

Short Title:

**Statistical Analysis Plan
GLJ576-P001/ NCT02730871**

Full Title:

**Statistical Analysis Plan
CQVJ499A2402 (GLJ576-P001)**

Protocol Title: Safety and Efficacy with Twice Daily Brinzolamide 1% /
Brimonidine 0.2% (SIMBRINZA) as an Adjunctive Therapy to
Travoprost 0.004% / Timolol 0.5% (DUOTRAV)

Protocol TDOC Number: TDOC-0051572

Author: 
Trial Statistician

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Approvals: See last page for electronic approvals.

Job Notes:

This is the third version (Version 3.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0, of the study protocol TDOC-0051572.

Executive Summary:**Key Objectives:**

The primary objective of this study is to demonstrate the additive IOP lowering effect of Brinzolamide 1%/Brimonidine 0.2% (dosed BID) when added to Travoprost 0.004%/Timolol 0.5% in subjects with either open-angle glaucoma or ocular hypertension who are currently on DUOTRAV (Travoprost/Timolol).

Decision Criteria for Study Success:

A success will be declared if the primary efficacy null hypothesis is rejected in favor of adjunctive therapy (SIMBRINZA plus DUOTRAV) relative to DUOTRAV alone. Success reflects greater mean reduction at Week 6 from baseline in IOP for the adjunctive therapy relative to DUOTRAV alone.

This study incorporates an interim analysis when 50% of the total planned subjects have completed or discontinued from the study. Thus, study success may be declared at the interim analysis or after the total planned subjects have completed or discontinued.

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1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

The primary objective of this study is to demonstrate the additive IOP lowering effect of Brinzolamide 1% / Brimonidine 0.2% (dosed BID) when added to Travoprost 0.004% / Timolol 0.5% solution in subjects with either open-angle glaucoma or ocular hypertension who are currently on DUOTRAV (Travoprost 0.004%/Timolol 0.5%).

1.2 Study Description

The study is a 6 week, multicenter, parallel group study in subjects with primary open-angle glaucoma and/or ocular hypertension and is divided into 2 sequential phases. Phase I of the study is the open-label Screening/Eligibility Phase, which includes a Screening Visit followed by 2 Eligibility Visits (E1 and E2). Phase II of the study is a randomized, double-masked treatment phase which includes on-therapy visits at Week 2 and Week 6 (Exit Visit) as shown in [Table 1-1](#).

Table 1-1 Study Plan by Treatment Groups

Treatment Group	Study Phase	
	Phase I (Screening/Eligibility Phase)	Phase II (Masked Treatment Phase)
	Screening and Eligibility Visits	Week 2 and Week 6 (Exit) Visits
SIMBRINZA + DUOTRAV	Begin dosing with DUOTRAV at 21:00 ±30 min on the evening of the screening visit if the subject dosed with DUOTRAV in the evenings prior to Screening, or begin dosing with DUOTRAV at 9:00 ±30 min the following day after Screening if the subject dosed with DUOTRAV in the mornings prior to Screening. <u>Mean IOP for both Eligibility Visits must be:</u> ≥ 19 mmHg and ≤ 28 mmHg in at least one eye at 09:00 time point <i>The same eye(s) must qualify at both 09:00 time points.</i> <i>The mean IOP in either eye must not be greater than 28 mmHg at any time point.</i>	SIMBRINZA BID (09:00 and 21:00) ±30 min And DUOTRAV QD (09:00 or 21:00) ±30 min
Vehicle + DUOTRAV		Vehicle BID (09:00 and 21:00) ±30 min And DUOTRAV QD (09:00 or 21:00) ±30 min

1.3 Randomization

A member of the Randomization Programming group at Alcon who is not part of the study team will generate the randomized allocation schedule(s) for masked Investigational Product (IP) assignment. Randomization will be central (no stratification for site) and implemented via Interactive Response Technology (IRT) system. Each subject number will be associated with treatment groups according to a random process. Subjects will be randomized in a 1:1 manner to receive treatment with either SIMBRINZA or Vehicle adjunctively to their DUOTRAV therapy.

1.4 Masking

This study is double-masked with subjects randomized to use SIMBRINZA or Vehicle for a duration of approximately 42 days. The Investigator, subject, Sponsor, and monitors involved in reporting, obtaining, and/or reviewing the clinical evaluations will not be aware of the specific masked treatment (SIMBRINZA or Vehicle) being administered. Both SIMBRINZA and Vehicle will be provided in identical masked bottles labeled with the protocol and kit numbers. This level of masking will be maintained throughout the conduct of the study.

However, DUOTRAV therapy is open labeled and will be dosed during the Phase I (Screening Visit through E2) and for the duration of Phase II of the study.

1.5 Interim Analysis

An interim analysis for efficacy is planned when 50% of the total planned subjects have completed or discontinued from the study. The objective of the interim analysis is to provide opportunity for early rejection of the null hypothesis that there is no difference in mean IOP change from baseline between SIMBRINZA and Vehicle adjunctive to DUOTRAV. A detailed description of the planned interim efficacy analysis is in Section 4.6. Study enrollment may be ongoing at the time of interim analysis. Masking to treatment assignment will be maintained at all investigational sites. Subject-level unmasking will be restricted to an internal unmasked statistician and statistical programmer performing the interim analysis.

2 ANALYSIS SETS

The final subject evaluability for all analysis sets will be determined prior to breaking the code for masked treatment assignment and locking the database.

2.1 Efficacy Analysis Sets

The primary analysis set for all primary, secondary [REDACTED] efficacy analyses will be the full analysis set (FAS).

All randomized subjects with a baseline assessment and who complete at least 1 scheduled on-therapy study visit will be evaluated in the full analysis set. Subjects will be analyzed as randomized in the FAS. For example, if a subject is given SIMBRINZA plus DUOTRAV when they were randomly assigned to receive Vehicle plus DUOTRAV, the subject will be analyzed according to the randomization schedule (i.e. Vehicle plus DUOTRAV) regardless of which treatment was actually received (SIMBRINZA plus DUOTRAV).

The Per Protocol Analysis Set (PPS) is a subset of all randomized subjects and excludes all data which have met any of the critical deviation criteria identified in the Deviations and Evaluability Plan (DEP). In addition, individual subject visits and data points with critical deviations may be excluded from the analyses involving the PPS. The Per Protocol Set (PPS) will be evaluated only for the primary efficacy endpoint to confirm results from the FAS.

2.2 Safety Analysis Set

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. The safety analysis set includes all subjects who received a dose of IP during the masked treatment phase.

For treatment-emergent safety analyses, subjects will be categorized under the actual treatment received.

Safety data is to be collected for each subject beginning at the time of informed consent. Adverse events (AEs) that occur prior to exposure to investigational products will be presented separately from the treatment-emergent AEs.

2.3 Pharmacokinetic Analysis Set

Not Applicable.

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

Subject characteristics and study conduct summaries include tables and listings such as subject disposition table, demographic tables (age, sex, race, ethnicity, iris color and region) and baseline characteristics (baseline IOP, baseline IOP category (< 19 mmHg, 19-24 mmHg,

> 24-28 mmHg) and diagnosis, for all analysis sets (efficacy and safety). Listings for treatment assignment, screen failures, subjects who terminated early from the study or discontinued treatment, and subjects excluded from key analysis sets will be generated. 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. Tables will be presented by treatment and overall.

Age will be summarized as a continuous variable as well as categorically (< 65 , ≥ 65 and furthermore as < 50 , $50-64$, ≥ 65). In addition, gender, race, ethnicity, iris color and region will be summarized as categorical variables.

4 EFFICACY ANALYSIS STRATEGY

The efficacy assessment between treatment groups will be analyzed based on the FAS. Significance testing will be at the significance level dependent upon the time of analysis (interim or final) as determined by the Haybittle-Peto boundary.

One eye from each subject will be chosen as the study eye and only the study eye will be used for analysis. If only 1 of a subject's eyes is dosed, the dosed eye will be selected as the study eye. If both eyes are dosed, the worse evaluable eye will be selected as the study eye. Worse eye is defined as the eye with the higher IOP at 9:00 averaged across the 2 eligibility visits. If both eyes are equal 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 then the right eye will be selected for analysis.

For time-specific IOP measurements, baseline corresponds to the average of subject time-matched IOP measurements at E1 and E2 visits on the study visit schedule.

4.1 Efficacy Endpoints

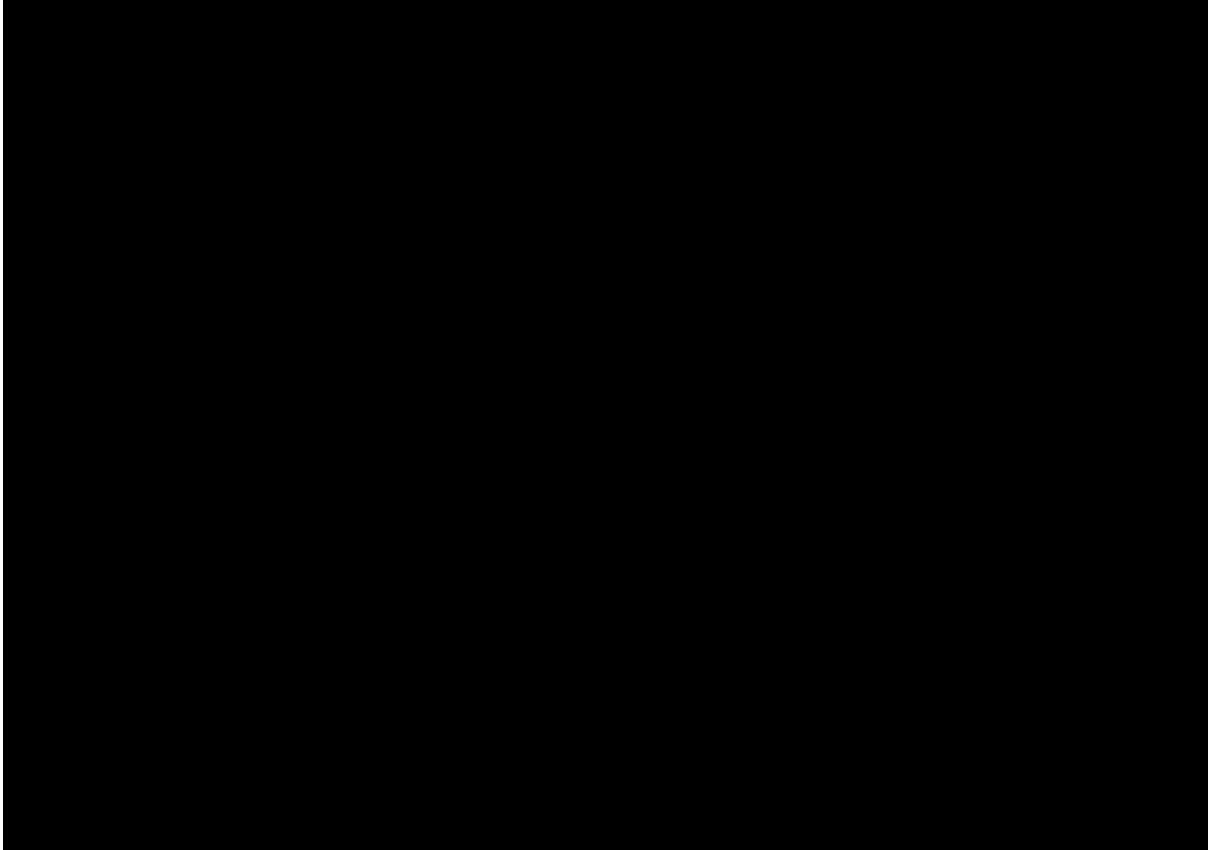
Primary Endpoint

The primary efficacy endpoint will be mean change from baseline in IOP at Week 6 (subject IOP changes from baseline averaged over the 09:00 and 11:00 time points).

Secondary Endpoints

- Mean IOP at Week 6
- Mean Percentage change from baseline in IOP at Week 6
- Mean IOP change from baseline at Week 6 at 11:00.

- Mean Percentage change from baseline in IOP at Week 6 at 11:00
- Mean IOP change from baseline at Week 6 at 9:00
- Mean Percentage change from baseline in IOP at Week 6 at 9:00



4.2 Efficacy Hypotheses

The null and alternative hypotheses for the primary analysis are:

$$H_0: \mu_{\text{SIMBRINZA+DUOTRAV}} = \mu_{\text{Vehicle+DUOTRAV}}$$

$$H_1: \mu_{\text{SIMBRINZA+DUOTRAV}} \neq \mu_{\text{Vehicle+DUOTRAV}}$$

where $\mu_{\text{SIMBRINZA+DUOTRAV}}$ refers to mean IOP change from baseline for subjects randomized to receive SIMBRINZA plus Travoprost 0.004% / Timolol 0.5%, and $\mu_{\text{Vehicle+DUOTRAV}}$ refers to mean IOP change from baseline for subjects randomized to receive Vehicle plus Travoprost 0.004% / Timolol 0.5%.

Thus, success will be evidenced by a greater reduction in mean IOP change from baseline at Week 6 for the adjunctive therapy (SIMBRINZA plus DUOTRAV) relative to Vehicle plus DUOTRAV.

The null and alternative hypotheses for the secondary endpoints are:

$$H_0: \mu_{\text{SIMBRINZA+DUOTRAV}} = \mu_{\text{Vehicle+DUOTRAV}}$$

$$H_1: \mu_{\text{SIMBRINZA+DUOTRAV}} \neq \mu_{\text{Vehicle+DUOTRAV}}$$

where $\mu_{\text{SIMBRINZA+DUOTRAV}}$ refers to mean of each secondary endpoint for subjects randomized to receive SIMBRINZA plus DUOTRAV, and $\mu_{\text{Vehicle+DUOTRAV}}$ refers to mean of the same endpoint in the corresponding group of subjects randomized to receive Vehicle plus DUOTRAV.



4.3 Statistical Methods for Efficacy Analyses

Primary Analysis

Treatment difference in mean IOP change from baseline will be examined based on the least squares means derived from an analysis of covariance model. The model will have IOP change from baseline as response variable and include fixed effect terms for baseline and treatment. The baseline term will be the average of the 9:00 AM and the 11:00 AM IOP measurements at the two eligibility visits. Change from baseline in IOP is calculated by taking the difference at each time point between the Week 6 value and the baseline value (averaged over the two eligibility visits) and then averaging the available differences. Within-group estimates of the mean change from baseline and associated two-sided 95% confidence intervals will be presented. Estimates of the difference in mean change from baseline in IOP between SIMBRINZA and Vehicle and associated two-sided 95% confidence interval will also be presented.

Evidence of efficacy will be deemed established if a reduction in mean IOP is greater for SIMBRINZA than for Vehicle, with the associated p-value less than specified by the Haybittle-Peto boundary (see table in Section 8). Note that a negative difference (SIMBRINZA minus Vehicle) in mean change from baseline in IOP indicates greater reduction in IOP from baseline in favor of SIMBRINZA. Primary inference will be based on the FAS. The primary analysis will be repeated on the PPS to investigate sensitivity of including subjects who do not completely conform to protocol requirements.

SAS pseudo-code is provided in the Appendix (see [Section 11.1](#)).

Secondary Analyses

Analyses of IOP at Week 6 and percentage change from baseline in IOP at Week 6 will use the same statistical methods employed for the primary endpoint.

Mean IOP at Week 6 is calculated by averaging the IOP measurements at both Week 6 time points (9:00 and 11:00).

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

- Obtain percentage differences from baseline for each of the 2 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

Analyses of IOP change and percent IOP change at each Week 6 time point will be based on a mixed model repeated measures (MMRM) with fixed effects of treatment, time point, and the interaction of treatment and time point; and the baseline (averaged over the eligibility visits) as a covariate.

Covariance structures such as unstructured (UN) will be used. Within-group estimates of the mean change from baseline and associated two-sided 95% confidence intervals will be presented. Note that a negative difference (SIMBRINZA minus Vehicle) in mean change from baseline in IOP indicates greater reduction in IOP from baseline in favor of SIMBRINZA.

SAS pseudo-code is provided in the Appendix (see [Section 11.1](#)).

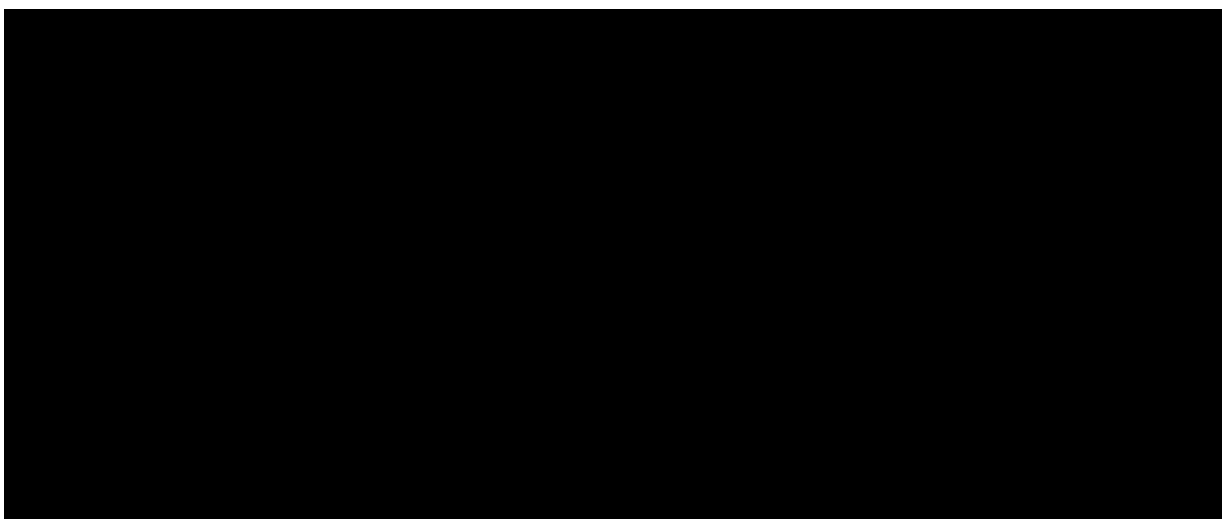


Table 4–1 summarizes the primary and secondary efficacy analyses.

Table 4–1 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint	Main vs. Sensitivity Approach	Statistical Method ^a	Analysis Set	Missing Data Approach
Primary				
Mean change from baseline in IOP at Week 6 (subject changes from baseline IOP averaged over the 09:00 and 11:00 measurements)	M	ANCOVA ^b	FAS	Likelihood-based ignorable analysis
Mean Change from baseline in IOP at Week 6(subject changes from baseline IOP averaged over the 09:00 and 11:00 measurements)	S	ANCOVA ^b	PPS	Likelihood-based ignorable analysis
Secondary				
Mean IOP at Week 6 (subject IOP averaged over the 09:00 and 11:00 measurements)	M	ANCOVA ^b	FAS	Likelihood-based ignorable analysis
Mean Percentage change from baseline in IOP at Week 6 (subject IOP percent change from baseline averaged over the 09:00 and 11:00 measurements)	M	ANCOVA ^b	FAS	Likelihood-based ignorable analysis
Mean Change from baseline in IOP at Week 6 at 11:00	M	MMRM ^c	FAS	Likelihood-based ignorable analysis
Mean Percentage change from baseline in IOP at Week 6 at 11:00	M	MMRM ^c	FAS	Likelihood-based ignorable analysis
Mean Change from baseline in IOP at Week 6 at 9:00	M	MMRM ^c	FAS	Likelihood-based ignorable analysis
Mean Percentage change from baseline in IOP at Week 6 at 9:00	M	MMRM ^c	FAS	Likelihood-based ignorable analysis
M=Main analysis approach; S=Sensitivity analysis approach ^a Further details on statistical models are outlined above in 4.3. ^b Analysis of covariance with fixed effect for treatment, and baseline IOP as covariate ^c Mixed models with fixed effects of treatment, time point, and the interaction of treatment and time point; with time matched baseline IOP as a covariate, and unstructured covariance structure				

4.4 Multiplicity Strategy

A gate-keeping strategy will be employed to ensure overall control of the type I error rate. The secondary efficacy hypotheses will be relevant only if the primary efficacy null hypothesis is first rejected at the level of significance (two-sided) dictated by the Haybittle-Peto boundary (see [Section 8](#)) at the interim or final analysis. Following the rejection of the primary efficacy null hypothesis, each secondary hypothesis will be tested following the order of the hypotheses as listed below. Each hypothesis will be relevant only if the preceding hypotheses have been rejected at the 5% level of significance (two-sided). The testing order (all based on IOP at Week 6) will be:

- Difference between treatments in mean change from baseline in IOP
- Difference between treatments in IOP
- Difference between treatments in percentage IOP change from baseline
- 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 9:00
- Difference between treatments in percentage IOP change from baseline at 9:00

Significance for a comparison will be claimed only if the null hypothesis is rejected ($p < 0.05$) for the previous endpoint in this series.

4.5 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses of IOP endpoints will be presented by treatment group to assess the consistency of treatment effect across various subgroups.

The primary endpoint (mean change in IOP at Week 6) will be summarized descriptively (N, mean, standard deviation), by treatment, in the following subgroups: age category (< 65 , ≥ 65 and furthermore as < 50 , $50-64$, ≥ 65), sex, race, baseline IOP (19-24 mmHg, $> 24-28$ mmHg), and region (EMEA = Belgium, Germany, Greece, Italy, Poland, Spain, UK; Asia = S. Korea, Malaysia, Taiwan, Australia; LACAR = Argentina, Chile, Colombia).

4.6 Interim Analysis for Efficacy

As previously stated, this study will incorporate an interim analysis for efficacy assessment when 50% of the total planned subjects have completed or discontinued from the study. The objective of the interim analysis is to provide an opportunity for early rejection of the null

hypothesis that there is no difference in IOP change from baseline between SIMBRINZA plus DUOTRAV and Vehicle plus DUOTRAV. In order to ensure Type I error is adequately controlled at the 5% level of significance (two-sided), a p-value boundary will be employed, specifically, the Haybittle-Peto boundary (Haybittle 1971). The Haybittle-Peto boundary ensures that the study stops for efficacy only if there is overwhelming evidence of efficacy.

The statistical method for efficacy at the interim analysis is the same as in [Section 4.3](#). The primary analysis will be performed on all subjects who have completed or discontinued the study at the time of the interim analysis. Subjects who are enrolled and ongoing at the time of the interim time point will not contribute to the primary analysis. The p-value obtained from the primary analysis will be evaluated against the p-value boundary as listed in [Section 8](#). The study will stop for efficacy if the p-value boundary is crossed with respect to the analysis of the primary endpoint. If the boundary is not crossed, the study will continue to conclusion.

If the efficacy stopping rule is met at the interim analysis, the main analysis for the primary hypothesis is the interim analysis. Analysis for the primary endpoint including subjects that did not contribute to the interim analysis but had been randomized at the time of the interim analysis (i.e. over-runs) will be reported as a supportive analysis. The main analysis for the secondary hypotheses will be based on the FAS population at the end of the study (i.e. subjects in the interim analysis plus over-runs).

Following a significant primary analysis at the interim analysis, the secondary hypotheses will be tested at the 5% two-sided level of significance. Testing will proceed in the order listed in [Section 4.4](#). If the primary analysis is not significant at the interim analysis, the secondary endpoints will be tested, following a significant primary final analysis, at the reduced alpha as listed in [Section 8](#) and in the order listed in [Section 4.4](#).

5 SAFETY ANALYSIS STRATEGY

5.1 Safety Endpoints

The safety endpoints are:

- Extent of exposure
- Automated perimetry
- Fundus parameters
- Best-corrected visual acuity (BCVA)
- Slit-lamp biomicroscopy examination

- Vital Signs (blood pressure, pulse rate)
- Adverse events

Relevant measurement scales for safety endpoints ([Table 11-1](#)) and a study plan for the planned assessments/procedures ([Table 11-2](#)) are presented in [Section 1](#).

5.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of the occurrence and characteristics of adverse events as well as the other safety endpoints.

5.3 Statistical Methods for Safety Analyses

All analyses will be performed on the safety set overall by treatment unless otherwise noted. Selected safety analyses will also be presented by two sets of age categories [both (18-64 years and ≥ 65 years) and (18-49, 50-64, ≥ 65)]. The safety analyses will consist of descriptive summaries of the data as relevant to the scale of data, eg, frequencies and percentages for adverse events, and mean changes in IOP from baseline as appropriate.

5.3.1 Extent of Exposure

Extent of exposure to investigational product is calculated as duration of exposure to masked IP received. For all randomized subjects exposed to masked IP, duration of exposure is defined as the last day of exposure to masked IP minus the first day of exposure to masked IP plus 1 day. In the event that the last day of exposure is unknown, the date of last contact with the subject will be used. The first instillation of investigational product is scheduled to occur on the evening of the Eligibility 2 Visit and the last instillation of investigational product is scheduled to occur at the Week 6 Visit (Day 42) following the 09:00 IOP measurement. Additionally, subjects exposed to investigational product with no visits after Day 1 or no date of last contact will have their extent of exposure documented as 1 day. Extent of exposure will be summarized as a continuous measure (N, mean, median, standard deviation, minimum and maximum) and by counts and percentages of subjects in the following categories: 0 days, 1 to 17 days, 18 to 42 days and > 42 days.

Extent of exposure will be presented overall and by demographic characteristics (age, sex, race, and age categories [both (18-64 years and ≥ 65 years) and (18-49, 50-64, ≥ 65)]) for the safety analysis set.

5.3.2 Adverse Events

The applicable definition of an Adverse Event (AE) is in the study protocol. All AEs occurring from when a subject signs informed consent to when a subject exits the study will be accounted for. Analysis and presentation of AEs occurring prior to the exposure to the masked IP will be separated from those occurring after treatment exposure where a comparative evaluation of treatment-emergent AEs is intended. A treatment-emergent AE is an event not present prior to exposure to masked IP or any event already present that worsens following exposure to masked IP. The period for treatment-emergent AE analysis starts from first exposure to the masked investigational product to 30 days after cessation of study treatment. Any event occurring after the treatment-emergent period will be considered post-treatment.

Descriptive summaries (n and %) for AEs will be presented by system organ class and preferred term and by preferred term only. In addition to an overall presentation of all AEs, reports will be generated for special classes of AEs such as most frequent AEs (defined as AEs with incidence of 1% in one or both treatment groups), ocular AEs, nonocular AEs, treatment-related AEs, serious AEs, and AEs resulting in treatment discontinuation. Selected AE analyses (all treatment-emergent ocular AEs and all nonocular AEs) will be presented by both sets of age categories (18-64 years and ≥ 65 years) and (18-49, 50-64, ≥ 65).

Presentation of ocular AEs will be overall, i.e. event occurring in one eye or both eyes will be counted once with respect to the subject level counts, but will be counted each time for the number of events. Ocular adverse events will be presented by subgroups (Age, Race, Gender, Ethnicity and Region). These reports will be supported by subject listings, as necessary.

A listing will be provided for AEs that occur after signing informed consent but prior to randomization and exposure to at least 1 dose of the masked IP. This listing will comprise all events occurring during this period in any subject who consented to participate in the study.

5.3.3 Automated Perimetry

Visual field assessments will be conducted at the Screening (Visit 1) and the Week 6/Exit visits. Baseline will be defined as the last measurement prior to exposure to the masked IP (i.e. Screening). The analysis eye will be selected as the average of each subject's right and left dosed eyes. If only one eye is dosed then this eye will be analyzed. Analysis of visual fields will use the data from the selected eye(s).

Separate analyses will be performed for each visual field device used. The analyses will include Mean Deviation, Mean Defect, Corrected Pattern Standard Deviation (CPSD) or

PSD, and Corrected Loss Variance (CLV), dependent upon the visual field device used (see Manual of Procedures Section 4.2 for details). Observed values and change from baseline values for the selected eye(s) will be presented descriptively (N, mean, median, standard deviation, minimum, and maximum) at each post-baseline visit including exit for each treatment.

5.3.4 Fundus Parameters

A dilated fundus examination will be performed to evaluate the health of the vitreous; retina/macula/choroid, optic nerve, and cup/disc ratio (see [Table 11-1](#) in the Appendix for the scale of each parameter). The dilated fundus examination will be conducted at the Screening (Visit 1) and Week 6/ Exit (Visit 5) visits. Baseline will be defined as the last measurement prior to exposure to investigational product (i.e. Screening).

For each fundus parameter, excluding cup/disc ratio, the worse eye will be used in the analysis. The worse eye is the dosed eye with the largest increase from baseline. If both dosed eyes have the same amount of increase, then the right eye will be selected. Note that the worse eye will be chosen on the parameter level, therefore it is possible that a given subject would have both eyes declared as worse eye (e.g. the right eye for retina and left eye for optic nerve).

For each dilated fundus parameter, counts and percentages of subjects who experience an increase from baseline to exit visit will be presented. A listing will be provided which presents all subjects with an increase in any fundus parameter at any visit compared to the grade for the same eye at baseline.

For cup/disc ratio, the analysis eye will be selected as the average of each subject's right and left dosed eyes. If only one eye is dosed then this eye will be the selected eye. Analysis of cup/disc ratio will use the data from the selected eye(s). Observed values and change from baseline values for the selected eye(s) will be presented descriptively (N, mean, median, standard deviation, standard error, minimum, and maximum), by vertical and horizontal axes, at each study visit including exit for each treatment.

5.3.5 Best Corrected Visual Acuity (BCVA)

Best corrected visual acuity will be assessed at the Screening, Eligibility 1 (09:00 hours), Eligibility 2 (09:00 hours), Week 2 (09:00 hours) and Week 6 (09:00 hours)/Exit Visits. Baseline will be defined as the last BCVA measurement prior to exposure to the masked IP (i.e. Eligibility 2 (09:00 hours)). The analysis eye will be selected as the eye with the largest decrease in the number of letters read from baseline to any visit (scheduled or unscheduled).

If both study eyes have the same level of worsening, the right eye will be selected. Analysis of BCVA will use the data from the selected eye.

Observed values and change from baseline values for the selected 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 selected 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 change from baseline to last on-treatment BCVA assessment or to any visit will be presented according to the following categories: ≥ 15 letter increase, 10-14 letter increase, 5-9 letter increase, no change (± 4), 5-9 letter decrease, 10-14 letter decrease, ≥ 15 letter decrease. For change to any visit, a subject 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 ≥ 15 letter decrease in BCVA from baseline to any visit.

5.3.6 Slit-Lamp Biomicroscopy

A slit-lamp examination (SLE) will be performed at the Screening, Eligibility 1 (09:00), Eligibility 2 (09:00), Week 2 (09:00), and Week 6 (09:00)/Exit Visits. Baseline will be defined as the last SLE measurement prior to exposure to masked IP (i.e. Eligibility 2 (09:00)). The analysis of the SLE will consist of increases from baseline in the presence of aqueous flare/cells and lens (see [Table 11-1](#) in the Appendix for the scale of each parameter). For each slit-lamp parameter, the eye showing the largest increase in slit-lamp grade from baseline to any visit (scheduled or unscheduled) will be used in the analysis. If both eyes have the same amount of increase, then the right eye will be selected. Note that the worse eye will be chosen at the parameter level; therefore it is possible that a given subject may not have the same worse eye for all parameters. The analysis of slit-lamp parameters will include the counts and percentages of subjects who experience an increase from baseline to any visit attended. In addition, a shift table showing slit-lamp grade at baseline relative to each scheduled post-baseline visit will be presented for each parameter.

A listing will be provided which presents all subjects with an increase in any slit-lamp parameter at any visit compared to the grade of the same eye at baseline.

5.3.7 Vital Signs (Blood Pressure, Pulse Rate)

Blood pressure and pulse rate will be evaluated at Screening, and every time point at E1, E2, Week 2, and Week 6/Exit Visits. The proximal baseline measurement for vital signs will be the average of the E1 and E2 Visits. For systolic and diastolic blood pressure, two measurements will be obtained at each Eligibility visit and the average pressure will be used for that visit. If the first two readings differ by more than 5 mmHg, a third reading will be taken and the average of the three values will be used. If three readings are available regardless of the above criteria (first two readings differ by more than 5 mmHg), the average of the three values will be used. A graphical representation of the mean actual parameter value over time by treatment will be provided.

Descriptive statistics (mean, standard deviation, N) by treatment group will be provided for each cardiovascular parameter at each scheduled visit and time point. The statistics will be given for the actual parameter value. A subject listing will be provided which contains data at baseline and each study visit and time point for each cardiovascular parameter.

Also, a subject listing will be provided which contains data for each abnormal cardiovascular finding. Each value will be categorized as low, normal, or high using the following normal ranges for subjects 18 or more years of age: pulse - 60 to 100 bpm; systolic blood pressure - 100 to 140 mm Hg, diastolic blood pressure - 60 to 90 mm Hg.

Finally, a subject listing corresponding to this shift in cardiovascular parameters will be presented for the overall safety population.

5.4 Interim Analysis for Safety

Not applicable.

6 PHARMACOKINETIC ANALYSIS STRATEGY

Not applicable.

7 ANALYSIS STRATEGY FOR OTHER ENDPOINTS

Not applicable.

8 SAMPLE SIZE AND POWER CALCULATIONS

With 108 evaluable subjects per treatment group in the primary efficacy analysis, there is at least 80% power to detect a 1.5 mmHg difference in mean change from baseline in IOP at Week 6 between the treatment groups. However, the required sample size to attain the same

power is 28 subjects per arm if the difference is 3.0 mmHg between treatment groups as suggested by expert opinion. Both calculations are based on the assumption of a common standard deviation for mean IOP of 3.9 mmHg and the use of a two-sample two-sided t-test performed at the $\alpha=0.05$ level of significance.

To mitigate the uncertainty about the expected treatment difference, a two look design with Haybittle-Peto boundaries will be used. Thus, this study will incorporate an interim analysis for efficacy assessment when 50% of total planned subjects have completed or discontinued from the study. The power to reject the null hypothesis at the single interim analysis when 50% of subjects have completed or discontinued the study is 28.2% if the expected mean difference is 1.5 and 92.2% if the expected mean difference is 3.0.

Look #	Sample Size	Efficacy p-value	P-value Boundary	Exit Probabilities		
				$\delta=0$	$\delta=1.5$	$\delta=3.0$
1	108	0.01	0.01	0.01	0.282	0.922
2	216	0.045	0.045	0.04	0.517	0.078
Sum of Exit Probabilities				0.05	0.799	1

Assuming a drop-out rate of 10%, approximately 120 subjects per treatment group will be randomized to ensure the required number of evaluable subjects in the final efficacy analysis.

Subjects will be randomized in a 1:1 ratio to receive either SIMBRINZA and DUOTRAV or Vehicle and DUOTRAV.

9 REFERENCES

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70(3):659-63.

10 REVISION HISTORY

This is the second version (Version 2.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0, of the study protocol TDOC-0051572.

Amendment #1

1. Changed author from [REDACTED] to [REDACTED]
2. Lowered the qualifying IOP criteria at both the Eligibility 1 and Eligibility 2 visits from ≥ 21 and ≤ 28 mmHg at 9:00 to ≥ 19 and ≤ 28 mmHg at 9:00.
3. Removed the 15:00 IOP measurement time point at all study visits.
4. Allowed subjects currently on treatment with Travoprost 0.004%/Timolol 0.5% for at least 28 days prior to screening in the morning or evening to be eligible for the study.
5. Incorporated an interim analysis for efficacy assessments when 50% of the total planned subjects have been completed or discontinued from the study.
6. Updated Statistical Analysis associated with the change in eligibility criteria.

Amendment #2

1. Changed author from [REDACTED] to [REDACTED].
2. Dummy SAS codes are moved to Appendix.
3. All listing details were delete and the variables reported in each listing are in the TFL shell document.
4. To test efficacy endpoints unstructured covariance (COV = "UN") will be used.
5. The baseline value used in the model as covariate was changed to the average of 9:00 Hr and 11:00 Hr values instead of the 09:00 AM IOP (averaged over the eligibility visits) to be consistent with the calculation of the primary endpoint.
6. Removed subgroup analysis (w.r.t. age, sex, baseline IOP category) of secondary efficacy end points.
7. [REDACTED]
8. Categorization by Duotrav type is removed as relevant information is not collected in CRF.
9. The plot reporting the percentage of subjects achieving IOP target will be reported by treatment group was removed.
10. For cup/disc ratio, the analysis eye will be selected as the average of each subject's right and left dosed eyes instead of the worst eye.
11. Minor edits of the text throughout the document.

11 Appendix

11.1 SAS Pseudo-code

SAS pseudo-code such as the following will be used to implement the procedures described in Section 4.3 for the primary endpoint:

```
proc mixed data = dataset;  
    class treatment subject;  
    model dIOPchange = baselineIOP treatment / ddfm=KR;  
    lsmeans treatment / cl diff  
    ods output diffs = diffs lsmeans = lsmeans;  
run;
```

SAS pseudo-code such as the following will be used to implement the procedures described in Section 4.3, for the secondary endpoint:

```
proc mixed data = dataset;  
    class treatment timepoint subject;  
    model IOPchange = baselineIOP treatment | timepoint/ ddfm=KR;  
    repeated timepoint/ type=UN subject=subject;  
    lsmeans treatment* timepoint/ cl diff;  
    ods output diffs = diffs lsmeans = lsmeans;  
run;
```

11.2 Study Tables for Reference

Table 11–1 Measurement Scales for Ophthalmic Assessments

Assessment	Scale	Parameter
Slit-Lamp Exam	0 – None 1 – Faint 2 – Moderate 3 – Marked 4 – Intense	Aqueous Flare
	Grade 0.0 – <1 cells Grade 0.5 – 1 to 5 cells Grade 1 – 6 to 15 cells Grade 2 – 16 to 25 cells Grade 3 – 26 to 50 cells Grade 4 – >50 cells	Aqueous Cells
	0 – Phakic 1 – Pseudophakic 2 – Aphakic	Lens
	0 – No opacity 1 – Any opacity 2 – Worsening of opacity 3 – Not Evaluable	Status of Lens
Fundus Parameters	0 – Absence of any opacity 1 – Presence of opacity in the vitreous	Vitreous
	0 – Normal. No evidence of previous inflammation or structural change 1 – Evidence of previous inflammation, now quiet; or previous structural change, now stable 2 – Evidence of active inflammatory process or acute structural change	Retina Macula Choroid
	0 – Normal. No damage 1 – Mild optic nerve damage, secondary to glaucoma including any rim loss (sloping or thinning) 2 – Moderate optic nerve damage, including cupping to disc margin at one or more points 3 – Severe optic nerve damage, nearly total cupping, only nasal rim or less present	Optic Nerve

Table 11-2 Overview of Study Plan

	Nominal Time ± Visit Window Limits						
	Visit 1* Screening	Visit 2* Eligibility 1	Visit 3 Eligibility 2 (Randomization)	Visit 4	Visit 5 Exit	Unscheduled Visit	Early Exit^a
Procedure/ Assessment		<i>1-5 days after Screening</i>	<i>3-5 days from E1</i>	<i>Day 14± 3 Days from E2</i>	<i>Day 42 ± 5 Days from E2</i>		
Informed Consent ^b	X						
Demographics	X						
Medical History	X						
Concomitant Medications	X						
Changes in Concomitant Meds		X	X	X	X	X	X
Inclusion/Exclusion	X						
Urine Pregnancy Test ^c	X				X		X
BCVA	X	X ¹	X ¹	X ¹	X ¹	X	X
Slit-Lamp Biomicroscopy	X	X ¹	X ¹	X	X ¹	X	X
Corneal Thickness (Pachymetry)	X						
Angle Width Screening (Gonioscopy)	X						
Dilated Fundus Exam	X				X	X	X
Visual Field Assessment (Automated perimetry)	X ^d				X ^e		X ^e
IOP	X			X ²		X	X
IOP (9:00, 11:00) +/- 30 minutes		X	X		X		
Blood Pressure	X			X ²		X	

	Nominal Time ± Visit Window Limits						
	Visit 1* <i>Screening</i>	Visit 2* <i>Eligibility 1</i>	Visit 3 <i>Eligibility 2</i> (Randomization)	Visit 4	Visit 5 <i>Exit</i>	Unscheduled Visit	Early Exit ^a
Procedure/ Assessment		<i>1-5 days after Screening</i>	<i>3-5 days from E1</i>	<i>Day 14± 3 Days from E2</i>	<i>Day 42 ± 5 Days from E2</i>		
Blood Pressure (9:00, 11:00)		X	X		X		
Pulse Rate	X			X ²		X	
Pulse Rate (9:00, 11:00)		X	X		X		
Dispense Study Meds	X		X				
Instill Meds in Office				X	X		
Adverse Events (Both Volunteered and Elicited)	X	X	X	X	X	X	X
Collect Study Meds					X		X
Exit Subject & Complete Exit Form					X		X

* Visit 1 and 2 may be combined if the subject IOP was measured at 9:00, DUOTRAV taken on the previous morning at 9:00 ± 1hour or evening at 21:00 ± 1hour and all other study assessments can be completed as per protocol.

¹ morning only

² 9:00 ± 2 hours

^a Perform assessments on subjects who discontinue study participation prior to Week 6 visit.

^b Must be signed/dated before study procedures are performed.

^c Required on all female subjects of childbearing potential.

^d VF can have been performed 30 days before Screening to E2 visit

^e May be conducted anytime during the visit.

Approval Page

Statistical Analysis Plan for GLJ576-P001 (CQVJ499A2402)

Safety and Efficacy with Twice Daily Brinzolamide 1% / Brimonidine 0.2%
(SIMBRINZA) as an Adjunctive Therapy to Travoprost 0.004% / Timolol 0.5%
(DUOTRAV)

Date:	Signed by:	Justification
21/7/18	[REDACTED]	I have authored this amended SAP and confirm to the best of my knowledge it is accurate.
	[REDACTED]	[REDACTED]

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
07/23/2018 20:13:23		
07/23/2018 20:58:53		