Short Title:

Statistical Analysis Plan CQVJ499A2401(Alcon GLH694-P001) / NCT02419508

Full Title:

Statistical Analysis Plan CQVJ499A2401(Alcon GLH694-P001)

Protocol Title:	Additive Effect of Twice Daily Brinzolamide 1% /Brimonidine 0.2% fixed dose combination as an adjunctive therapy to a prostaglandin analogue
Project Number:	CQVJ499A2401(Alcon GLH694-P001)
Protocol TDOC Numbers:	TDOC-0051182 & TDOC-0050474
Author:	[redacted] Lead Statistician
Version:	Amendment 3.0, 06MAR2018
Approvals:	See last page for electronic approvals.
Job Notes:	

This version of the Statistical Analysis Plan is based on Version 3.0, of the study protocol TDOC-0050474.

Executive Summary:

Key Objectives:

The primary objective of this study is to demonstrate the additive effect of twice daily brinzolamide 1% / brimonidine 0.2% (SIMBRINZA) in subjects with either open-angle glaucoma or ocular hypertension who are currently on a prostaglandin analogue monotherapy (PGA).

Decision Criteria for Study Success:

Success will be declared if the primary efficacy null hypothesis is rejected at the 5% level of significance (two-sided) in favor of adjunctive therapy (SIMBRINZA plus PGA) relative to PGA alone. Success reflects greater mean reduction at Week 6 from baseline in diurnal IOP for the adjunctive therapy relative to PGA alone.

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1 Study Objectives and Design

1.1 Study Objectives

The primary objective of this study is to demonstrate the additive effect of brinzolamide 1%/ brimonidine 0.2% (SIMBRINZA) in subjects with either open-angle glaucoma or ocular hypertension who are currently on a prostaglandin analogue monotherapy.

1.2 Study Description

The study is a 6 week, multicenter, parallel group study in subjects with 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 and Run-In/Washout Phase followed by 2 Eligibility Visits (E1 & 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).

Table .1–1 Study Plan by Treatment Groups

<table>
<tr><th rowspan="3">Treatment Group</th><th colspan="2">Study Phase</th></tr>
<tr><td>Phase I
(Screening/Eligibility Phase)</td><td>Phase II
(Treatment Phase)</td></tr>
<tr><td>Screening and Eligibility Visits</td><td>Week 2 and Week 6 (Exit) Visits</td></tr>
<tr><td>SIMBRINZA + PGA

(TRAVATAN PQ 0.004%, or XALATAN 0.005%, or LUMIGAN 0.01%)</td><td rowspan="2">Begin dosing with PGA analogue at bedtime on the evening of the screening visit
&
Washout of all other IOP-lowering medications

<u>In at least one eye* Mean IOP at each Eligibility Visit at 9:00 Hrs time point must be:</u>
≥ 19 mmHg and < 32 mmHg
<u>(while on PGA monotherapy)</u>
*This qualifying eye must be the same eye for each Eligibility Visit
The mean IOP in either eye must not be greater than or equal to 32 mmHg at any time point.</td><td>SIMBRINZA BID
(09:00 and 21:00 Hrs)

PGA QD
(at bedtime)</td></tr>
<tr><td>Vehicle + PGA

(TRAVATAN PQ 0.004%, or XALATAN 0.005%, or LUMIGAN 0.01%)</td><td>Vehicle BID
(09:00 and 21:00 Hrs)

PGA QD
(at bedtime)</td></tr>
</table>

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 implemented in an Interactive Response Technology (IRT) system. Each subject number will be associated with treatment groups according to a random process.

The randomization will be stratified by study region and type of PGA therapy (LUMIGAN, XALATAN or TRAVATAN). For each of the three study-specific PGA types within each region, subjects will be randomized 1:1 to SIMBRINZA or vehicle, to ensure balanced treatment assignment within each region and PGA type.

1.4 Masking

This study is double-masked with subjects randomized to use SIMBRINZA or vehicle for a duration of approximately 42 days. However, PGA 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. 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. Each kit will contain 1 bottle of masked IP or PGA. Kits containing PGA will also be labeled to identify the PGA, protocol and kit numbers. This level of masking will be maintained throughout the conduct of the study.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 Analysis Sets

2.1 Efficacy Analysis Sets

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 set. For example if a subject is given SIMBRINZA plus PGA when they were randomly assigned to receive Vehicle plus PGA, the subject will be analyzed according to the randomization schedule (i.e. Vehicle plus PGA) regardless of which treatment was actually received (SIMBRINZA plus PGA).

The **per protocol set (PPS)** will be evaluated only for the primary efficacy endpoint to confirm results from the FAS.

PPS is a subset of the FAS and excludes all subjects who have met any of the critical deviation criteria identified in the Deviation and Evaluability Plan (DEP). In addition, individual subject visits and data points with critical deviations may be excluded from the analysis involving the PPS. Evaluability for all subjects will be determined prior to breaking the code for masked treatment assignment.

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

2.2 Safety Analysis Set

Safety analyses will be conducted using the **Safety Set** defined to include all subjects who received a dose of masked IP (i.e. not the run-in medication). In the safety set subjects will be categorized under the actual treatment received. Subjects who took incorrect study treatment will be included in the group corresponding to the first treatment received.

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, gender, race, ethnicity, iris color and region) and baseline characteristics (baseline diurnal IOP, baseline IOP category :19-26 mmHg, 27-32 mmHg, assigned PGA monotherapy, corneal thickness and diagnosis) .

Demographic and baseline characteristics will be reported for the FAS, while disposition table for all screened subjects.

Listings for treatment assignment by investigator, screen failures by reason, subjects who terminated early from the study or discontinued treatment, and subjects excluded from key analysis sets will be reported. 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. Diurnal baseline IOP and corneal thickness will be summarized as continuous variables. In addition, baseline IOP category (19-26 mmHg, 27-32 mmHg), assigned PGA monotherapy, corneal thickness (≤ 0.55 mm, > 0.55 mm to 0.60 mm and > 0.60 mm and diagnosis will be summarized as categorical variables.

4 Efficacy Analysis Strategy

The efficacy assessment between treatment groups will be analyzed based on the FAS. If not otherwise specified, all significance testing will be at the 5% level (two-sided).

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 AM 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 AM averaged across the 2 eligibility visits. If both eyes are equal then the right eye will be selected for analysis.

Note: For IOP measurements, baseline corresponds to the average of IOP measurements at E1 and E2 visits on the study visit schedule.

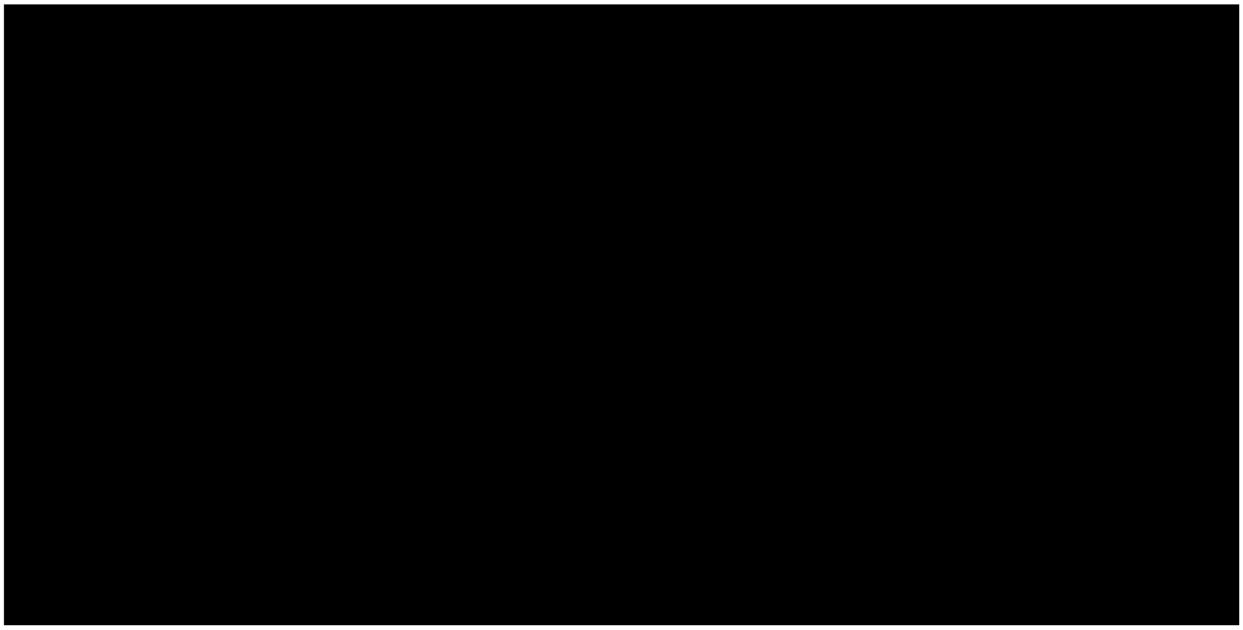
4.1 Efficacy Endpoints

Primary Endpoint

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

Secondary Endpoints

- Mean diurnal IOP (subject IOP averaged over the 09:00 and 11:00 Hr. time points) to Week 6
- Mean diurnal IOP percent change from baseline (subject IOP percent change from baseline averaged over the 09:00 and 11:00 Hr. time points) to Week 6.
- Mean change from baseline in IOP at 11:00 at Week 6
- Mean percentage change from baseline in IOP at 11:00 at Week 6
- Mean change from baseline in IOP at 9:00 at Week 6
- Mean percentage change from baseline in IOP at 9:00 at Week 6



4.2 Efficacy Hypotheses

The null and alternative hypotheses for the primary analysis are:

$$H_0: \mu_{SIMBRINZA+PGA} = \mu_{Vehicle+PGA}$$

$$H_1: \mu_{SIMBRINZA+PGA} \neq \mu_{Vehicle+PGA}$$

where $\mu_{BrinzBrim+PGA}$ refers to mean diurnal IOP change from baseline for subjects randomized to receive SIMBRINZA plus PGA, and $\mu_{Vehicle+PGA}$ refers to mean diurnal IOP change from baseline for subjects randomized to receive Vehicle plus PGA.

Thus, success reflects greater mean reduction in diurnal IOP change from baseline at Week 6 for the adjunctive therapy (SIMBRINZA plus PGA) relative to PGA alone. This is evidenced by greater mean diurnal IOP change from baseline which corresponds with the mean change from baseline value being "more" in the adjunctive therapy group.

The null and alternative hypotheses for the secondary endpoints are:

$$H_0: \mu_{SIMBRINZA+PGA} = \mu_{Vehicle+PGA}$$

$$H_1: \mu_{SIMBRINZA+PGA} \neq \mu_{Vehicle+PGA}$$

where $\mu_{BrinzBrim+PGA}$ refers to mean of each secondary endpoint for subjects randomized to receive SIMBRINZA plus PGA, and $\mu_{Vehicle+PGA}$ refers to mean of the same endpoint in the corresponding group of subjects randomized to receive Vehicle plus PGA. Thus, success reflects greater mean estimate for the adjunctive therapy relative to PGA alone.

[redacted]

4.3 Statistical Methods for Efficacy Analyses

All endpoints will be summarized using standard descriptive summary statistics, on the FAS, consistent with the type of variable (continuous vs. categorical).

Primary Analysis

Treatment differences in mean diurnal IOP change from baseline will be examined with a pair-wise test at each scheduled on-therapy visit with Week 6 as the primary endpoint.

Pair-wise tests will be based on the least squares means derived from using a mixed model repeated measures analysis (MMRM). The model will include factors for PGA, region, treatment, visit, and treatment by visit interaction. Baseline diurnal IOP will be included in the model as a covariate.

Covariance structures such as unstructured (UN), variance components (VC), compound symmetry (CS), autoregressive [AR(1)], and Toeplitz (Toep) will be considered. The best fitting structure, based on Akaike Information Criterion (AIC) will be selected. Within-treatment and between treatment estimates of mean change from baseline in mean diurnal IOP, the associated standard error, 95% confidence interval and p-value will be provided.

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

The primary analysis will be based on the FAS and repeated on the PPSsubjects .

Secondary Analyses

Analysis of treatment differences of all secondary endpoints, outlined below, will use the same methods as those for the primary endpoint and it will be based on the FAS.

- Mean diurnal IOP (subject IOP averaged over the 09:00 and 11:00 Hrs. time points) to Week 6
- Mean diurnal IOP percent change from baseline (subject IOP percent change from baseline averaged over the 09:00 and 11:00 Hrs. time points) to Week 6.
- Mean change from baseline in IOP at 11:00 at Week 6
- Mean percentage change from baseline in IOP at 11:00 at Week 6
- Mean change from baseline in IOP at 9:00 at Week 6
- Mean percentage change from baseline in IOP at 9:00 at Week 6

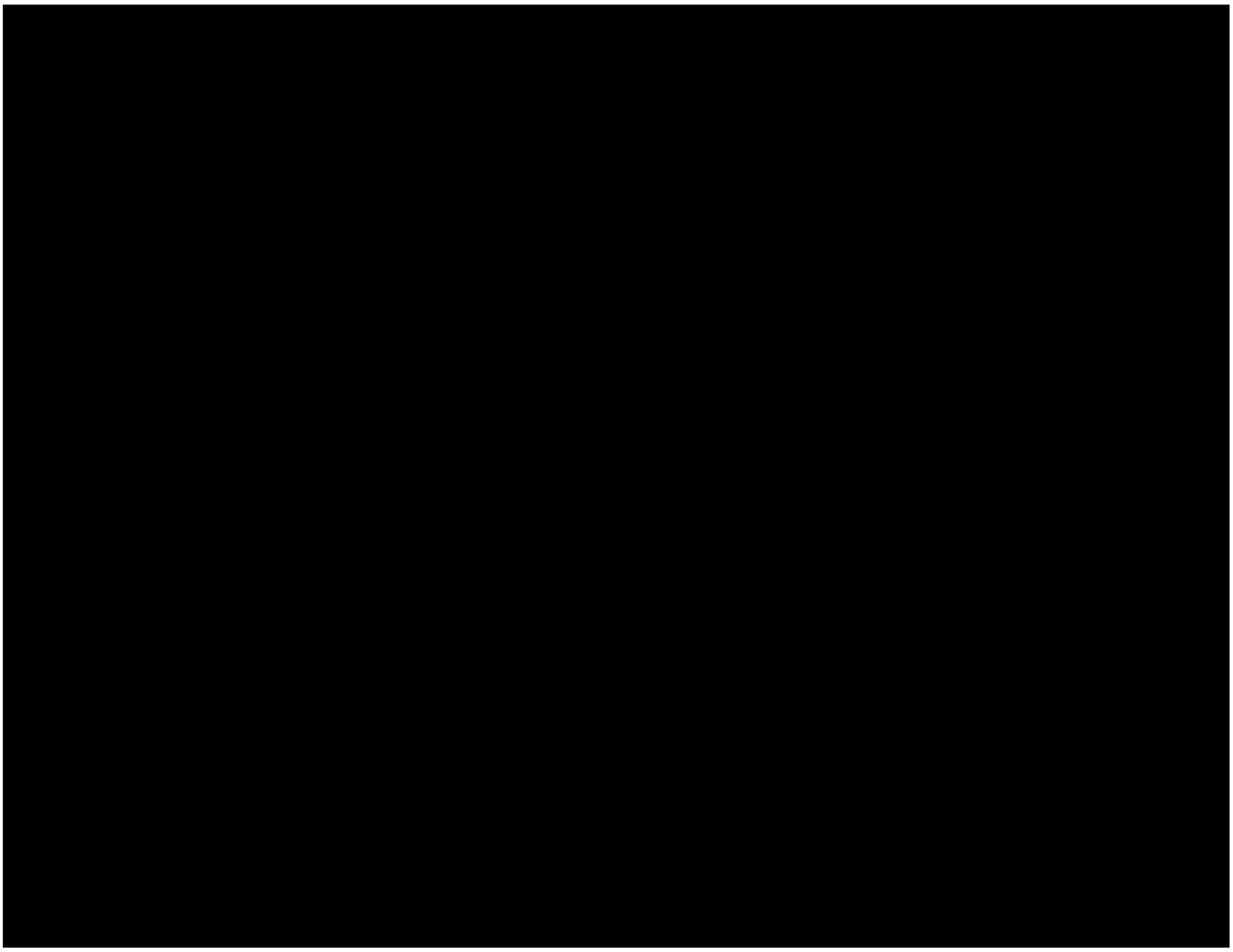


Table 4-1 summarizes the key efficacy analyses.

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

Endpoint	Main vs. Sensitivity Approach†	Statistical Method‡	Analysis Set	Missing Data Approach

Primary				
Mean change from baseline in diurnal IOP at Week 6 (subject changes from baseline IOP averaged over the 09:00 and 11:00 Hrs time points)	M	MMRM[§]	FAS	Likelihood-based ignorable analysis
Mean change from baseline in diurnal IOP at Week 6	S	MMRM[§]	PP	Likelihood-based ignorable analysis
Secondary				
Mean diurnal IOP (subject IOP change from baseline averaged over the 09:00 and 11:00 Hrs time points) to Week 6	M	MMRM[§]	FAS	Likelihood-based ignorable analysis
Mean diurnal IOP percent change from baseline (subject IOP percent change from baseline averaged over the 09:00 and 11:00 Hrs time points) to Week 6	M	MMRM[§]	FAS	Likelihood-based ignorable analysis
Mean change from baseline in IOP at 11:00 at Week 6	M	MMRM[§]	FAS	Likelihood-based ignorable analysis
Mean percent change from baseline in IOP at 11:00 at Week 6	M	MMRM[§]	FAS	Likelihood-based ignorable analysis
Mean change from baseline in IOP at 9:00 at Week 6	M	MMRM[§]	FAS	Likelihood-based ignorable analysis
Mean percentage change from baseline in IOP at 9:00 at Week 6	M	MMRM[§]	FAS	Likelihood-based ignorable analysis

[†]M=Main analysis approach; S=Sensitivity analysis approach
[‡]Further details on statistical models are outlined above in 4.3.
[§]Mixed models with repeated measures

4.4 Multiplicity Strategy

To ensure type I error is controlled over the set of study hypotheses at the 5% level of significance (two-sided), a fixed sequence testing strategy will be employed. The testing order (all efficacy endpoints at Week 6) will be:

- Difference between treatments in mean change from baseline in diurnal IOP
- Difference between treatments in mean diurnal IOP
- Difference between treatments in mean percentage diurnal 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

The primary end point will be summarized descriptively (N, mean, standard deviation), by treatment, in subgroups of age category (<65, ≥65 and furthermore as <50, 50-64, ≥65), sex, race, baseline IOP (19-26 mmHg, 27-32 mmHg), region, PGA run-in monotherapy, and corneal thickness (≤ 0.55 mm, > 0.55 mm to 0.60 mm and > 0.60 mm).

In addition, descriptive summary statistics will be provided for subjects with 16:00 IOP measurements on the following endpoints:

- IOP at each visit and time point
- Change from baseline in IOP at each visit and time point
- Diurnal IOP at Week 6
- Change from baseline in diurnal IOP at Week 6

4.6 Interim Analysis for Efficacy

Not applicable.

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 exam
- Vital Signs (Blood pressure, Pulse rate)
- Adverse events

Relevant measurement scales for safety endpoints (Table 10.2-1) and a study plan for the planned assessments/procedures (Table 10.2-2) are presented in the Appendix.

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. .

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 Hr. 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 45 days and >45 days.

Extent of exposure will be presented overall and by demographic characteristics (age, gender, race, ethnicity, and age categories (<65 years and ≥ 65 years and <50, 50-64, ≥65).

5.3.2 Automated Perimetry

Visual fields will be conducted at the Screening and the last visit at 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 worse eye at the parameter level. 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), and Corrected Loss Variance (CLV), dependent upon the visual field device used. 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.

5.3.3 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 Study Table 11-1in the Appendix for the scale of each parameter). The dilated fundus examination will be conducted at the Screening and Week 6/Exit 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.

5.3.4 Best Corrected Visual Acuity (BCVA)

Best corrected visual acuity will be assessed at the Screening, Eligibility 1 (09:00 Hr.), Eligibility 2 (09:00 Hr.), Week 2 (09:00 Hr.) and Week 6 (09:00 Hr.)/Exit Visits. Baseline will be defined as the last BCVA measurement prior to exposure to the masked IP (i.e. Eligibility 2 (09:00 Hr.)). 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 worse 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.

5.3.5 Slit Lamp Examination (SLE)

A SLE will be performed at the Screening, Eligibility 1 (09:00 Hr.), Eligibility 2 (09:00 Hr.), Week 2 (09:00 Hr.), and Week 6 (09:00 Hr.)/Exit Visits. Baseline will be defined as the last SLE measurement prior to exposure to masked IP (i.e. Eligibility 2 (09:00 Hr.)). The analysis of the SLE will consist of increases from baseline in the presence of aqueous flare/cells and lens (Table 11-1). For each slit-lamp parameter, the eye showing the largest increase in slit-lamp grade from baseline to any visit 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 will be presented.

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.

5.3.6 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. The statistics will be given for the actual parameter value. In addition, number and percentage of subjects with abnormal vital signs by visit and time point. A shift table from baseline will be presented for each parameter collected. For this purpose 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.

A patient listing with data at baseline and each study visit for each parameter as well as , a listing with data for each abnormal cardiovascular finding will be provided.

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

5.3.7 Treatment-Emergent Adverse Events

The applicable definition of an Adverse Event (AE) is in the study protocol. In the outputs, it will be referred to as treatment-emergent adverse events. Any pre-existing medical condition or signs/symptoms present in a subject prior to the start of the study (i.e., before informed consent is signed) should be recorded in the baseline history section of the CRF. Any medical occurrences having an onset after informed consent but prior to the start of study treatment (i.e., initiation of treatment with test article) should also be recorded in the baseline history section within the CRF. These occurrences 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 exposure to the masked IP to study exit.

Descriptive summaries (n and %) for treatment-emergent AEs will be presented by system organ class and preferred term. In addition reports will be generated for the most frequent treatment-emergent AEs (with incidence of 1% in one or both treatment groups), ocular AEs, non-ocular AEs, treatment-related AEs, serious AEs and AEs resulting in treatment discontinuation. 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. These reports will be supported by subject listings, as necessary.

A table and listing will report deaths.

Only subject listings 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.

5.4 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 81 evaluable subjects per treatment group in the primary efficacy analysis, there is at least 90% power to detect a difference in mean change from baseline in diurnal IOP at Week 6 of 2.0 mmHg between the treatment groups. This calculation is based on the assumption of a common standard deviation for mean change from baseline in diurnal IOP as small as 3.5 mmHg and as large as 3.9 mmHg and the use of a two-sample two-sided t-test performed at the α=0.05 level of significance.

Assuming a drop-out rate of 10%, approximately 90 subjects per treatment group will be enrolled to ensure the required number of evaluable subjects in the primary efficacy analysis.

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

9 References

None.

10 Revision History

This is the first revision (Version 2.0) to the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol recreated as TDOC-0050474. This is the first revision to the original protocol with a reference number of TDOC-0018786.

[redacted]

2. Table .1–1, Study Plan by Treatment Groups, updated to align with revised protocol criteria for the Mean IOP Visit requirement of < 32 rather than ≤ 32 at the eligibility visits.

[redacted]

Amendment 2

This is the second revision (Version 3.0) to the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 3.0 of the study protocol recreated as TDOC-0050474. This is the third revision to the original protocol with a reference number of TDOC-0018786.

1. [redacted]

2. Global change: Remove 16:00 IOP collection time point at all visits.

3. Global change: Reduce E1 & E2, 09:00 am, IOP inclusion criteria (#3) from ≥ 21 and < 32 mmHg to ≥ 19 and < 32 mmHg.

4. Changed Secondary Endpoints from

    - Mean change from baseline in IOP for each time point (9:00, 11:00, 16:00) at Week 6
    - Mean percentage change from baseline in IOP to Week 2 for each time point (9:00, 11:00, 16:00) at Week 6

    to

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

5. Removed identification of specific participating regions, i.e., (EU (Europe, Australia), LACAN (Latin America, Canada))

6. Revised wording in Sample Size Justification to add phrase “change from baseline in diurnal” after “standard deviation from mean”

7. Changed wording in Efficacy Analysis sentence from

    - Unless otherwise specified, all statistical analyses will be at the 5% level

    to

    - Unless otherwise specified, all significance testing will be at the 5% level (two-sided)

8. Updated Adverse Events section

9. Added subset analysis of subjects with 16:00 IOP measurements

10. Study Plan updated to only include 9:00 and 11:00 time points

Amendment 3

Minor editing changes were made following dry run meeting and to harmonize the analysis plan with the TLF (mock up tales) document.

1. [redacted]
2. Patients were replaced with subjects .
3. Section 2.2 the pre-treatment analysis set was deleted.
4. Section 3 text change to specify that the baseline and demographic characteristics will not be reported for all analysis sets but only for the FAS. Baseline values will not be reported by time point.
5. Section 4.3 and 4.5 , 5.3.6 some minor rewording but not content change.
6. Section 5.3 changed to delete the reporting of all safety analysis by age subgroup. The reporting of each safety parameter will be discussed in the appropriate section.
7. Section 5.3.1 a second age group (<50, 50-64, ≥65) for subgroup analysis has been added.
8. All listing details were delete the variables reported in each listing are in the TFL shell document.
9. Adverse event were replaced by treatment emergent adverse event to be consistent with the TLF document.
10. Section 5.3.7 a deaths listing and table has been added.
11. Section 5.3.2 definition of the baseline has been updated to harmonized to what used in the TLF documentation.

11 Appendix

11.1 SAS Pseudo-code

SAS pseudo-code such as the following will be used to implement the procedures described in Section 4.3.1.:

```
proc mixed data = dataset noclprint order=internal;
        class treatment visit subject pga region;
        model  dIOPchange = baselineIOP pga region treatment | visit;
        repeated visit/ type=UN subject=subject(treatment);
        lsmeans treatment  visit;
        lsmeans treatment*visit/ slice=visit cl diff;
run;
```

The comparisons will be extracted from the SAS statement “lsmeans treatment*visit/ slice=visit cl diff” at Week 6.

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 Study Plan

Activity	Screen	Eligibility 1[a]		Eligibility 2 (3-8 days from Eligibility Visit 1)		Week 2 (14 ± 3 days from Eligibility 2)		Week 6 (Exit) Visit (42 ± 3 days from Eligibility 2)		UNSC Visit	Early Exit[b]
		09:00	*11:00*	*09:00*	*11:00*	*09:00*	*11:00*	*09:00*	*11:00*		
Informed Consent[c]	X										
Demographics	X										
Med Hx & Con. Meds	X										
Change in Med Hx/Con Meds		X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X	X	X	X						
Urine Pregnancy Test[d]	X[f]								X[f]		X[f]
Best-Corrected VA	X	X		X		X		X		X	X
Automated Perimetry	X[e]								X[f]		X[f]
Slit-Lamp Exam	X	X		X		X		X		X	X
IOP (Goldmann)	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy	X										
Pachymetry	X										
Dilated Fundus Exam	X								X	X	X
Blood Pressure & Pulse Rate	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Meds	X				X						
Instill Study Meds in Office						X		X			
Adverse Event	X	X	X	X	X	X	X	X	X	X	X
Collect Study Meds				X				X		X	X
Exit Subject & Complete Exit Form									X		X

a E1 should be conducted from 1 to 29 days after Screening, according to the run-in/washout schedule.
b Perform assessments on subjects who discontinue study participation prior to Week 6 visit.
c Must be signed/dated before study procedures are performed.
d Required on all female subjects of childbearing potential.
e At Screening (preferably) or in between Screening and E2.
f May be conducted anytime during the visit.

Approval Page

Statistical Analysis Plan
for
GLH694-P001 (CQVJ499A2401)

Additive Effect of Twice Daily Brinzolamide 1% /Brimonidine 0.2% Fixed Dose Combination as an Adjunctive Therapy to a Prostaglandin Analogue

Date:	Signed by:	Justification
07/03/18	[redacted]	have authored this amended SAP and confirm to the best of my knowledge it is accurate.
	[redacted]	

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
03/09/2018 04:57:41	[redacted]	[redacted]
03/12/2018 09:55:08	[redacted]	[redacted]