NOVARTIS

Clinical Development

QVJ499

CQVJ499A2404 / NCT03150160

A 6-week, Double Masked, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Twice-daily Brinzolamide 1% / Brimonidine 0.2% Fixed Dose Combination as an Adjunctive Therapy to Travoprost 0.004% in Reducing Intraocular Pressure in Patients With Normal Tension Glaucoma

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1 Study information

Study title: A 6-week, Double Masked, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Twice-daily Brinzolamide 1% / Brimonidine 0.2% Fixed Dose Combination as an Adjunctive Therapy to Travoprost 0.004% in Reducing Intraocular Pressure in Patients With Normal Tension Glaucoma

Test drug/investigational product: Brinzolamide 1%/Brimonidine 0.2% / QVJ499

Indication studied: Normal tension glaucoma

Study design: See study title

Sponsor: Novartis

Protocol identification: Protocol no. CQVJ499A2404

Development phase of study: IV

Study initiation date: 21-Sep-2017 (first patient first visit)

Early termination date: 09-Nov-2017

Study completion date: 04-Dec-2017 (last patient last visit)

Principal Investigator: Professor [redacted]

Company/Sponsor signatory: [redacted], M.Sc, Novartis Pharmaceuticals Corporation, [redacted]

Statement: This study was conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Report date(s): 09-Apr-2018 (content final)

Earlier reports from the same study: None

2 Synopsis

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4 List of abbreviations and definition of terms

AE	Adverse Event
BCVA	Best Corrected Visual Acuity
BID	bis in die (twice a day)
CFB	Change from baseline
CRF	Case Report Form (paper or electronic)
DSM	Drug Supply Management
EDC	Electronic Data Capture
ETDRS	Early Treated of Diabetic Retinopathy Study
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
OAG	Open Angle Glaucoma
PGA	Prostaglandin Analogue
PPS	Per Protocol analysis set
QD	quaque die (once a day)
RDC	Remote Data Capture
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
WHO	World Health Organization

5 Ethics

5.1 Independent ethics committee or institutional review board

The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each center, as listed in Appendix 16.1.3.

5.2 Ethical conduct of the study

The study was conducted according to the ethical principles of the Declaration of Helsinki.

5.3 Patient information and consent

Informed consent was obtained from each patient in writing at the screening visit. The study was described by the Investigator or designee, who answered any questions, and written information was also provided.

Samples of the written information given to each patient and the consent form are presented in Appendix 16.1.3.

6 Investigators and study administrative structure

The administrative structure of the study, including internal and external participants, is described in Appendix 16.1.4-Section 1.

A list of Investigators, their affiliations and their qualifications, plus that of other important staff is provided in Appendix 16.1.4-Section 2.

Novartis staff analyzed this study and authored this report. The signatures of the Principal or Coordinating Investigator, the Sponsor's Responsible Medical Officer, and the report authors are provided in Appendix 16.1.5.

7 Introduction

7.1 Background

Glaucoma is a group of progressive optic neuropathies, caused by the degeneration and death of retinal ganglion cells and the axons that form the optic nerve, which may lead to visual field deterioration if left untreated (Weinreb and Khaw 2004).

Prostaglandin analogues (PGAs) are often preferred as initial monotherapy because of their intraocular pressure (IOP)–lowering efficacy, low frequency of systemic side effects, and lower frequency of instillation compared with older therapies such as beta-blockers (Nasser and Stewart 2006, Stewart et al 2005, Stewart et al 2008). One of the commonly used topical IOP lowering PGAs used to treat elevated IOP is travoprost. Travoprost 0.004% solution is marketed by Novartis under trade names Travatan® and Travatan Z®.

Despite the efficacy of the PGAs, a significant proportion of patients require more than one medication to reach target IOPs. Clinicians must often add medications or switch to more powerful fixed dose combination drops in order to reach target pressures and manage the disease, after initiation of a prostaglandin analogue (PGA).

The fixed dose combination of brinzolamide 1% and brimonidine 0.2% is marketed under the trade name Simbrinza®. In two pivotal studies, Simbrinza, dosed twice daily (BID), has been shown to lower IOP ~ 27-38% from untreated baselines (Aung et al 2014, Gandolfi et al 2014). The mechanisms by which brinzolamide 1% and brimonidine 0.2% lowers IOP differs from PGAs and thus Simbrinza may be a suitable adjunctive therapy for patients on a PGA that require further IOP lowering. Hence, the combination of PGA + Simbrinza should be evaluated to understand the IOP lowering effect further.

7.2 Purpose

The purpose of this study was to determine the incremental IOP lowering that is achieved when Simbrinza, BID, is used adjunctively to Travatan in patients with normal tension glaucoma that may benefit from further IOP lowering. Data from this study was intended for publications and to provide health care practitioners with important treatment guidance on the use of Simbrinza in this clinical setting.

The study was prematurely terminated on 09-Nov-2017 due to administrative reasons, and not based on any safety or efficacy concerns (see further details in Section 9.4.9). All participating sites were promptly notified to stop enrollment and to discontinue ongoing patients.

8 Study objectives

8.1 Primary objective and related endpoint

Primary Objective	Endpoint for primary objective
To demonstrate that Simbrinza is superior to placebo in lowering diurnal IOP when added to baseline Travatan therapy	Change from baseline (on Travatan) in diurnal IOP in the study eye at Week 6

8.2 Secondary objectives and related endpoint

Secondary Objectives	Endpoints for secondary objectives
To evaluate the differences between Simbrinza and placebo in diurnal IOP percentage change from a Travatan baseline therapy	Percentage IOP change from baseline (on Travatan) in diurnal IOP at Week 6
To evaluate the differences between Simbrinza and placebo in diurnal IOP, from a Travatan baseline therapy	Diurnal IOP at Week 6
To evaluate the differences between Simbrinza and placebo in IOP change at each time point, from a Travatan baseline therapy	Change from baseline in IOP for each time point at Week 6
To evaluate the differences between Simbrinza and placebo in IOP percentage change at each time point, from a Travatan baseline therapy	Percentage change from baseline in IOP for each time point at Week 6

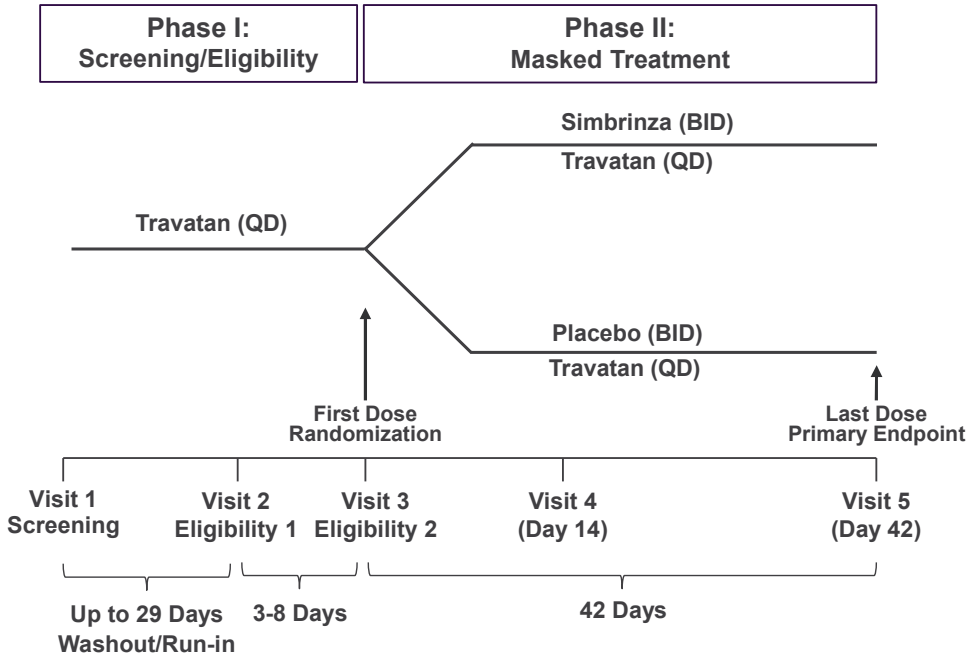
8.3 Exploratory objectives and related endpoints

Refer to Appendix 16.1.1-Protocol-Section 2.1 for exploratory objectives and related endpoints.

9 Investigational plan

9.1 Study design

Figure 9-1 Study design



BID: twice a day, QD: once a day.

This was a multicenter, randomized, double-masked, two-arm, placebo-controlled, parallel-group study in patients with normal tension glaucoma who were insufficiently controlled on travoprost 0.004% (Travatan) monotherapy. Approximately 200 patients were planned to be randomized and treated for up to 11 weeks, whilst they were to receive double-masked study medication for 6 weeks.

The study was divided into 2 sequential phases for a total of 5 visits:

- Phase I: a Screening/Eligibility phase
- Phase II: the Masked Treatment Phase

For full details of study design refer to Appendix 16.1.1-Protocol-Section 3.1

9.2 Discussion of study design, including the choice of control groups

Normal tension glaucoma patients are a difficult to manage sub-group of open angle glaucoma (OAG) patients that have lower baseline pressures than OAG patients with elevated IOP. This study was designed to investigate the incremental IOP lowering that is achieved when

Simbrinza is added to Travatan (a PGA) which is often used as initial therapy to lower IOP. Understanding the magnitude of further IOP lowering that could be achieved by the addition of Simbrinza to Travatan in a low baseline setting, could only be achieved with a placebo comparator and could provide essential data to health care practitioners.

The study was designed to minimize the study length and assessments, while ensuring scientific validity: the two eligibility visits were to minimize regression to the mean and increase the likelihood of stable IOP entry data; the Day 14 visit allowed patient safety to be monitored during the masked treatment phase; the primary assessments were at 42 days to minimize patient time in the trial. IOP assessments at 09:00 and 11:00 allowed collection of a trough IOP (12 hours post dose) and a peak IOP (2 hours post dose), respectively.

Selection bias was reduced by randomization and ascertainment bias by masking of the patient and the Investigator / study staff who made the study assessments.

The placebo control allowed for assessment of the additive effects of Simbrinza, adjunctive to Travatan, with a minimization of bias through masking the patients and the study personnel who conducted the assessments.

9.3 Population

The study population consisted of adult and elderly patients 18 years of age or older, with previously documented normal tension glaucoma (IOP < 22 mmHg and glaucomatous damage) and had inadequately controlled IOP while on a Travatan monotherapy (IOP ≥ 16 and < 22 mmHg in the study eye).

9.3.1 Inclusion criteria

Key inclusion criteria

- Mean IOP measurements in at least 1 eye ≥ 16 and < 22 mmHg at 09:00 while on a Travatan monotherapy at two consecutive visits (same eye at Visits 2 & 3 to be eligible for the study).
- Mean IOP must be < 25 mmHg in the other eye at any time point up to randomization.

Inclusion criteria are described in details in Appendix 16.1.1-Protocol-Section 4.1

9.3.2 Exclusion criteria

Key exclusion criteria

- Patients with a central cornea thickness < 500 µm and > 600 µm as measured by pachymetry in either eye.
- Patients with Schaffer angle Grade < 2 in either eye, as measured by gonioscopy (extreme narrow angle with complete or partial closure).
- Patients with a cup/disc ratio greater than 0.80 in either eye.
- Patients with severe central visual field loss in either eye or field loss threatening fixation in either eye. Severe central visual field loss is defined as a sensitivity of less than or equal to 10 dB in at least 2 of the 4 visual field test points closest to the point of fixation.
- Chronic, recurrent or severe inflammatory eye disease in either eye (from screening).

- Clinically significant or progressive retinal disease such as retinal degeneration, diabetic retinopathy, or retinal detachment in either eye.

Exclusion criteria are described in details in Appendix 16.1.1-Protocol-Section 4.2

9.4 Treatment

9.4.1 Investigational and control treatment

Simbrinza (brinzolamide 1%/brimonidine 0.2%) eye-drops suspension was supplied in opaque DROP-TAINER® bottle with a masked label indicating that the product is for investigational use only. Placebo eye-drops solution (identical to Simbrinza but did not have active ingredients) was supplied in opaque DROP-TAINER® bottle with a masked label indicating that the product is for investigational use only. Travatan (travoprost 0.004%) eye-drops solution was supplied in a DROP-TAINER® bottle and was unmasked (open label) product.

All test materials were supplied by Novartis Drug Supply Management (DSM). The batch and formulation numbers of Simbrinza, Travatan and placebo are provided in Table 9-1.

A listing of patients receiving each batch of test material is provided in Appendix 16.1.6.

Table 9-1 Study medication formulation and batch numbers

Study drug and strength	Formulation control number	Batch number
Simbrinza (brinzolamide 1%/brimonidine 0.2%)	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Travatan (travoprost 0.004%)	[redacted]	[redacted]

9.4.2 Treatment arms

Patients were assigned at Visit 3 (Eligibility 2) to one of the following two treatment arms in a ratio of 1:1:

- **Arm 1:** Simbrinza (eye drops dosed in the morning and in the evening) + Travatan (eye drops dosed in the evening)
- **Arm 2:** Placebo (eye drops dosed in the morning and in the evening) + Travatan (eye drops dosed in the evening)

9.4.3 Treatment assignment

Refer to Appendix 16.1.1-Protocol-Section 5.3 for details of randomization procedures.

The randomization scheme for patients was reviewed and approved by a member of the Novartis Randomization Office. The randomization list is provided in Appendix 16.1.7.

9.4.4 Treatment masking

Patients, investigator staff, persons performing the assessments, and data analysts remained masked to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data were kept strictly confidential until the time of unmasking, and were not accessible by anyone else involved in the study. (2) The identity of

the treatments was concealed by the use of masked study drugs that were identical in packaging, labeling, and schedule of administration.

Unmasking was only permitted in the case of patient emergencies (see Appendix 16.1.1-Protocol-Section 5.5.9) and at the conclusion of the study.

Refer to Appendix 16.1.1-Protocol-Section 5.4 for further details on treatment masking.

9.4.5 Treating the patient

9.4.5.1 Patient numbering

Each patient was uniquely identified in the study by a combination of his/her center number and a 5-digit Patient Number. Refer to Appendix 16.1.1-Protocol-Section 5.5.1 for full details on patient numbering.

9.4.5.2 Dispensing the study treatment

Each study site was supplied with masked study drug (Simbrinza or placebo) in packaging of identical appearance labeled with the protocol and kit numbers. Travatan was provided open label containing the protocol and unique kit number.

The masked study drug and Travatan were dispensed as described in Appendix 16.1.1-Protocol-Section 5.5.2.

9.4.5.3 Supply, storage and tracking of study treatment

For details on handling of study treatment, refer to Appendix 16.1.1-Protocol-Section 5.5.3.1.

9.4.5.4 Instructions for prescribing and taking study treatment

General instructions:

- Patients wearing contact lenses had to remove the lenses before instillation of either medication. Following instillation of the study medications, the patient had to wait approximately 15 minutes after the last dose before re-inserting lenses.
- Patients had to shake masked study medication before use.
- Patients were not allowed to discard any unused or empty bottles and bring all Travatan and masked study medication bottles to the study visit.

Appendix 16.1.1-Protocol-Section 5.5.4 describes the detailed instructions for Travatan administration during screening/eligibility phase, and Travatan and masked study medication administration during masked treatment phase.

All kits of investigational treatment assigned by the Interactive Response Technology (IRT) were recorded in the IRT system.

The investigator promoted compliance by instructing the patient to apply the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient was instructed to contact the investigator if he/she was unable for any reason to apply the study drug as prescribed.

9.4.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions were not permitted.

9.4.5.6 Rescue medication

Rescue medication was not permitted in this study. If an Investigator felt a patient was not adequately controlled on study medications, they were discontinued from receiving the study treatment and were managed accordingly to usual care.

9.4.6 Concomitant treatment

The Investigator instructed the patient to notify the study site about any new medications he/she took after the start of the study drug.

All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study were required to be recorded on the Concomitant medications/Significant non-drug therapies after start of study drug Case Report Form (CRF). All anti-IOP medications administered at the time of the Screening Visit were recorded on the Ocular Anti-Hypertensive Medications CRF.

Use of the treatments displayed in Appendix 16.1.1-Protocol-Section 5.5.8-Table 5-1 were not allowed after screening.

9.4.7 Discontinuation of study treatment and premature patient withdrawal

Patients could voluntarily withdraw from the study for any reason at any time. A patient could be considered withdrawn if he or she stated an intention to withdraw, failed to return for visits, or became lost to follow-up for any other reason.

The Investigator was obliged to discontinue study drug for a given patient or withdraw the patient from the study if, on balance, he/she believed that continuation would be detrimental to the patient's well-being.

Refer to Appendix 16.1.1-Protocol-Section 5.6.2 for details on discontinuation of study treatment, Appendix 16.1.1-Protocol-Section 5.6.3 for details on withdrawal of informed consent and Appendix 16.1.1-Protocol-Section 5.6.4 for details on patients lost to follow-up.

9.4.8 Emergency unmasking of treatment assignment

Refer to Appendix 16.1.1-Protocol-Section 5.5.9 for emergency code breaking details.

9.4.9 Early study termination

According to Appendix 16.1.1-Protocol-Section 5.6.5, the study could be terminated by Novartis at any time for any reason. This could include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). If this was necessary, the patient was to be seen as soon as possible and treated as a prematurely withdrawn patient. The Investigator could be informed of additional procedures to be followed in order to ensure that adequate consideration was given to the protection of the patient's interests. The Investigator was responsible for informing the

Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the study.

This study was terminated early due to administrative reasons, and not based on any safety or efficacy concerns. Investigators were instructed to bring the ongoing patients for an Exit Visit as soon as possible. Study medications were stopped at the time of the Exit Visits. The Investigators informed the IECs of the early termination of the trial.

9.4.10 Treatment exposure and compliance

All Travatan and masked study treatment dispensed and returned were recorded in the Drug Accountability Log.

Refer to Appendix 16.1.1-Protocol-Section 6.3 for further details.

9.5 Efficacy and safety assessments

9.5.1 Visit schedule

The study visits and procedures are presented in Appendix 16.1.1-Protocol Section 6-Table 6-1 which lists all of the assessments and indicates with an "X" the visits at which they were performed.

All activities performed during eligibility visits E1 (Visit 2) and E2 (Visit 3) are listed in Appendix 16.1.1-Protocol Section 6-Table 6-2.

All activities performed during week 2 (Visit 4) and week 6 (Visit 5, exit) are listed in Appendix 16.1.1-Protocol Section 6-Table 6-3.

Refer to Appendix 16.1.1-Protocol-Section 6 for additional details of visit schedule and assessment.

9.5.2 Efficacy assessments

9.5.2.1 Assessment of efficacy

Intraocular pressure (IOP) measurement

All IOP measurements were to be performed in both eyes at each visit with a Goldmann applanation tonometer as described in Appendix 16.1.1-Protocol-Section 6.4.1.

Two consecutive IOP measurements were taken for each eye. The applanation probe was withdrawn from the eye between the two measurements.

Time of first IOP measurement was recorded in the source document and in Electronic Data Capture (EDC). The same procedure was repeated on the contralateral eye.

9.5.2.2 Appropriateness of efficacy assessments

Assessments described in the protocol are standard ophthalmic assessments for this indication and patient population.

9.5.3 Safety assessments

9.5.3.1 Assessment of safety

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug. Safety evaluation included vital signs (blood pressure and pulse rate), ophthalmic examinations (automated perimetry, slit-lamp exam, dilated fundus examination, and best corrected visual acuity) and pregnancy test (for women of childbearing potential).

Full information about the definition of AEs and SAEs, the procedures for reporting them is given in the Appendix 16.1.1-Protocol-Section 7.

Refer to Appendix 16.1.1-Protocol-Section 6.5 for details of all safety assessments.

9.5.3.2 Appropriateness of safety assessments

The safety assessments selected are standard for this indication/patient population.

9.5.4 Other assessments

Gonioscopy and Pachymetry were not part of safety assessments, and were only performed at Screening Visit. Refer to Appendix 16.1.1-Protocol-Section 6.6 for details of these assessments.

9.6 Data quality assurance

9.6.1 Monitoring

The responsibility for site monitoring resided with the Novartis field monitors. Details of the monitoring procedures are described in Appendix 16.1.1-Protocol-Section 8.1

9.6.2 Data collection

Designated Investigator staff entered the data required by the protocol into iMedidata Remote Data Capture (RDC) system. They were not given access to the system until adequately trained. Documented training on RDC system was completed by the designated Investigator site staff before their access was granted.

9.6.3 Database management and quality control

Novartis staff reviewed the data entered into the CRFs by investigational staff for completeness and accuracy and instructed the site personnel to make any required corrections or additions. Queries were sent to the investigational site using an electronic data query. Designated Investigator site staff were required to respond to each query and confirm or correct the data.

Concomitant medications entered into the database were coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 terminology.

Randomization codes and data about all study treatment dispensed to the patient and all IRT recorded dosage changes were tracked using an IRT.

9.6.4 Quality assurance and auditing

There were no audits or Health Authority inspections conducted at sites participating in this study.

9.7 Statistical methods

This section describes the statistical analyses that were planned as per the protocol and statistical analysis plan (SAP). See Section 9.8.3 where the changes in planned analyses and the reason for them are detailed.

9.7.1 Data analysis

9.7.2 Analysis sets

The analysis sets defined as per the protocol and SAP were:

All enrolled analysis set included all patients who signed an Informed Consent Form (ICF) and were assigned patient numbers. This analysis set was used to summarize patient disposition and pre-treatment AEs.

All randomized analysis set included all enrolled patients who were randomized to treatment.

Safety analysis set: included all patients exposed to at least one dose of any study therapy. Patients in the safety analysis set were analyzed according to the treatment received.

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

Per protocol analysis set (PPS) a subset of all patients in the FAS and excluded all data which met any of the critical deviation criteria identified in the SAP. In addition, individual patient visits and data points that did not satisfy protocol criteria could be excluded from the PPS.

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

9.7.3 Patient disposition, demographics and other baseline characteristics

All patients who signed informed consent were accounted in patient disposition.

Patient disposition table were to present the number and percentage of patients for the following:

- Screened/Run in
- Screen/ Run in Failure
- Entered the double-masked phase
- Completed the double-masked phase
- Discontinued the double-masked phase
- Reason for discontinuation

Details of the planned data analysis for patient demographics and other baseline characteristics are presented in Appendix 16.1.1-Protocol-Section 9.2.

9.7.4 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration and concomitant therapies were to be listed by treatment group and patient. Extent of exposure, as a continuous variable and categorically, was to be analyzed with summary statistics, using the Safety Analysis Set.

9.7.5 Analysis of the primary variable

9.7.5.1 Variable

The primary efficacy endpoint in this study was 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 was the FAS.

9.7.5.2 Statistical hypothesis, model, and method of analysis

Refer to Appendix 16.1.1-Protocol Section 9.4.2.

9.7.5.3 Supportive analyses

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

9.7.6 Analysis of secondary efficacy variables

9.7.6.1 Efficacy

Analyses of treatment differences of secondary endpoints was planned to use the same methods as those for the primary endpoint. Hypothesis tests were to use the same null and alternative hypotheses as in Appendix 16.1.1-Protocol Section 9.4.2, with μ representing the mean for the variable being tested.

See Appendix 16.1.1-Protocol-Section 9.5.1 for details of the planned statistical analysis of secondary efficacy endpoints.

9.7.7 Safety analyses

The planned safety analyses consisted 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.

Frequency and percentage of patients were to be provided for each categorical variable by treatment group.

9.7.8 Handling of missing values/censoring/discontinuations

Missing observations were not to be imputed. The statistical models that were employed and the associated analyses were robust under the missing completely at random and the missing at random assumptions.

9.7.9 Sample size calculation

With 90 evaluable patients per treatment group in the primary efficacy analysis, there was 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 was 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 were to be randomized to ensure the required number of evaluable patients in the final efficacy analysis.

9.7.10 Power for analysis of key secondary variables

Not applicable

9.7.11 Interim analysis

No formal interim analysis was planned for this study.

9.8 Changes in the conduct of the study or planned analyses

9.8.1 Protocol amendments

The study protocol was amended once. The original protocol and amendment are provided in Appendix 16.1.1. Previous sections of this report describe the study conduct as amended. The key features of Amendment 1 (12-Apr-2017) are given below:

Amendment 1 introduced the following changes:

- Section 4.2 Exclusion criteria: to clarify that it is not clinically relevant to measure both horizontal and vertical cup/disc ratio to exclude patients (exclusion criteria)
- Section 9.5.2 Safety variables: Data for fundus parameters and slit-lamp exam will no longer be collected
- Other editorial changes

9.8.2 Other changes in study conduct

See Section 9.4.9.

9.8.3 Changes in planned analysis

At the time of the premature termination of this study, only one patient was randomized. Therefore, the planned efficacy and safety analyses could not be performed.

The patient data reports generated from the clinical database reporting efficacy measure and key safety data are the only results presented in this report.

10 Study patients

10.1 Disposition of patients

At the time of the premature termination of this study, four patients at three participating centers in Republic of Korea had signed the Informed Consent Form. Of these four patients:

- One patient ([redacted]) did not complete the screening visit and did not receive any study medication. (Appendix 16.3)
- Two patients ([redacted]) completed screening and were in the run-in phase, taking open-label Travatan run-in medication. (Appendix 16.3)
- One patient ([redacted]) was randomized, taking open-label Travatan medication plus masked Placebo. (Appendix 16.3)

10.2 Protocol deviations

No protocol deviations were reported (Appendix 16.3).

11 Efficacy evaluation

11.1 Data sets analyzed

Not applicable.

[redacted]

[redacted]

11.3 Measurements of treatment compliance

Not applicable.

11.4 Efficacy results and tabulations of individual patient data

11.4.1 Analysis of efficacy

The IOP measurements at each visit for the one patient who was randomized to placebo ([redacted]) are provided in Table 11-2 below.

Table 11-2 IOP measurements at each visit for patient [redacted]

Eye	Visit 2 IOP (mmHg)		Visit 3 IOP (mmHg)		Visit 4 IOP (mmHg)		Exit Visit IOP (mmHg)
	09:00	11:00	09:00	11:00	09:00	11:00	
Right	FR: 20	FR: 19	FR: 19	FR: 16	FR: 16	FR: 16	FR: 18
	SR: 19	SR: 19	SR: 19	SR: 16	SR: 14	SR: 15	SR: 19
Left	FR: 16	FR: 20	FR: 18	FR: 16	FR: 15	FR: 15	FR: 17
	SR: 17	SR: 20	SR: 19	SR: 16	SR: 14	SR: 15	SR: 18

FR: First Reading; SR: Second Reading.

Source: Appendix 16.3

11.4.1.1 Primary efficacy results

Not applicable.

11.4.1.2 Secondary efficacy results

Not applicable.

11.4.1.3 Exploratory efficacy results

Not applicable.

11.4.2 Statistical and analytical issues

Not applicable.

11.4.3 Tabulation of individual response data

Not applicable

11.4.4 Drug dose, drug concentration and relationships to response

Not applicable

11.4.5 Drug-drug and drug-disease interactions

Not applicable

11.4.6 By-patient displays

Individual patient data generated from clinical database for all patients are provided in Appendix 16.3.

11.4.7 Summary of efficacy results

The IOP measurements at each study visit for the one patient who was randomized to placebo, can be found in Table 11-2.

12 Safety evaluation

12.1 Extent of exposure

12.1.1 Dosage

The planned doses in the study were:

Phase I (Run-in period): One drop of Travatan applied topically to the affected eye(s) once daily (evening).

Phase II (Masked Treatment Phase): Eligible patients were assigned to one of the following two treatment arms in a ratio of 1:1

- **Arm 1**: One drop of Simbrinza applied topically to the affected eye(s) in the morning and evening + one drop of Travatan applied topically to the affected eye(s) in the evening.

- **Arm 2**: One drop of Placebo applied topically to the affected eye(s) in the morning and evening + one drop of Travatan applied topically to the affected eye(s) in the evening.

12.1.2 Patient exposure

- Patient [redacted] did not receive any study medication (Appendix 16.3).
- Patient [redacted] received open label Travatan from [redacted] to [redacted] (Appendix 16.3).
- Patient [redacted] received open label Travatan from [redacted] to [redacted] (Appendix 16.3).
- Patient [redacted] received open label Travatan from [redacted] to [redacted] (the date of last dose of open label Travatan was inadvertently captured as [redacted] on the 'Exposure' page of eCRF; however, the actual date was [redacted]) and masked placebo from [redacted] to [redacted] (Appendix 16.3).

12.1.3 Concomitant medication

Concomitant medications taken by the one patient who was randomized to placebo ([redacted]) included diltiazem HCL 90 mg, losartan potassium 100 mg and apixaban 10 mg for hypertension (Appendix 16.3).

No concomitant medications data were reported for the other patients (Appendix 16.3).

12.2 Adverse events

12.2.1 Display of adverse events

One non-serious AE (common cold) was reported by the one patient who was randomized to placebo ([redacted]) (Appendix 16.3).

12.2.2 Analysis of adverse events

The reported AE of common cold was mild in severity and was not related to the study medication (Appendix 16.3).

12.2.3 Listing of adverse events by patient

No AE listing was generated as there was only one AE reported.

12.3 Deaths, other serious adverse events and other significant adverse events

There were no deaths, serious adverse events and other significant adverse events reported in the study. Therefore no listings were generated, and no narratives were required.

12.4 Clinical laboratory evaluation

No laboratory evaluations (hematology, clinical chemistry and urinalysis) were performed in this study.

12.5 Vital signs, physical findings and other observations related to safety

12.5.1 Vital signs

The vital signs measurements at visit for the one patient who was randomized to placebo ([redacted]) are provided in Table 12-1 below.

Table 12-1 Vital signs measurements at each visit for patient [redacted]

Vital Sign	Visit 2		Visit 3		Visit 4		Early Exit Visit
	09:00	11:00	09:00	11:00	09:00	11:00	
PR	72 bpm	74 bpm	94 bpm	84 bpm	84 bpm	76 bpm	94 bpm
SBP	135 mmHg	132 mmHg	138 mmHg	135 mmHg	132 mmHg	124 mmHg	140 mmHg
DBP	83 mmHg	81 mmHg	82 mmHg	83 mmHg	82 mmHg	79 mmHg	93 mmHg

PR: pulse rate; SBP: systolic blood pressure; DBP: diastolic blood pressure

Source: Appendix 16.3

12.5.2 Electrocardiogram

Not applicable

12.5.3 Best corrected visual acuity (BCVA)

The Early Treated of Diabetic Retinopathy Study (ETDRS) visual acuity score at each visit for the one patient who was randomized to placebo ([redacted]) are provided in Table 12-2 below.

Table 12-2 BCVA measurements at each visit for patient [redacted]

Eye	Visit 2 09:00	Visit 3 09:00	Visit 4 09:00	Early Exit Visit
Right eye	69	74	73	72
Left eye	75	69	72	65

Source: Appendix 16.3

12.5.4 Special safety topics

None.

12.6 Summary of safety results

There were no deaths or SAEs reported during the study.

One non-serious AE (common cold) was reported by the one patient who was randomized to placebo ([redacted]). The AE of common cold was mild in severity and was not related to the study medication.

There were no AEs leading to discontinuation reported during the study.

The vital signs measurements and ETDRS visual acuity scores at each study visit for the one patient who was randomized to placebo ([redacted]), can be found in Table 12-1 and Table 12-2, respectively.

13 Discussion and overall conclusions

This was a phase IV study with the objective of evaluating the efficacy (incremental IOP lowering that could be achieved) and safety of Simbrinza (brinzolamide 1% / brimonidine 0.2% fixed dose combination) BID when used as an adjunctive therapy to Travatan (travoprost 0.004%) in patients with normal tension glaucoma, that may benefit from further IOP lowering. The study was terminated prematurely with only one patient randomized at that time. The reason for premature termination was administrative, and not based on any safety or efficacy concerns.

Conclusions:

Due to the early study termination and limited data, efficacy and overall safety profile of Simbrinza as an adjunctive therapy to Travatan could not be analyzed; therefore, this study could not report any conclusion.