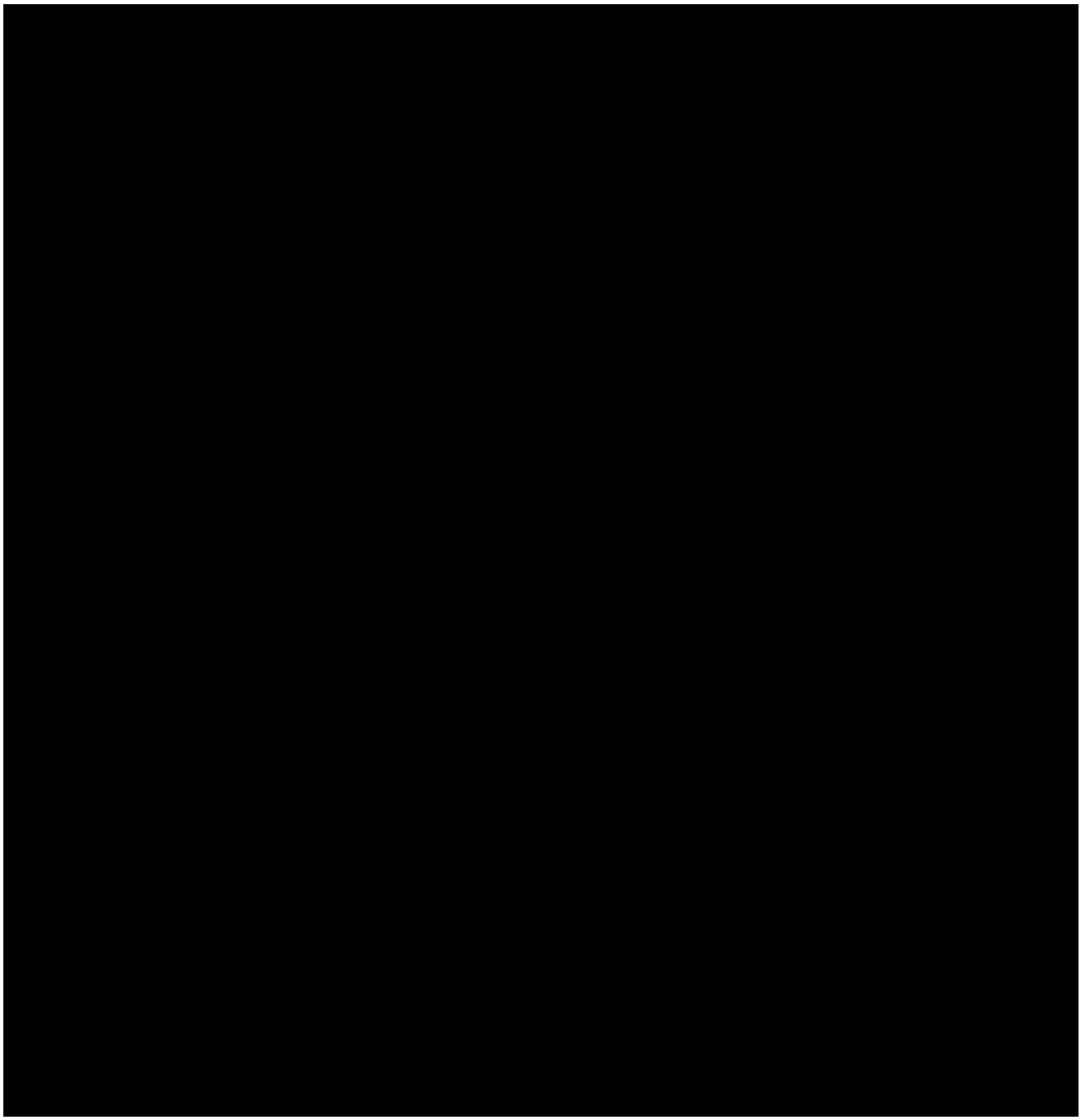
In addition, a shift table showing the frequency and percentage of patients reporting each Week 12 DRSS by baseline DRSS value will be presented. A visual display of the percentage of patients experiencing no change from baseline, a one-step and two-step improvement in DRSS from baseline to Week 12 or one-step worsening will be created. Similar summaries will be prepared using DRSS data collected from the non-study eye.

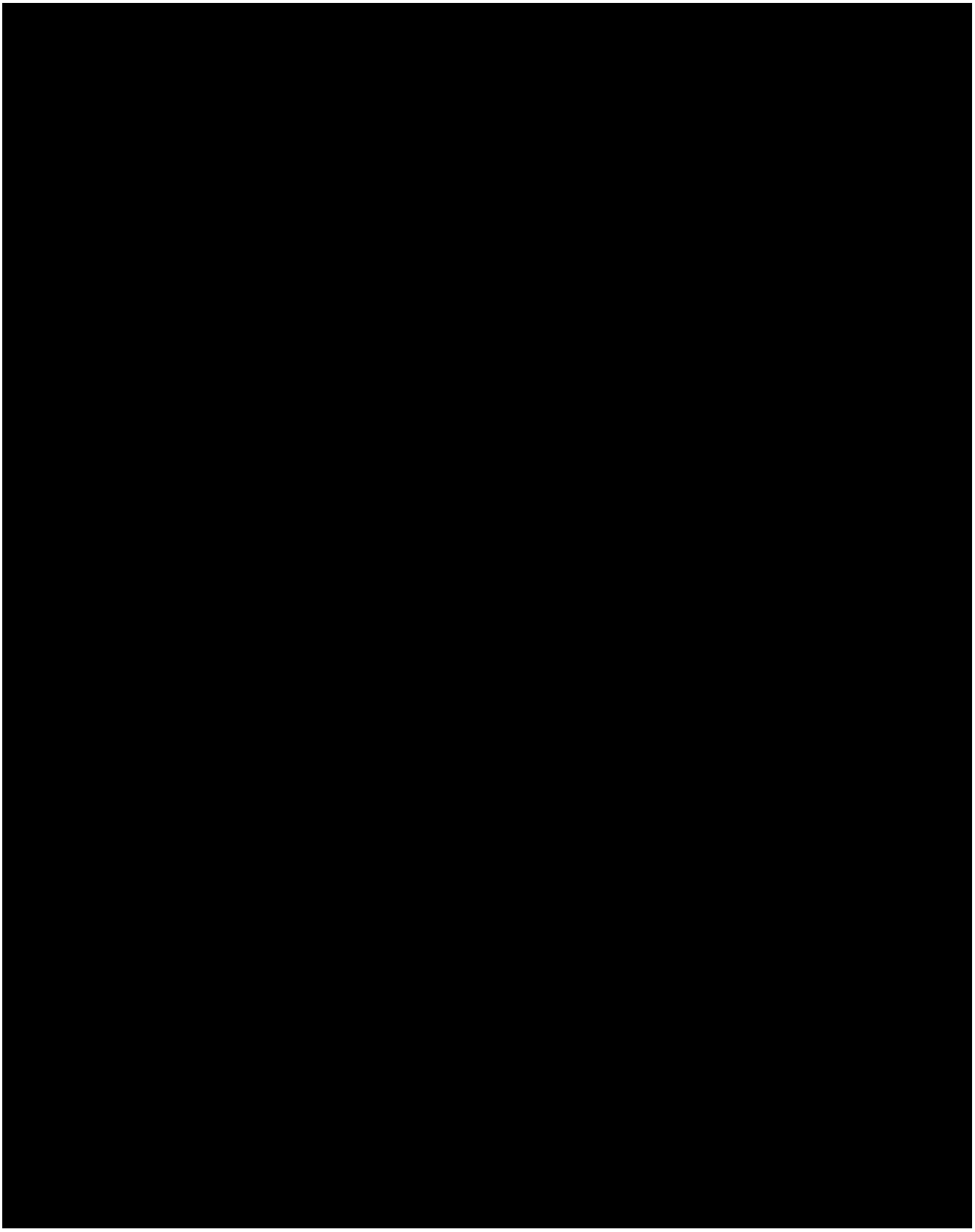
If a sufficient number of patients report improvement of 2 steps or more in the study eye, logistic regression analyses adjusted for visit, treatment and baseline visual acuity will be performed as exploratory analyses. The resulting odds ratios at each time point and corresponding 95% confidence interval will be presented, if modeling is possible.

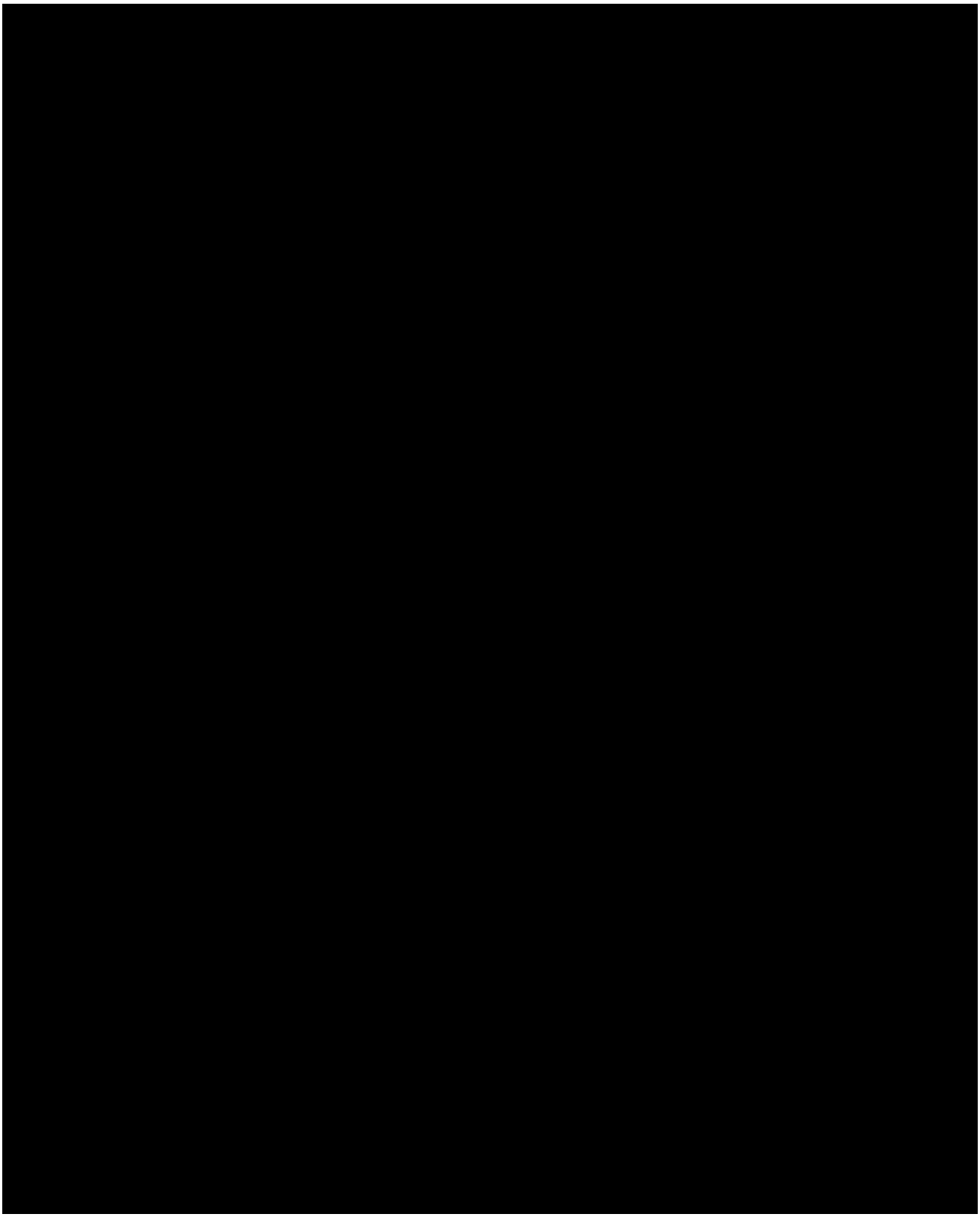
[redacted]

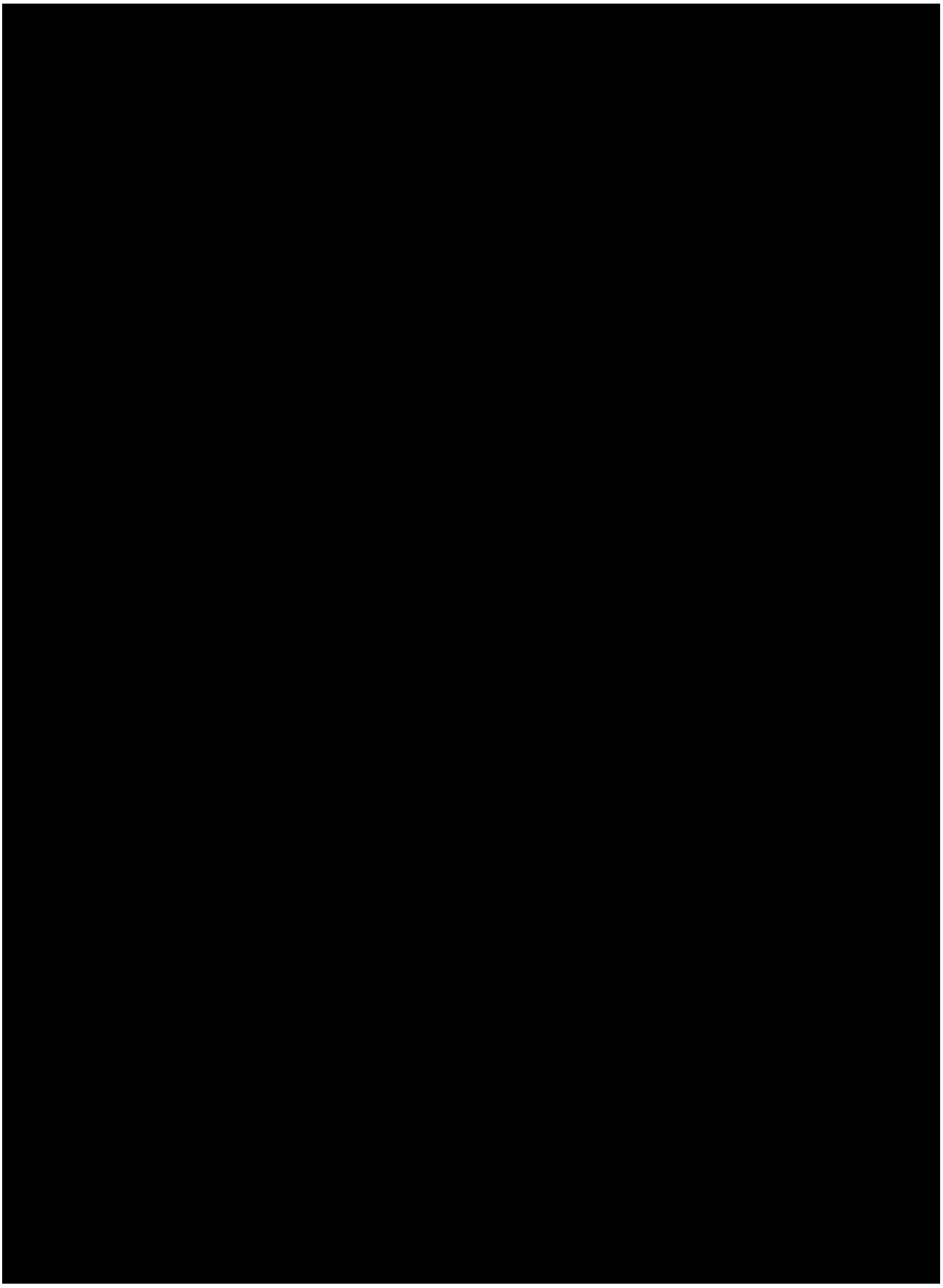
Additionally, analyses described in this section will be repeated using the PPS instead of the FAS.

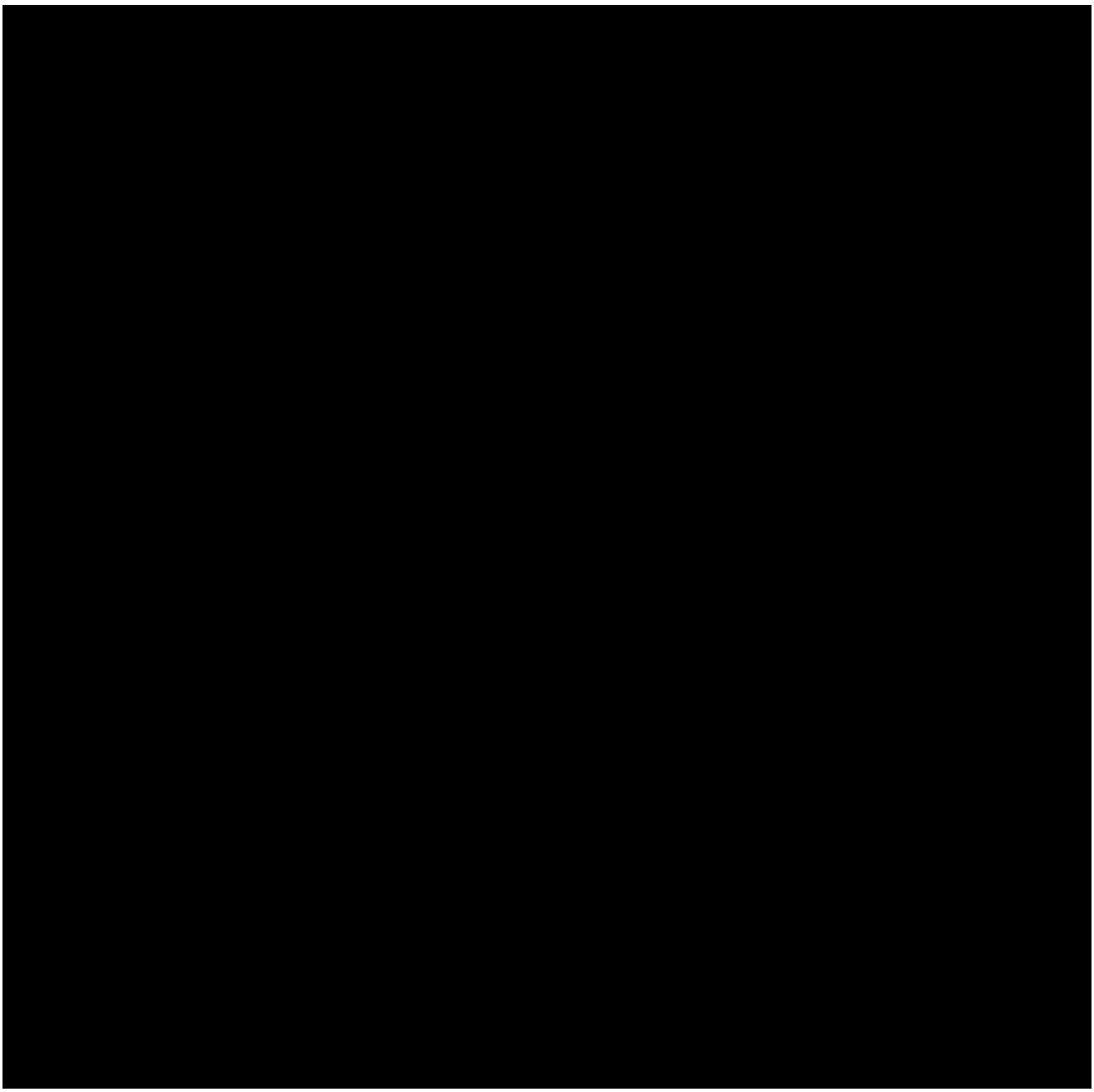
[redacted]

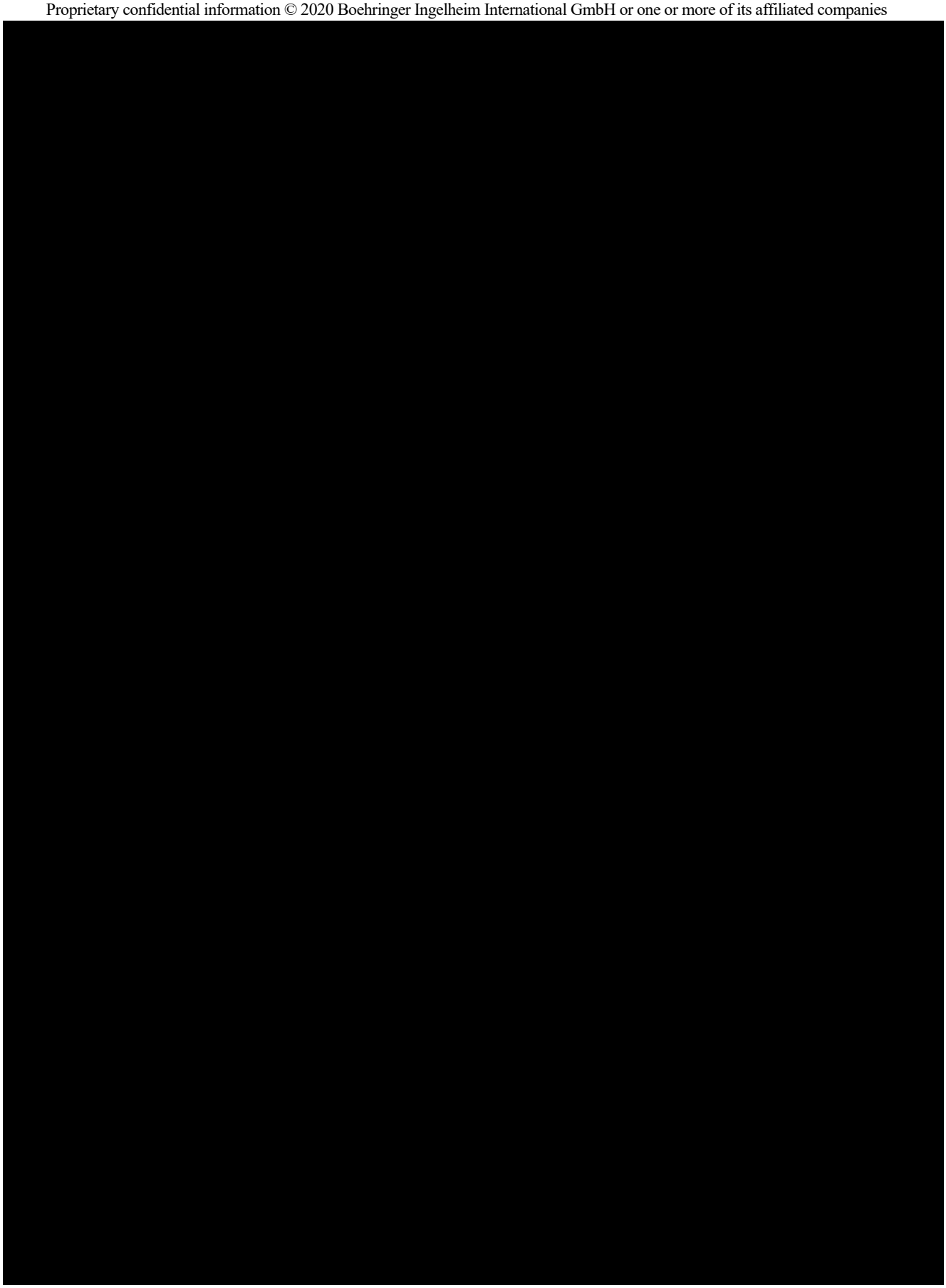


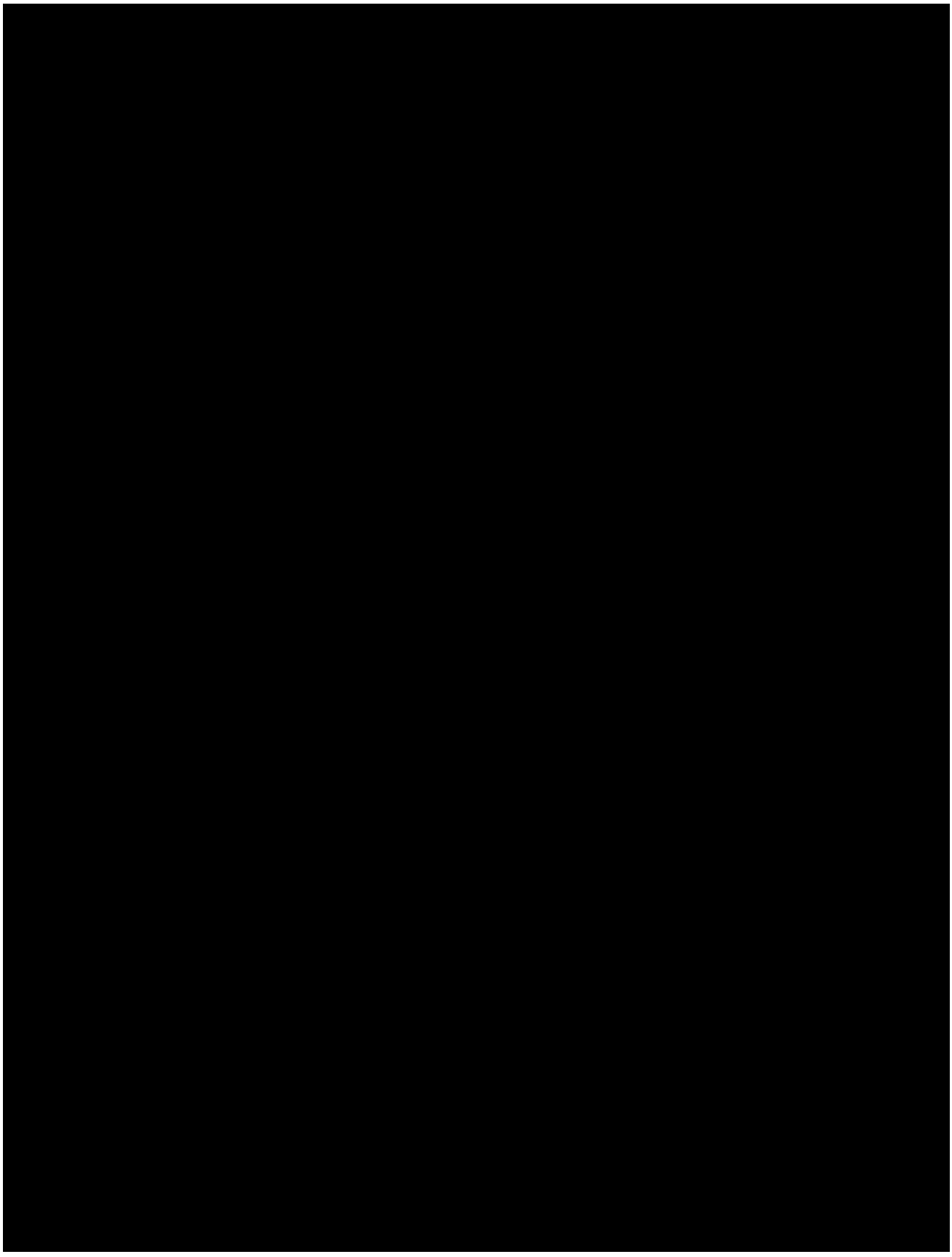


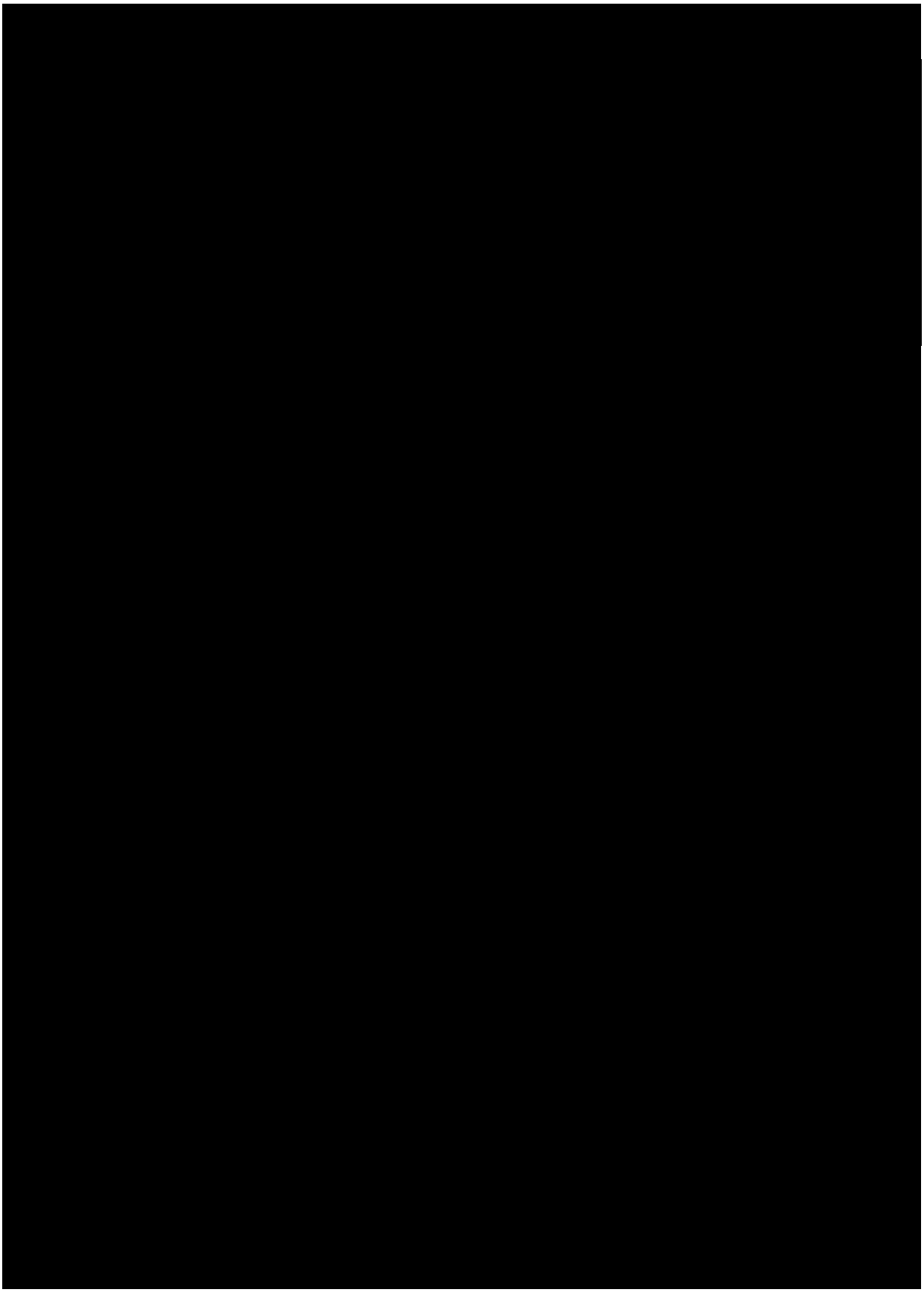


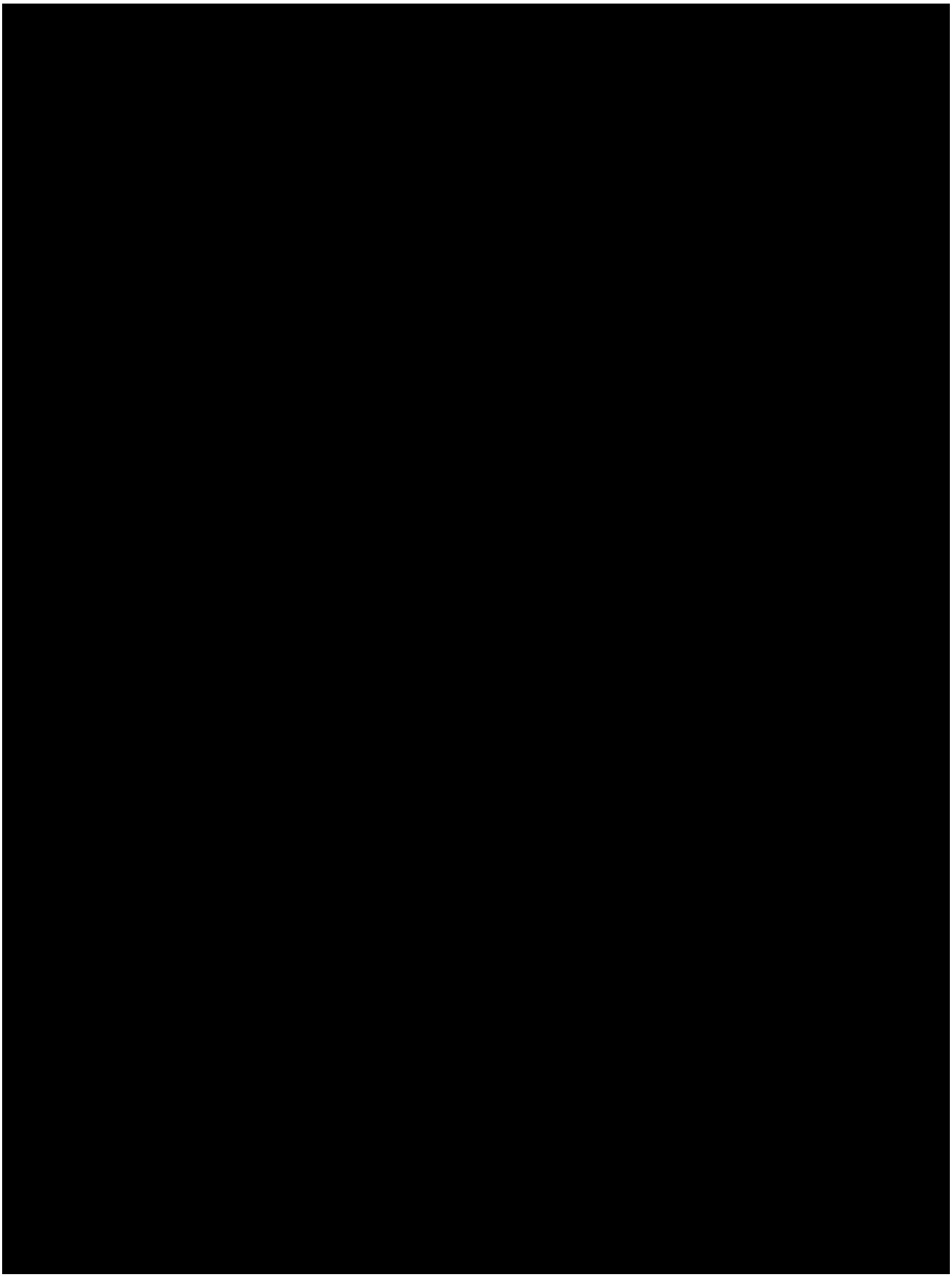












## 7.7 EXTENT OF EXPOSURE

Basis for the assessment of treatment exposure will be the amount of trial medication and the duration of exposure in days calculated across the on-treatment period for each patient. Standard summary statistics will be displayed by treatment arm. In addition, the number and percentage of patients in exposure categories defined as 0 to 6 weeks, >6 to 12 weeks will be summarized.

## 7.8 SAFETY ANALYSIS

Safety analyses will be performed on the treated set (TS).

### 7.8.1 Adverse events

Unless otherwise specified, the analyses of AEs will be descriptive. All analyses of AEs will be based on the number of patients reporting an AE and not on the number of events. The reporting and analyses of AEs will follow the BI guideline for analyses and presentation of adverse event data (12). All AEs will be coded using the most current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at the time of database lock. The intensity of AEs will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

For analysis, multiple AE occurrences will be collapsed into one event if all of the following conditions apply:

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

The analyses of AEs will be based on the concept of treatment emergent adverse events. Consistent with the REP definition provided in Section 6.1, all AEs with onset dates between the date of first treatment administration and date of last follow-up will be assigned to the randomized treatment. All AEs occurring before first treatment administration will be assigned to screening. For details on the treatment definition, see Section 6.1.

According to ICH E3 (13), AEs classified as 'other significant' need 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 hematological and other lab abnormalities or which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at an MQRM.

An overall summary of AEs will be presented. This summary will include the following event categories:

- All AEs
- Drug-related AEs
- AEs leading to treatment discontinuation
- Serious AEs (SAEs)
- AESI
- Highest CTC grade
- Ocular AEs

The frequency and percentage of patients with AEs will be summarized by treatment, primary system organ class (SOC), and preferred term (PT) in each of the following tables:

- All AEs
- Drug-related AEs
- AEs leading to treatment discontinuation
- Drug-related AEs leading to treatment discontinuation
- SAEs
- Drug-related SAEs
- AEs leading to death
- AEs of special interest (AESI)
- Other significant AEs according to ICH E3 (13).

Per CTP Section 5.2.6.1.4, AESIs for this trial are events of hepatic injury defined by an elevation of AST and/or ALT ≥ 3 fold upper limit of normal (ULN) combined with an elevation of bilirubin ≥ 2 fold ULN measured in the same blood draw, or aminotransferase (ALT and/or AST) elevations ≥ 10 fold ULN. AEs related to these definitions will be summarized as AESIs.

Additionally, a table summarizing time to first AE from date of first dose of study drug will be presented by treatment arm, SOC and preferred term.

**Primary endpoint: Ocular AEs**

In additional to standard adverse event tables, separate summaries will be provided to address the primary endpoint and secondary safety endpoints. The frequency and percentage of patients reporting ocular AEs, as identified by the investigator as an ocular event on the AE eCRF, will be summarized by treatment, highest CTC grade, primary SOC, and PT for the primary endpoint analysis. The number and percentage of patients in each treatment arm

reporting specific ocular symptoms will be summarized and will be displayed by associated event in a listing. Additional summaries of serious ocular AEs, drug-related ocular AEs, serious drug-related ocular AEs, and ocular AEs leading to discontinuation will be provided, if any such events are reported. A Kaplan-Meier plot displaying time to first ocular event following first dose of study drug will be provided.

To assess the impact of the COVID-19 pandemic on this trial, adverse events reported after 01MAR2020 in the subset of patients active in the trial as of 01MAR2020 will be reported and listed in the CTR. Overall summaries of the subset of all AEs and subset of ocular AEs with start dates prior to 01MAR2020 will be reported separately. In additional, frequencies of AEs reported during the follow-up period will be reported in the subset of patients who completed the trial prior to 01MAR2020 and in the subset of patients who completed the trial after 01MAR2020.

**Secondary endpoint: Non-ocular AEs**

A separate set of the tables specified above for ocular AEs will be generated to summarize patients reporting AEs not identified as ocular AEs. These summaries will address the analysis of the secondary safety endpoint. The data will be summarized by treatment, MedDRA primary SOC, and PT.

For further details on the summarization of AE data, refer to BI guidelines (5,12).

### 7.8.2 Laboratory data

The analyses of laboratory data [redacted] will be descriptive in nature and will be based on BI standards (6).

For continuous safety laboratory parameters, standardized and normalized values will be derived as well as the differences from baseline. The process of standardization and normalization as well as standard analyses for safety laboratory data are described in the BI guidance for the display and analysis of laboratory data (6).

Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference ranges at baseline, the last measurement on treatment and the last post-treatment follow-up. Descriptive statistics will be provided by treatment group for baseline, on-treatment values, values collected during follow-up visits and for changes from baseline. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities as defined for the XLAB macro.

The Estimated Glomerular filtration rate as assessed by the CKD-EPI formula is calculated as:

eGFR (ml/min/1.73 m²) = 141 *min(SCr/κ, 1)α *max(SCr/κ, 1)-1.209 *0.993Age *1.018 [if female] * 1.159 [if black]

where SCr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1. The process of standardization and normalization as described in the guidance document (6) does not apply. Additionally, the shift tables for eGFR will use the following categories (similar to the staging of renal impairment): eGFR ≥ 90; 60-<90; 30-<60; and<30.

Clinically relevant findings in laboratory data will be reported as AEs and will be analyzed as part of AE analyses.

### 7.8.3 Vital signs

Descriptive summaries of vital signs and body weight values over time and for the difference from baseline will be provided.

Clinically relevant findings in vital signs data will be reported as AEs and will be analyzed as part of AE analyses.

### 7.8.4 ECG

All evaluations of ECG data will be based on data from the ECGS.

For quantitative endpoints, listings of individual data with notable findings flagged will be provided in Appendix 16.2. For patients with any notable finding in quantitative ECG recordings, a separate listing with corresponding time profiles will be created as an end-of-text display.

Comments regarding the ECG recordings will be provided in a listing.

For categorical ECG endpoints, frequency tables will be provided. Findings of ECG abnormalities from morphological analyses will also be analyzed as categorical endpoints.

Descriptive statistics (N, mean, SD, min, median, max) will be provided for absolute values of QTcF, HR, QT, PR and QRS. Changes from baseline over time will also be presented for these values. Time profiles of mean and SD of change from baseline while on treatment will be displayed graphically by treatment.

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying the random coefficient model described in Section 9.1.1 using all time points. A scatterplot of QTcF vs RR including the overall regression line will be included in the Statistical Appendix of the CTR. The resulting (fixed effect) slope together with two-sided 95% confidence intervals will be included in the footnote for this plot.

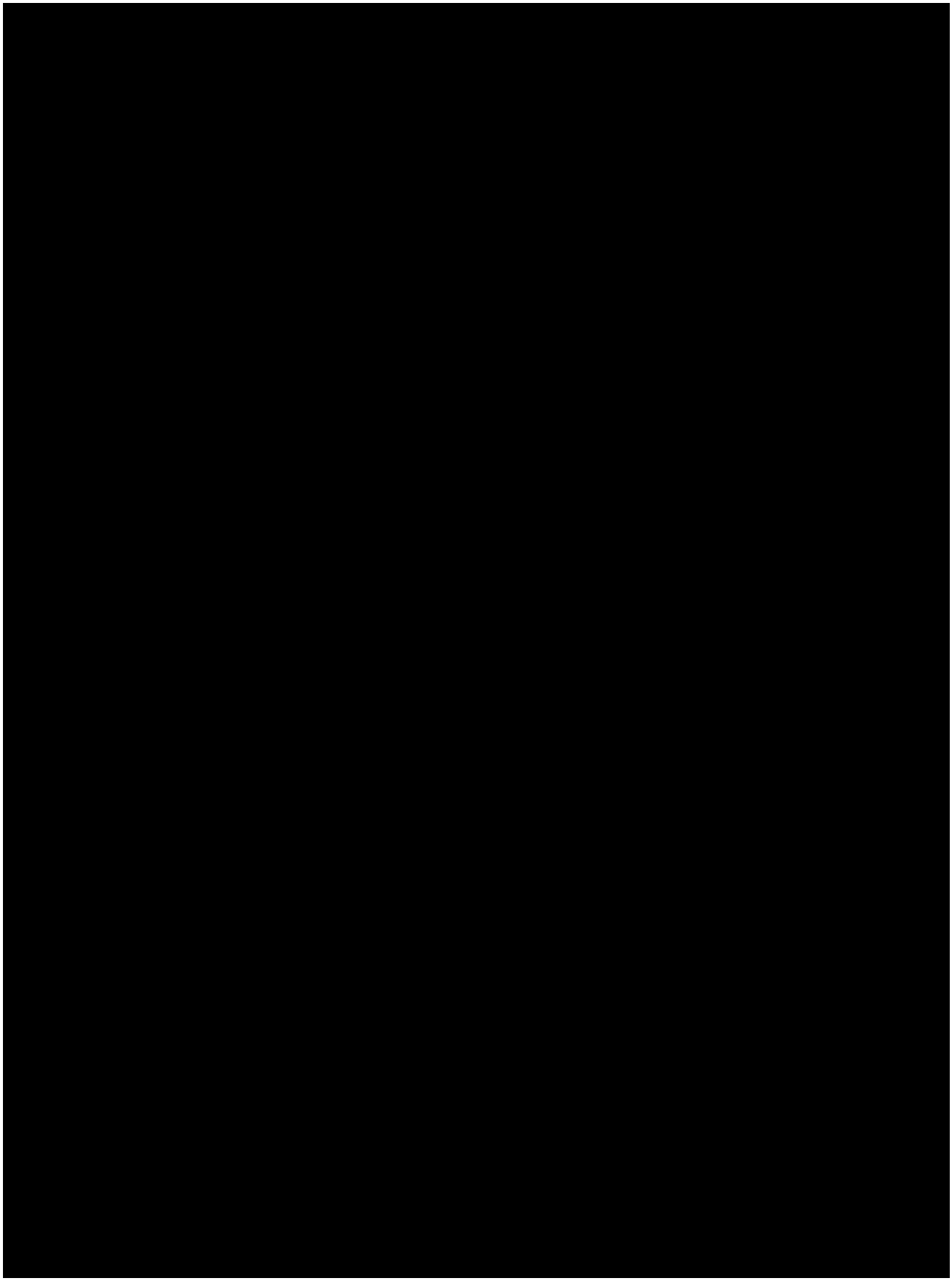
### 7.8.5 Others

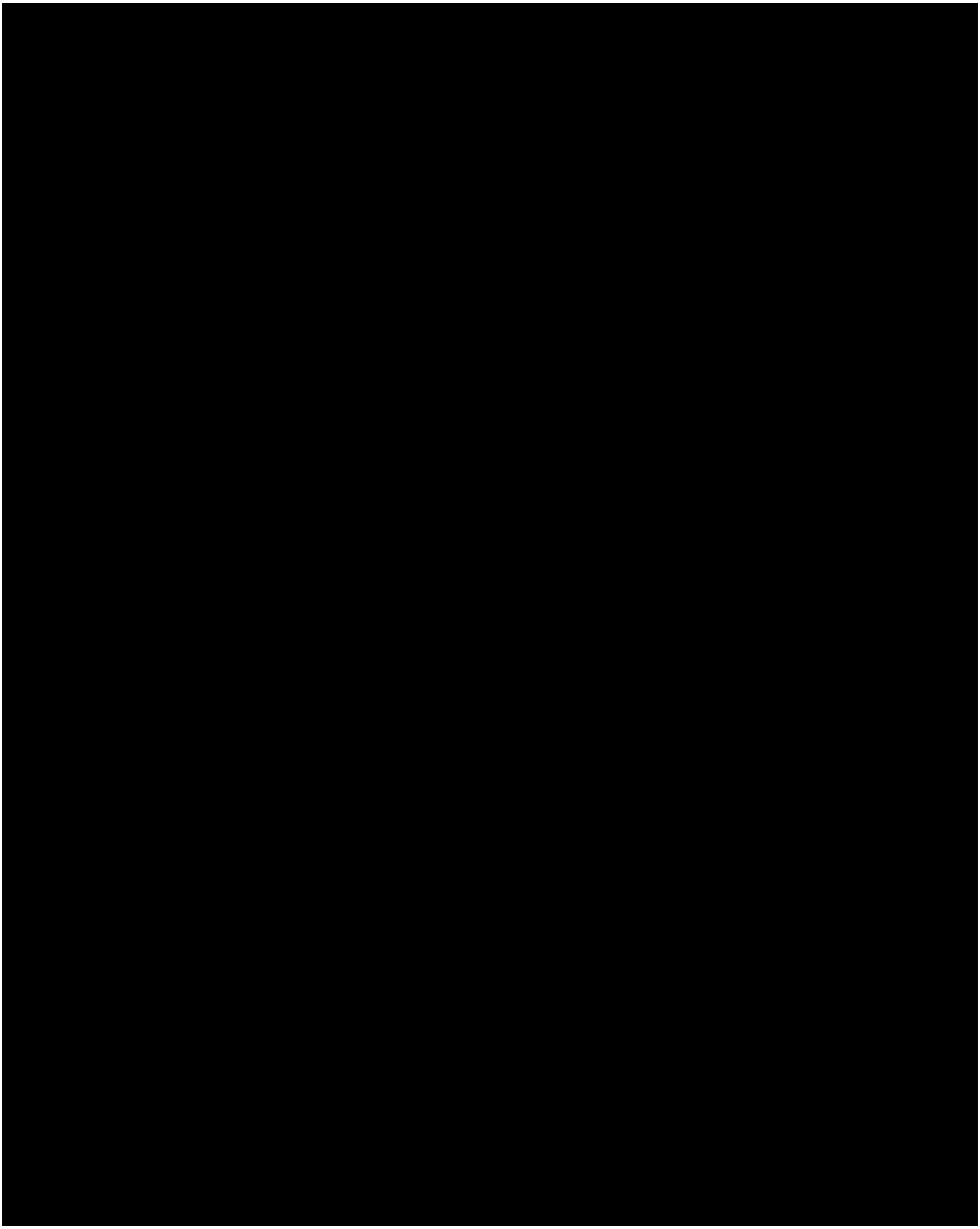
[redacted]

For future disclosure of trial results, specific data summaries will be included in the CTR or CTR appendices. Required displays will be specified in the technical TSAP.

# 8. REFERENCES


| | |
|---|---|
| 1. | *CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version. |
| 2. | *001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON. |
| 3. | *001-MCS-37-473:* “Performing a Pharmacometric Analysis”, current version; IDEA for CON. |
| 4. | *001-MCS-40-413:* “Identify and Manage Important Protocol Deviations”, current version; IDEA for CON. |
| 5. | *001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON. |
| 6. | *001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON. |
| 7. | R15-1346: Chan ISF, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 55, 1202-1209, 1999. |
| 8. | *BI position paper:* “Standards for Inferential Analyses; 1.1 Analyses of Continuous Endpoints – Parallel Group Studies” |
| 9. | *001-MCS-36-472_RD-01:* “Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies”, current version; IDEA for CON. |
| 10. | *001-MCS-36-472_RD-03:* “Description of Analytical Transfer Files and PK/PD Data Files”, current version; IDEA for CON. |
| 11. | *001-MCG-311:* “Pharmacometric Dataset Generation”, current version; IDEA for CON. |
| 12. | *001-MCG-156*: "Analysis and presentation of adverse event data from clinical trials", current version; IDEA for CON. |
| 13. | *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 |
| 14. | R10-2920: Ring A; Statistical models for heart rate correction of the QT interval. Stat Med 29, 786-796, 2010. |





# 10. HISTORY TABLE

Table 10: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| 1 | **29-JUN-2020** | [redacted] | All | This is the final TSAP prior to DBL; based on initial TSAP approved 12-SEP-2017. |