NOVARTIS

Global Medical Affairs

Brinzolamide 1% / Brimonidine 0.2% "Simbrinza"

CQVJ499A2404 / NCT03150160

Additive effect of twice-daily Brinzolamide 1% / Brimonidine 0.2% fixed dose combination as an adjunctive therapy to travoprost 0.004% patients with normal tension glaucoma

Statistical Analysis Plan (SAP)

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28-Aug-2017	Prior to DB lock	Creation of final version	N/A - First version	NA

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
BID	bis in die (twice a day)
CAI	Carbonic Anhydrase Inhibitor
CCT	Central Corneal Thickness
CFR	US Code of Federal Regulations
CLV	Corrected Loss Variance
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CPSD	Corrected Patterns Standard Deviation
CRO	Contract Research Organization
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
ETDRS	Early Treated of Diabetic Retinopathy Study
FAS	Full Analysis Set
GAT	Goldman Applanation Tonometer
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
MAOI	Monoamine Oxidase Inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
OAG	Open Angle Glaucoma
OCT	Optical Coherence Tomography
OD	Oculus Dexter (right eye)
OS	Oculus Sinister (left eye)
OU	Oculus Uterque (both eyes)
PGA	Prostaglandin Analogue
p.o.	oral(ly)
PPS	Per Protocol analysis set
PSD	Patterns Standard Deviation
QD	quaque die (once a day)
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SCR	Screening
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
TID	three times a day
UNSC	Unscheduled
VA	Visual Acuity
WHO	World Health Organization

1   Introduction

The purpose of this Statistical Analysis Plan (SAP), is to describe the implementation of the statistical analyses planned in the study protocol for the production of the clinical study report (CSR). This document is aligned with Version 00 of the original clinical study protocol dated 11-Feb-2017.

1.1   Study design

Figure 1-1   Study design
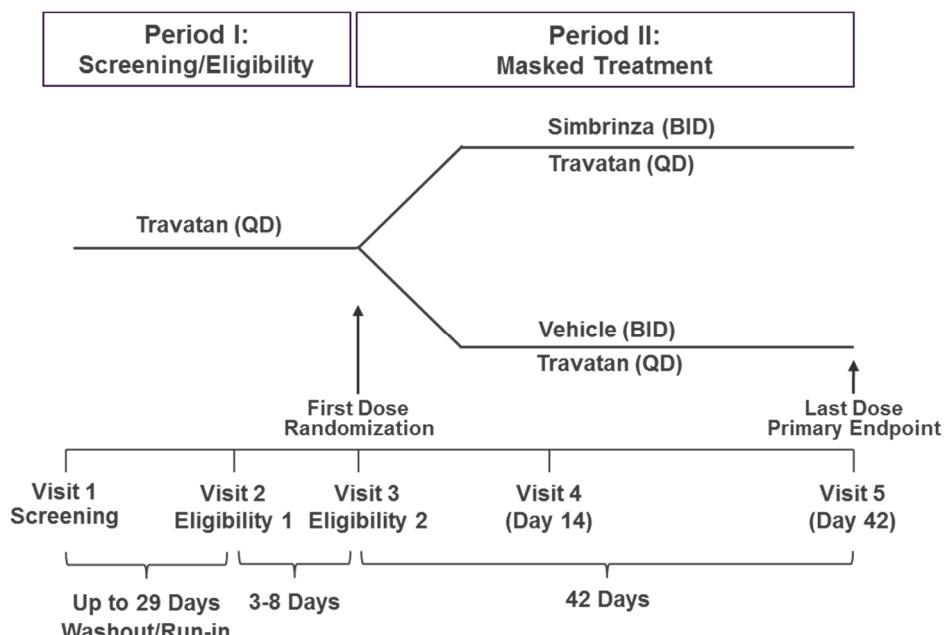
This study is a multicenter, randomized, double-blind, 2-arm, parallel-group study in patients with normal tension glaucoma who are insufficiently controlled on Travatan 0.004% monotherapy. About 200 patients will be randomized in a 1:1 ratio to either Simbrinza + Travatan or vehicle + Travatan and treated for up to 10 weeks whilst they will receive double-masked study medication for 6 weeks. The randomization will be stratified by study site. This study is divided into 2 sequential periods for a total of 5 visits.

Phase I of the study is a Screening/Eligibility Phase which includes Screening Visit and 2 Eligibility Visits (E1 and E2). The intent of the Screening/Eligibility Phase is to identify eligible patients for this study, including a determination of baseline IOP measurements at E1 and E2 Visits while on Travatan monotherapy.

Period II is the randomized, masked Treatment Phase which includes 2 on-therapy visits at Week 2 and Week 6 (Exit Visit). The primary analysis time point is at Week 6. A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol (Visit 5/ Day 42).

The analysis will be performed after DBL following the end of study, defined as 30 days after last patient last visit. (LPLV). No interim analysis is planned for this study.

1.2   Study objectives and endpoints

Objectives and related endpoints

Objectives	Endpoints	Analysis
Primary		Refer to Section 2.5
• To demonstrate that Simbrinza is superior to vehicle in lowering diurnal IOP when added to baseline Travatan therapy	• Change from baseline in diurnal IOP in the study eye at Week 6	
Secondary		Refer to Section 2.7
• To evaluate the differences between Simbrinza and vehicle in diurnal IOP percentage change from baseline	• Percentage IOP change from baseline in diurnal IOP at Week 6	
• To evaluate the differences between Simbrinza and vehicle in diurnal IOP	• Diurnal IOP at Week 6	
• To evaluate the differences between Simbrinza and vehicle in IOP change at each time point from baseline	• Change from baseline in IOP for each time point at Week 6	
• To evaluate the differences between Simbrinza and vehicle in IOP percentage change at each time point from baseline	• Percentage change from baseline in IOP for each time point at Week 6	
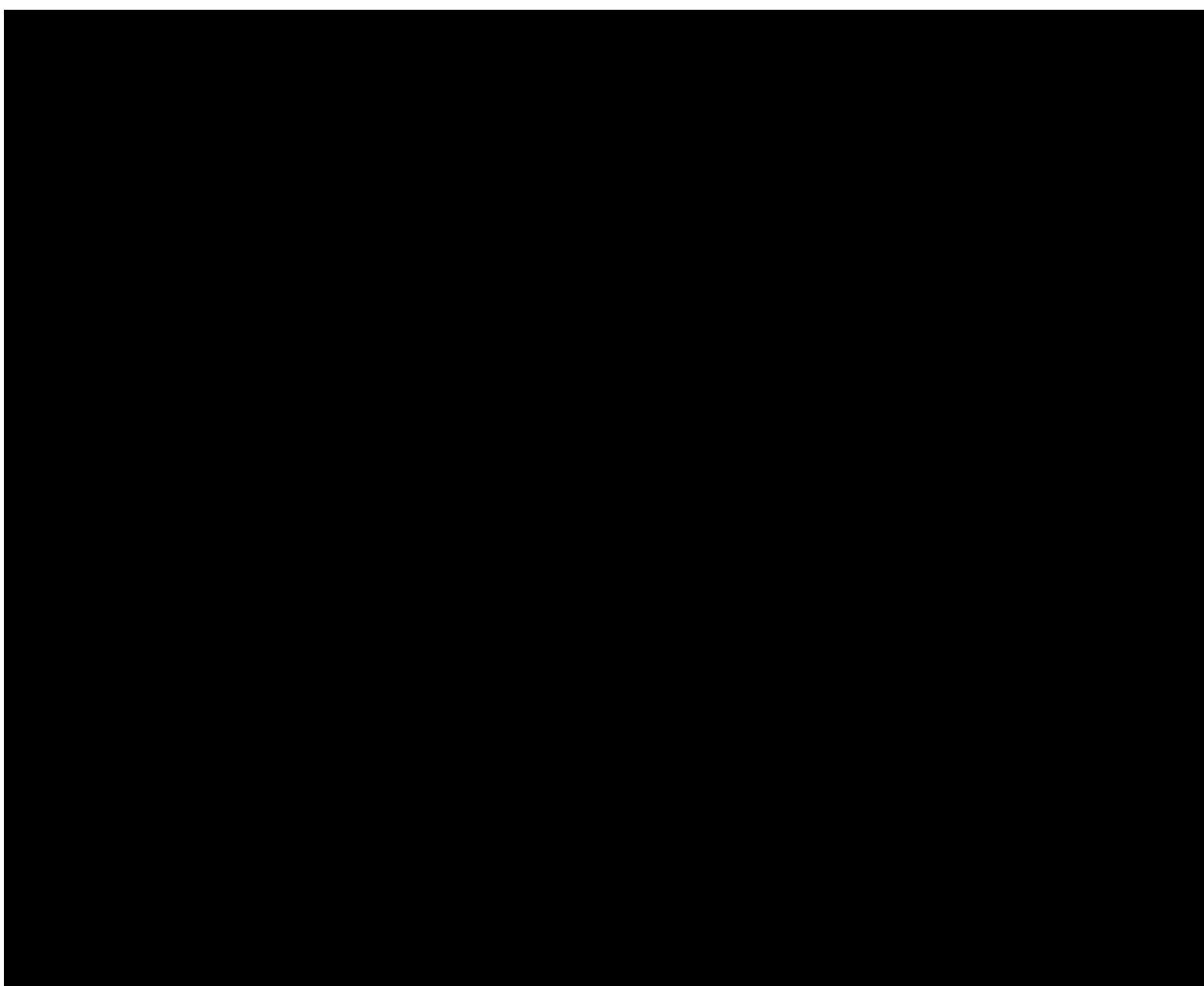
2   Statistical methods

2.1   Data analysis general information

The final analysis will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

One eye from each patient will be chosen as the study eye and only the study eye will be used for efficacy analysis. If only 1 of a patient's eyes is dosed, or if both are dosed but only one eye is diagnosed with normal tension glaucoma, the dosed normal tension glaucoma eye will be selected as the study eye. If both eyes are dosed, and are both diagnosed with normal tension glaucoma, the worse evaluable eye will be selected as the study eye. Worse eye is defined as the eye with the higher IOP at 09:00 averaged across the 2 eligibility visits. If both eyes are equal at 09:00 IOP, then the worse eye will be defined as the eye with the higher IOP at 11:00 averaged across the 2 eligibility visits. If both eyes are equal at 09:00 and 11:00 IOP then the right eye will be selected for analysis.

2.1.1   General definitions

Investigational drug, will refer to Simbrinza only. Whereas, ***study treatment*** will refer to the combination drugs Simbrinza (bid), Travatan (qd), Vehicle (bid).

The term investigational treatment may also be referred to as ***study treatment*** which is used throughout this document.

The term study drug can be used to refer to investigational and components of study treatment.

Date of first administration of study treatment

The date of first administration of study treatment is defined as the date patient receives the first dose of study treatment after being randomized to one study arm.

Date of last administration of study treatment

The date of last administration of study treatment is defined as the date patient receives the last dose of study treatment.

Baseline

Baseline IOP assessment is defined as the average of the non-missing IOP measurements at visits 2 and 3. For all other assessment baseline is the non-missing measurements at visit 3.

Study Periods or Phases

There are two periods in this study: Period 1 for screening and Eligibility, and Period 2 for the blinded treatment.

Study day

The study day, describes the day of the event or assessment date in Period 1 or 2 after enrollment, relative to the reference start date.

Last contact

The last time the investigator or a designated study personal contacted the patient to collect some information or complete some study procedures.

2.2   Analysis sets

Enrolled and Randomized

All enrolled analysis set includes all patients who signed an ICF and are assigned patient numbers. This analysis set will be used to summarize patient disposition and pre-treatment AEs.

All randomized analysis set includes all patients who are randomly assigned to receive a study treatment.

Full Analysis Set

Full analysis set (FAS) includes all randomized patients with IOP measurement at baseline who had at least one on-treatment assessment. This analysis set will be the primary analysis set for IOP endpoints. Patients in the FAS will be analyzed according to randomized treatment.

Per protocol set (PPS)

Per protocol analysis set (PPS) consists of a subset of all patients in the FAS and excludes all data which have met any of the critical deviation criteria identified in Section 5.5. In addition, individual patient visits and data points that do not satisfy protocol criteria may be excluded from the PPS.

The final patient evaluability will be determined prior to breaking the code for masked treatment assignment and locking the database.

The number and percentage of patients in each analysis set will be summarized based on all randomized patients. In addition, a listing will be produced to show the patient inclusion/exclusion into each of the analysis sets with the corresponding reason(s) for exclusion.

If protocol deviations do occur, then the data from specific patients, visits, or evaluations may be excluded from analysis. The criteria and determination of clinically significant protocol deviations will be data based and finalized prior to the database lock.

Safety

The Safety analysis set includes all patients exposed to at least one dose of any study therapy. Patients in the safety analysis set will be analyzed according to the treatment received.

2.2.1 Subgroup of interest

To determine whether the treatment effect is consistent, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be provided for the following subgroups:

- age categories (<65, ≥65 years) and (< 50, 50 – 64, ≥ 65);
- sex (female, male);
- baseline IOP categories (16-<19 mmHg, ≥19-21 mmHg).

The subgroup analyses will be based on the FAS.

2.3 Patient disposition, demographics and other baseline characteristics

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. Patient characteristics summaries include tables and listings such as demographics [(age (continuous and categorically as <65, ≥ 65 and also as < 50, 50 – 64, ≥ 65), gender, race, ethnicity, iris color, and region]) and baseline characteristics (baseline IOP by time point, baseline diurnal IOP, baseline IOP category (16-<19 mmHg, ≥19-21 mmHg), corneal thickness, and diagnosis for the FAS. All descriptive summary statistics will be

displayed with n and % for categorical data, and with mean, standard deviation, median, minimum, and maximum for continuous data.

2.3.1 Patient disposition

All patients who signed informed consent will be accounted for in Patient disposition. The number and percentage of patients who entered the run-in period and the number and percentage of screen failures will be based on all enrolled (signed informed consent) patients.

The number and percentage of patients who either discontinued treatment, died or experienced an AE during the run-in period as well as the number and percentage of randomized patients will be based on all patients who entered the run-in period.

The number and percentage of patients in the FAS, in the safety analysis set, in the PPS will be based on all randomized patients. In addition, the number and percentage of patients and number and percentage of patients who completed the study and those who discontinued the study will be based on all randomized patients. The reasons for discontinuation and the deaths that occurred during the double-blind phase will be summarized based on all randomized patients.

Patient disposition table will present the followings:

- Screened/Run in

- Screen/ Run in Failure

- Entered the double-blind phase

- Completed the double-blind phase

- Discontinued the double-blind phase

- Reason for discontinuation

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The extent of drug exposure will be analyzed by phase both as continuous and categorical variable with summary statistics, using the Safety Set. The categories are: (1 - 14 Days); (15 - 28 Days); (29 - 45 Days) and > 45 Days.
No summaries of treatment compliance are planned.

2.4.2 Prior, concomitant and post therapies

All prior and concomitant medications will be coded using WHO Drug Dictionary and will be summarized by ATC (Anatomical Therapeutic Chemical) class coding Level 3 and preferred name using counts and percentages. Within each summary, events will be sorted alphabetically. Details regarding WHO-DD version will be included in the footnote in the tables/listings.

Prior medications are medications, which started and stopped prior to the patient's study treatment start date.

Concomitant medications are medications which:

- started prior to, on, or after the patient's study treatment start date;
- AND ended on or after the patient's study treatment start date, or were ongoing at the end of the study.

A summary of concomitant medication use will be presented overall and by visit.

Note: If medication start dates are partial, the start date will be imputed as the earliest possible date, and stop date as the latest possible date. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified as concomitant.

2.5   Analysis of the primary objective

The primary objective of this study is to demonstrate that Simbrinza is superior to vehicle in lowering diurnal IOP when added to baseline Travatan therapy.

2.5.1   Primary endpoint

The primary efficacy endpoint in this study is the change from baseline (CFB) to week 6 in diurnal IOP.

CFB Diurnal IOP = average of change from baseline at 9:00 and 11:00 time points, with baseline being the average of the E1 and E2 IOP by time point.

The primary analysis set for the efficacy analysis will be the FAS.

2.5.2   Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be an assessment of differences between treatments in mean change from baseline in diurnal IOP (average of change from baseline at 9:00 and 11:00 time points, with baseline being the average of the E1 and E2 IOP by time point) at Week 6. The null and alternative hypotheses for the primary analysis are:

$$H_0: \mu_{Simbrinza+Travatan} = \mu_{Vehicle+ Travatan}$$
$$H_1: \mu_{Simbrinza+Travatan} \neq \mu_{Vehicle+ Travatan}$$

where $\mu_{Simbrinza+Travatan}$ refers to actual mean diurnal IOP change from baseline for patients randomized to receive brinzolamide / brimonidine plus Travatan, and $\mu_{Vehicle+Travatan}$ refers to actual mean diurnal IOP change from baseline for patients randomized to receive Vehicle plus Travatan.

The treatment difference (Simbrinza – Vehicle) in mean diurnal IOP change from baseline will be analyzed using a mixed model for repeated measures (MMRM) with terms for treatment, visit, visit by treatment interaction and baseline IOP as covariate. Covariance structures such as unstructured (UN) will be used. Least squares mean estimates within treatment and for the difference of the treatments along with their associated 2-sided 95% confidence intervals will be provided.

A greater reduction from baseline in diurnal IOP at Week 6 on the adjunctive therapy (Simbrinza plus Travatan) relative to Vehicle plus Travatan, i.e. negative treatment difference in mean diurnal IOP change from baseline to Week 6, will indicate IOP-lowering advantage for the adjunctive therapy (Simbrinza plus Travatan) over Vehicle plus Travatan.

To address multiplicity associated with testing one primary endpoint and several secondary endpoints, a fixed testing procedure will be used for hypothesis testing of primary and secondary endpoints, and is further described in .

2.5.3 Handling of missing values/censoring/discontinuations

The analysis of change from baseline in diurnal IOP will be a likelihood-based approach via MMRM, without explicit data imputation. The MMRM analyses are robust to data that are missing at random.

2.5.4 Supportive analyses

The primary analysis will be repeated using the per protocol set in order to assess its robustness in regard to deviations.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

Not applicable.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.6.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

The secondary objectives for this study are:

- To evaluate the differences between Simbrinza and vehicle in diurnal IOP percentage change from a Travatan baseline therapy.

- To evaluate the differences between Simbrinza and vehicle in diurnal IOP (on Travatan baseline therapy).

- To evaluate the differences between Simbrinza and vehicle in IOP change at each time point from a Travatan baseline therapy.

- To evaluate the differences between Simbrinza and vehicle in IOP percentage change at each time point from a Travatan baseline therapy.

2.7.1 Secondary endpoints

The secondary endpoints for this study corresponding to the above objectives are:

- Percentage IOP change from baseline (PCFB) in diurnal IOP at Week 6.

- Diurnal IOP at Week 6 in each treatment arm.

- Change from baseline in IOP for each time point at Week 6.

- Percentage change from baseline in IOP for each time point at Week 6.

2.7.2 Statistical hypothesis, model, and method of analysis

The null and alternative hypotheses for each secondary endpoint are:

$$H0: \mu_{Simbrinza+Travatan} = \mu_{Vehicle+Travatan}$$

$$H1: \mu_{Simbrinza+Travatan} \neq \mu_{Vehicle+Travatan}$$

where $\mu_{Simbrinza+Travatan}$ refers to the mean for patients randomized to receive brinzolamide / brimonidine plus Travatan, and $\mu_{Vehicle+Travatan}$ refers to the mean for patients randomized to receive Vehicle plus Travatan for each respective secondary endpoint.

At the subject level, diurnal IOP percentage change from baseline is constructed as follows:

- Obtain percentage differences from baseline for each of the time point-matched IOPs at Week 6 (e.g. [(IOP Week 6 09:00 minus baseline IOP 09:00) / baseline IOP)]*100 and similarly for the 11:00 time point)

- Obtain mean of the percentage changes from baseline at Week 6

The analysis of the difference between the treatment groups with respect to the secondary endpoints will be based on the same approach described above for the primary endpoint.

A fixed testing procedure will be used for hypothesis testing of primary and secondary endpoints. The secondary efficacy hypotheses will be relevant only if the primary efficacy null hypothesis is first rejected at the 5% level (two-sided). The testing order for the secondary hypotheses (all based on IOP at Week 6) will be:

- Difference between treatments in percentage diurnal IOP change from baseline

- Difference between treatments in diurnal IOP

- Difference between treatments in IOP change from baseline at 11:00

- Difference between treatments in percentage IOP change from baseline at 11:00

- Difference between treatments in IOP change from baseline at 09:00

- Difference between treatments in percentage IOP change from baseline at 09:00

Significance for a comparison will be claimed only if the null hypothesis is rejected for the previous endpoint in this series.

The primary dataset for the analyses of the secondary endpoints is the Full Analysis Set. However, the analyses will be repeated using the per protocol set.

2.7.3 Handling of missing values/censoring/discontinuations

For these analyses, missing observations will not be imputed. The statistical models that will be employed and the associated analyses are robust under the missing completely at random and the missing at random assumptions.

2.8 Safety analyses

The safety assessments in this study are automated perimetry, fundus parameters, best-corrected visual acuity (BCVA), slit-lamp exam, blood pressure, pulse rate and adverse events. The safety analyses will consist of descriptive summaries of the data as relevant to the scale of data, e.g., frequency and percent for adverse events, and mean changes from baseline as appropriate.

Observed values for each continuous variable will be presented descriptively (N, mean, standard deviation, median, minimum and maximum) at each visit by treatment group. Change from baseline will be summarized similarly. Frequency and percentage of patients will be provided for each categorical variable by treatment group.

2.8.1 Adverse events (AEs)

The number of patients reporting any adverse event (AE) and the incidence of each AE will be summarized by treatment group. Incidence (frequency and percentages) of all the AEs will be presented by: Preferred Term (PT), System Organ Class (SOC) and PT. The adverse events will also be presented by severity (Mild; Moderate; Severe) and by relationship (Related; Not related) to study treatments.

Adverse events leading to study discontinuation, AEs leading to death and AEs that occurred in at least 5% of the patients will be summarized by treatment group and presented by SOC and PT, as well as by PT alone.

Any AE starting after the first dose of study treatments with a missing severity will be classified as severe. If a subject reports an AE more than once within that SOC/PT, the AE with the worst case severity will be used in the corresponding severity summaries.

Serious adverse events will be summarized by treatment group and presented by SOC and PT, as well as by PT alone. Treatement related SAEs will also be reported by SOC and PT.

All the adverse events (SAEs) will be summarized for the following subgroups: Age categories (<65, ≥65 years) and (< 50, 50 – 64, ≥ 65); Sex (female, male).

Note: All AEs and SAEs will be summarized by study periods and corresponding listings will be provided. Furthermore, listings will be provided for all post-treatment adverse events or serious adverse events. A post-treatment event will be defined as any adverse event that occurs 30 days post treatment, having been absent during treatment, or worsens relative to the treatment state.

2.8.1.1 Adverse events of special interest / grouping of AEs

There are no adverse events of special interest in this study.

2.8.2 Deaths

All on study reported deaths will be summarized by treatment group and a listing will be provided.

2.8.3 Laboratory data

No laboratory evaluations will be performed during this study, except urine pregnancy test for women of childbearing potential therefore, no laboratory data will be summarized.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

Assessment of vital signs will include sitting blood pressure (systolic, diastolic measurement

in mm Hg) and pulse rate (in beats per minute). These parameters will be measured at Screening, Visit 1 (Eligibility 1), Visit 2 (Eligibility 2), Visit 3 (Baseline), Visit 4 (Day 14), and Visit 5 (Day 42) / Exit visit.

For the blood pressure (systolic and diastolic blood pressure), two measurements, separated by two minutes, will be obtained. If either of the systolic or diastolic readings differ by more than 5 mmHg, then a third blood pressure reading should be taken and recorded.

Pulse rate and both mean systolic and mean diastolic blood pressure measurements (sites must calculate the mean values) will be collected at each visit.

Each value will be categorized as low, normal or high using the normal ranges as in the table below. A shift table reporting baseline and post-baseline values at visit will be reported. For each vital sign parameter, counts and percentages of subjects who experience any abnormal findings during the study will be also presented.

Vital Sign Normal Ranges

Age Range	Vital sign Parameters		
	Heart Rate (BPM)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
All	60 to 100	100 to 140	60 to 90
BPM = Beats per minute mmHg = millimeters of mercury			

Vital signs summaries will be reported also by age (<65, ≥ 65 years) and (< 50, $50 - 64$, ≥ 65); Sex (female, male).

A subject listing will be provided which contains data for each abnormal finding for each vital sign parameter. The variables listed will include treatment, investigator number, patient number, age, sex, race, ethnicity, visit number for abnormal finding, the actual value, and normal range (low/high).

2.8.4.3 Automated Perimetry

Automated perimetry assessment will be conducted at Screening, Visit 1 (Eligibility 1) and at and Visit 5 (Day 42) / Exit visit. All visual fields must be reliable at Screening before study drug dispensation at Visit 3 (E2).

The counts and percentages of patients with unreliable visual fields at Week 6 will be presented overall and by subgroups, such as: age (< 65, ≥ 65, and < 50, $50 - 64$, ≥ 65), sex (female, male).

A listing will be provided which presents all patients with unreliable visual fields with the following variables: treatment, investigator, patient, age, sex, race and ethnicity.

2.8.4.4 Best Corrected Visual Acuity (BCVA)

Visual acuity assessment will be conducted at Screening, Visit 1 (Eligibility 1), Visit 2

(Eligibility 2), Visit 3 (Baseline), Visit 4 (Day 14), and Visit 5 (Day 42) / Exit visit.

Observed values and change from baseline values for the study eye will be presented descriptively (N, mean, median, standard deviation, standard error, minimum, and maximum) at each study visit for each treatment. A plot of mean change in BCVA by study visit and by treatment with error bars representing +/- 1 standard error will be presented using the study eye. The x-axis will be study visit and the y-axis will be the change in BCVA from baseline.

Counts and percentages of subjects who experience pre-specified category of worst change from baseline across all post-baseline assessments and category of change from baseline to last on-treatment BCVA assessment will be presented according to the following categories: ≤4 letter decrease or improvement, 5-9 letter decrease, 10-14 letter decrease, ≥15 letter decrease.

For change to any visit, a patient will be counted only in the category that represents their worst change from baseline across all post-baseline assessments. A listing will be provided which presents all subjects with a ≥10 letter decrease in BCVA from baseline to any visit. The listing will include the following variables: treatment, investigator, subject, age, sex, race, ethnicity, visit, baseline value, value at the visit and a change from baseline value. All summaries will also be reported by age (<65, ≥65 years) and (< 50, 50 − 64, ≥ 65); sex (female, male).

2.9   Pharmacokinetic endpoints

Not applicable.

2.10   PD and PK/PD analyses

Not applicable.

2.11   Patient-reported outcomes

Not applicable.

2.12   Biomarkers

Not applicable.

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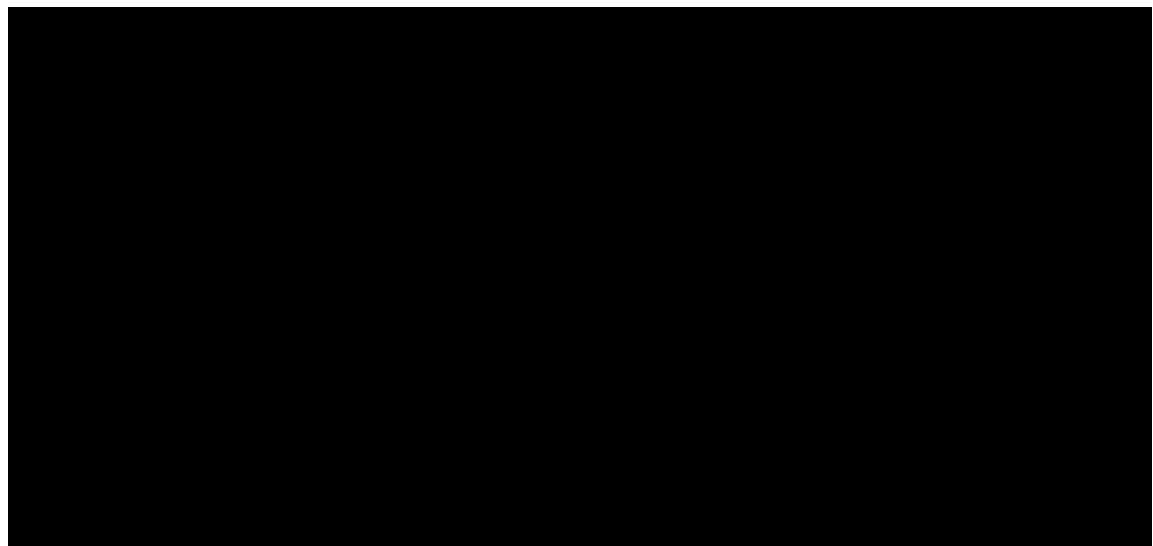
2.14   Interim analysis

No formal interim analysis is planned for this study.

3   Sample size calculation

With 90 evaluable patients per treatment group in the primary efficacy analysis, there is approximately 80% power to detect a difference in mean change from baseline in diurnal IOP at Week 6 of 1.5 mmHg between the treatment groups. This calculation is based on the assumption of a common standard deviation for mean IOP of 3.5 mmHg and the use of a two-sample two-sided t-test performed at the $\alpha = 0.05$ level of significance.

Assuming a drop-out rate of 10%, approximately 100 patients per treatment group will be randomized to ensure the required number of evaluable patients in the final efficacy analysis.

4   Change to protocol specified analyses

The analyses stated above are consistent with the study protocol.

5   Appendix

5.1   Imputation rules

5.1.1   Study drug

In order to impute the missing/partial start or end dates of the study drug, we will first set two reference dates: the date of randomization and the end of study visit date. Using these dates, the algorithm will be applied as follows:

- When the whole study drug start date is missing, the imputed date is the randomization date.
- When the study drug start day and month are missing, the imputed day and month are the randomization day and month.
- When the study drug start month is missing, the imputed month is the randomization month.
- When the study drug start day is missing, the imputed day is the randomization day.
- When the whole study drug end date is missing, the imputed the date is the end of study visit date.
- When the study drug end day and month are missing, the imputed day and month are the end of study visit day and month.
- When the study drug end month is missing, the imputed month is the end of study visit month.
- When the study drug end day is missing, the imputed day is the end of study visit day.

5.1.2   AE date imputation

Adverse event end date imputation

When the end date of an adverse event is partial or missing the following algorithm will be applied

- If the AE end date year is missing or AE is ongoing, the end date will not be imputed
- If the AE end date month is missing, the imputed end date should be set to the earliest of 31DECYYY or date of death
- If the AE end date day is missing, the imputed end date should be set to the earliest of the last day of the month or the date of death
- If the imputed AE end date is less than the existing AE start date then use AE start date as AE

Adverse event start date imputation

When the start date of an adverse event is partial or missing the following algorithm will be applied:

Before imputing AE start date, find the AE start reference date.

- If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
- Else AE start reference date = treatment start date

Impute AE start date -

- If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
- If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
  - If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
  - Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
- If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
  - If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
  - Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
- If the AE start date year value is equal to the treatment start date year value
  - And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
  - Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
  - Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
- If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3   Concomitant medication date imputation

Concomitant medication (CM) end date imputation

- If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.

- Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).

- If the CM end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).

- If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.

When the start date of a concomitant medication is partial or missing the following algorithm will be applied:

- If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.

- If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
  - If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
  - Else if the CM month is not missing, the imputed CM start date is set to the midmonth point (15MONYYYY).
- If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
  - If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
  - Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
- If the CM start date year value is equal to the treatment start date year value:
  - And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior to treatment start date.
  - Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
  - Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).
- If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.2   AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology . Details regarding MedDRA version will be included in the footnote in the tables/listings.

5.3   Laboratory parameters derivations

Not applicable.

5.4   Statistical models

5.4.1   Primary analysis

The methodology is described in Section 2.5

A mixed model repeated measures (MMRM) model

The MMRM model (implemented via SAS procedure MIXED) is used for the analysis of change from baseline, in which treatment, visit, and treatment-by-visit interaction will be included as fixed-effect factors and baseline sub-scale score as a covariate, with a common unstructured covariance matrix (UN). The least squares mean and associated standard error for each treatment at each time point will be presented by using LSMEANS statement. Other

covariance structures such as variance components (VC), compound symmetry (CS), autoregressive [AR(1)], and Toeplitz (Toep) will be considered.

Moreover, least squares means, associated two-sided 95% confidence interval and two-sided p-value of treatment difference at each time point will be presented as well by using ESTIMATE statement.

The SAS syntax is specified as follows:

```
PROC MIXED DATA  = <input_dataset> ORDER = data;
  CLASS <treat_var> <time_point>;
  MODEL <change> = <treat_var> <time_point> <base_var>
                   <treat_var>*<time_point>/DDFM =kr SOLUTION;
  REPEATED <time_point>/SUB=<patient>(<treat_var>) TYPE=un;
  LSMEANS <treat_var> <treat_var>*<time_point>/OM;
  ESTIMATE 'Week 2'  <treat_var> 1 -1
                   <treat_var>*<time_point>   1  0
                                             -1  0  /cl;
  ESTIMATE 'Week 6'  <treat_var> 1 -1
                   <treat_var>*<time_point>   0  1
                                              0 -1   /cl;
RUN;
```

where change   = change from baseline
       treat_var   = treatment group
       base_var   = baseline sub-scale score
       time_point   = scheduled post-baseline visits (Week 2,6)

patient   = patient's ID

5.5   Rule of exclusion criteria of analysis sets

Table 1   Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01	Written informed consent not obtained prior to study assessments	Excluded from PP analysis
INCL03	Ability to simultaneously wash out the effects of non-study IOP lowering medications according to the following minimum time schedule AND establish a Travatan monotherapy baseline (Phase I, screening/washout period)	Excluded from PP analysis

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL04	Mean IOP measurements in at least 1 eye ≥ 16 and < 22 mmHg at 09:00 while on a Travatan monotherapy at two consecutive visits	Excluded from PP analysis
INCL06	Documented diagnosis of normal tension glaucoma (defined as glaucomatous optic neuropathy in the presence of normal IOP < 22 mmHg). Documented optic disk changes, visual field deterioration or optical coherence tomography (OCT) changes can serve as objective markers of damage	Excluded from PP analysis
EXCL01	Use of other investigational drugs within 5 half-lives of screening, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer	Excluded from PP analysis
EXCL03	Patients taking medications prohibited by the protocol	Excluded from PP analysis
EXCL05	Pregnant or nursing (lactating) women	Excluded from PP analysis
EXCL07	Patients with any form of glaucoma other than open angle glaucoma in either eye.	Excluded from PP analysis
EXCL08	Patients with a central cornea thickness < 500 μm and > 600 μm as measured by pachymetry in either eye.	Excluded from PP analysis
EXCL09	Patients with Schaffer angle Grade < 2 in either eye, as measured by gonioscopy.	Excluded from PP analysis
EXCL12	Chronic, recurrent or severe inflammatory eye disease in either eye.	Excluded from PP analysis
EXCL13	Ocular trauma or surgery within the past 6 months in either eye; ocular infection or laser surgery within the past 3 months in either eye	Excluded from PP analysis
EXCL14	Clinically significant or progressive retinal disease such as retinal	Excluded from PP analysis

Deviation ID	Description of Deviation	Exclusion in Analyses
	degeneration, diabetic retinopathy, or retinal detachment in either eye	
EXCL17	Current or anticipated treatment with any psychotropic drugs that augment an adrenergic response	Excluded from PP analysis
EXCL18	Concurrent use of a monoamine oxidase inhibitor	Excluded from PP analysis
COMD01	Use of prohibited medication during the study	Excluded from PP analysis
TRT01	OL Travatan treatment deviation (>3 consecutive doses missed)	Excluded from PP analysis
TRT01	Masked treatment deviation (>3 consecutive doses missed)	Excluded from PP analysis

Table 2   Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
ENR	NA	Not having informed consent; Not having passed the screening phase (screening failure)
RAN	NA	Not randomized
FAS	NA	Not in RAN; Mistakenly randomized and no double-blind study drug taken
PPS	INCL01, INCL03, INCL04, INCL06, EXCL01, EXCL03, EXCL05, EXCL07, EXCL08, EXCL09, EXCL12, EXCL13, EXCL14, EXCL17, EXCL18, EXCL19, COMD01 TRT01	Not in FAS; Discontinued the study early
SAF	NA	No double-blind study drug taken

6   Reference

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3.   Greenland S, Lanes S and Jara M (2008). Estimating effects from randomized trials with discontinuations: the need for intent-to-treat design and G-estimation. Clinical Trials, 5, 5–13.

4.   Lan KKG, DeMets DL (1983). Discrete sequential boundaries for clinical trials. Biometrika, 70, 649-53.

5.   Smith B, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT and Forgue ST (2000). Confidence Interval Criteria for Assessment of Dose Proportionality. Pharmaceutical Research, 17(10), 1278-83.